Receptol® oral spray for Corona virus treatment and prevention

A new coronavirus, declared as Global Health Emergency by WHO, 2019-nCoV was first identified in Wuhan, the capital of China's Hubei province, after people developed SARS like pneumonia. The incubation period (time from exposure to the development of symptoms) of the virus is 2-10 days and can be contagious during this time. Symptoms include fever, coughing, and breathing difficulties. Without a clear cause of 2019-nCoV, treatments with existing vaccines is not effective.

The Receptol® oral spray, Globally Patented (USA Patent # US 9,249,188 B2) is a new Immunity Drug (NID) providing mode of action in a vaccine like manner with active immunity, can be used for treatment and as preventative vaccine in dealing with current 2019-nCoV epidemic. Receptol® consists of cell to cell communicator Nano informational peptides (Radha108) & proline-Rich Polypeptides (PRPs) from colostrum, Mother's 1st milk after the birth of the child or calf.

Numerous Studies have shown that Receptol® spray will deliver nanopeptide crossing blood brain barrier and have great effectiveness in treating many immunity disease including all viral infections. As a natural product, Radha-108 Nanopeptides have no side effects which can be taken safely by all age and are not species specific.

Receptol® shows great effectiveness in treatment of retrovirus such as HIV, Swine Flu and SARS like conditions caused by Coronavirus. An accelerated, prospective Phase III global efficacy and safety studies for Receptol® (containing API of Radha 108 Nanopeptides) was conducted for HIV Positive patients with 10 years follow up showed significant resolution of all symptoms and pharmacological effects with low to NILL Viral Load.

Once RADHA108 series get absorbed in the blood stream through buccal mucosa or transdermal route and crosses the Blood Brain Barrier (BBB), they act on Pituitary gland in brain and cell to cell communicator informational proteins (RADHA108) in RECEPTOL® will active in mitigating cell fusion. RADHA108 series has shown to dock on glycoprotein receptor on the cell surface and thus closing doors and windows for viral entry into the cell surface & immune cells in particular.

Coronaviruses is enveloped positive- RNA viruses characterized by club-like spikes that project from their surface. It has unusually large RNA genome, four main structural proteins. spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins as virus particles. S protein is cleaved by a host cell furin-like protease into two separate polypeptides noted S1 and S2. The initial attachment of the virion to the host cell is initiated by interactions between the S protein and its receptor.

The S-protein/receptor interaction is the primary determinant for a coronavirus to infect a host species and also governs the tissue tropism of the virus. Receptol® nanopeptides can block the attachment of S protein like In case of well-studied mode of action in treatment of retrovirus infection such as HIV and Swine flu.

Receptol® oral spray invented via Dr Pawan Saharan, Founder, Biomix USA, Australia and INDIA (www.biomix.in) can be an answer to prevent & treat current epidemic of 2019-nCoV as its Mode of Action is similar to that of AIDS for which global studies with 10 years follow is done.

Receptol®'s RADHA108 series nanopeptide will not only dock on S glycoprotein receptor on the cell surface to mitigate cell fusion closing doors and windows for all viral entry but will also stimulate the maturation of immature thymocytes into either helper or suppressor T cells, T help cells will help produce antibodies against 2019nCoA, Suppressor T cells, on the other hand, deactivate other lymphocytes after an infection has been cleared to avoid damage to healthy tissues. Receptol® will help to produce memory T cells, in order to expedite the production of antibodies for future infection in all human hosts.

Health for All

Via

Receptol®

A Paradigm shift in Healthcare

Treatment to Prevention

Dr. Pawan Saharan

डॉ. हर्ष वर्धन
Dr. Harsh Vardhan

FTS.77610...../2014/VIP/HFM
स्वास्थ्य एवं परिवार कल्याण मंत्री
भारत सरकार
Minister of Health & Family Welfare
Government of India

18 September, 2014

MESSAGE

It gives me an immense pleasure to release the book, Health for All via Receptol®, authored by Dr. Pawan Saharan.

The book gives detailed account of health benefit of colostrum. I understand that its research & development programme, clinical trials & manufacturing facility at AMUL dairy was supported by Govt. of India.

I wish Dr. Pawan Saharan, Chairman of Biomix Network Ltd., the very best.

(Dr. Harsh Vardhan)

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Receptol® Oral Spray

1. Introduction

The Receptol® oral spray consisting of Radha 108 Nano peptides stimulates body's own immune system as a broadspectrum immunomodulator & antiviral to fight against several diseases & prevents all communicable infections. It is a natural product manufactured by Nanobiotechnology patented proprietary processes from bovine colostrum (1st Milk after Birth).

Keywords: Colostrum, Receptol®, Nanopeptide, Radha108, immune-modulator

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Our health is directly influenced by our immune system. A balanced and healthy immune system is centre to the body's ability to defend against infections. "It is our ability to create a healthy immune system that represents the greatest potential for gains in human health".

After 10+years of research with the help of eminent group of scientists, at Biomix we have invented a product called Receptol® Oral spray, which will enable people to lead longer & healthier lives via building body's own immune system naturally, through state of the art US Product patented technology.

Receptol® is manufactured at cGMP, ISO certified by TUV Nord Germany nano biotech Biomix facility located at world's largest AMUL dairy in Gujarat India. Receptol® oral spray consisting of Radha108 Nanopeptides, isolated from mammalian colostrum with vaccine like antiviral and immnomodulator activity via building body's own immune system and attachment inhibition on the cell surface receptors.

The mammalian colostrums derived nanopeptides for broadspectrum viral and recurrent infections along with 58 approved indications by US PTO with a method of isolation thereof, Patented product with ***U.S. Patent No. 9,249,188*** *on February 02, 2016 &* ***US product Patent US 8,518,454 B2;*** South Africa Patent # 2011/04687; Singapore patent # 172793; European Patent Application #. 09827010.1.

The mode of action of Radha 108 informational proteins in Receptol® are active in mitigating cell fusion. Radha 108 series docks on glycoprotein receptor on the cell surface thus closing entry for viruses like foreign antigens entry into the immune and other cells. Radha 108 series gets absorbed in the blood stream through buccal mucosa and crosses the Blood Brain Barrier (BBB).The levels of Interleukins and Cytokines are increased substantially. Supports regulation of thymus via producing functionally active NK cells. Radha108 augments cell-mediated immunity & activates T-cell precursors to produce helper & suppresser T-cells increasing CD4/8 counts. Radha 108 promotes growth & differentiation of stem cells in response to any disease.

Receptol® essentially is a complex cocktail of compounds derived from bovine lacteal sources. These compounds include Proline-Rich Polypeptides (PRPs), glycoprotein, growth factors, neurotransmitters, cytokines (IFN-alpha, IFN-beta) produced from PRPs, and enzymes. Other immune factors present include: Trypsin Inhibitors, Glycoconjugates, Orotic Acid, Alpha 1-Antitripsin, Alpha 1-Fetoprotein, Alpha 2-Macroglobulin, Alpha 2- AP Glycoprotein, C3 & C4, Orosomucoids, Lyozyme, Thiocyanate, Peroxidase, Xanthine Oxidase, Vitamins A, B12, E, and Sulfur. Each of these compounds has specific functions in the human body.

Numerous studies have shown the effectiveness of Receptol® in eliminating or alleviating symptoms of herpes, chronic fatigue syndrome, Epstein Barr, hepatitis, secondary infection due to AIDS, Candida, cancer and many other disorders. Studies have also shown continual use provides the greatest benefit, with maximum immune activity occurring 24 to 48 hours after initial dosing.

Receptol® are a kin to vaccines. But, rather than expose the patient's immune system to the actual disease or a deactivated version of the same, Receptol® expose the patient's immune system to the memory of a health threat-whether foreign or native-and the knowledge of how to best respond to protect itself.

The uniqueness of Receptol is in Radha 108 8 sequences of amino acid monomers responsible for providing mode of action in a vaccine like manner with active immunity that led to US and European Patent and license authorities to grant exclusivity for 58 indications including Cancer, Auto immune disease like RA etc., Allergy & Asthma, infectious disease like AIDS and hepatitis etc. for 21 years. Such attributes are missing in all other colostrum forms available world over.

2. Background of Invention

There are approximately 6 trillion cells in the human body. Let's use this analogy; Imagine this huge network of cells is a massive computer network, where each human cell is a personal computer linked to this network with various control servers housed in the human brain. Overwhelming idea isn't it. Well it is difficult to imagine our bodies to be so sophisticated but in reality our bodies operate 100 or a 1000 times faster than the world's fastest supercomputer and that's even we are laying half asleep in our favor chair watching "Seinfield" on a Tuesday night.

You can appreciate to successfully operate this system we need to eat and drink to provide the energy and nutrients just to sustain this system. If we stopped eating or drinking we would die within a few day or weeks. No rocket-scientist has to tell us that. I agree. However, feeding our bodies with foods that have little or no nutritional value, foods that the body finds difficult to digest, and too much food really is hard on the human body.

The life span of the human body has not increased much in the last thirty years, "We take it to death". Even with the trillions and trillions of dollars we have spent on synthetic chemicals that drug companies 'push us' to take are not extending our lives. Consider the side effects of these drugs and how they damage other normal functions of the human body. We have to take other drugs to counteract the side effects of the first drugs. Not cool. So what are we to do? Let the "drug company monster" that finances a lot of government decisions dictate to us what synthetic chemicals we should and should not put in our bodies. Ever heard about the first amendment, "home of the free and land of the brave", Freedom of Information act, etc.

Well why don't we stand up, get educated and stop listening to lawyers and politicians. Let' give our human cells this "Freedom of Information". What am I talking about? I'm talking about starting to operate our human bodies the way they were meant to be operated. What, how? By providing our human body with the correct foundations or "operating software" to build all natural biochemicals that the human body itself is supposed to make. "Operating Software you mean like WINDOWS XP" Exactly, a huge computer network or even a personal computer cannot operate without software.

So what is this software that our body needs to function? These are many-many small protein sequences built so that they can contain coded information necessary to build the biochemicals that human cells need to operate. These can be call Informational Proteins or InfopeptidesTM. They have little or no calories and even a small amount can "restart the cells operating system" so it can function correctly. Just like the WINDOWS software for a personal computer. Now if our cells are given the tools to function correctly like they are supposed to, then they can harmonize together just like a symphony orgestra, or a huge computer network.

If we eat a well- balanced diet, maybe take a vitamin and minerals supplement, drink plenty of clean water, we will end up building a super immune system, maintain strong bones, we will feel better, don't feel tired all the time, and one may never hear the words "drug plan co-payment" again. The human body is designed to live 120 years. This is the birth-right of your cells in your body and that can be achieved without any side-effects when taking these small proteins. They are the same small human proteins or peptides that we were given by our mothers during breastfeeding. This treatment has no conflicts with any drugs currently used and can be used with traditional drug medicines. These peptides we received contained the operating software necessary to restart our 'baby cells' and to protect us

from all those nasty germs and bugs. Now as we get older, after all those hangovers, worry, stress, etc. our bodies get warn down over time and we naturally break down those Informational Proteins.

Just like the 6 million dollar man, "we do have the technology, we can rebuild him", by taking these Informational Proteins as a supplement. Just like taking a vitamin and mineral supplement. All you do is pump 2-3 sprays in your month (about 3ml), then allow these Informational Proteins to be absorbed into the mucous membrane in your mouth over a period of about 20-30 seconds. To have a strong functioning body, take the product once or twice a day. One doesn't need to take more than this to get the Information transferred to our cells, just like we don't need to install the computer software more than once or twice to operate our personal computers.

3. All about colostrums

3.1 What is colostrum?

It is the first milk that a mother produces immediately after giving birth. Colostrum is nature's perfect first food. It is the pre-milk substance produced from the mother's breasts of all mammals during the first 24-48 hours of lactation. Colostrum supplies immune and growth factors and a perfect combination of vitamins and minerals to insure the health, vitality and growth of the newborn.

It is estimated that colostrum triggers at least fifty processes in the new-born, including transferring all the immune factors and the entire memory from the mother's own immune system.

Medical Research has shown that the most important immune and growth factors for humans can be provided from bovine colostrum. It is biologically transferable to all mammals including man and is much higher in immune factors than human mother's colostrum. Laboratory analyses of both immune and growth factors from bovine colostrum indicate that they are identical to those found in human colostrum except for the fact that the levels of these factors are significantly higher in the bovine version.

Bovine colostrum is actually 40 times richer in immune factors than human colostrum. For example, human colostrum contains 2% of IgG (immuno-globulin G) while cow colostrum contains 86% of IgG, the most important of the immunoglobulins found in the body. Doctors also discovered that cows' colostrum contains special glycoproteins that are extremely effective at protecting the immune and growth factors in colostrum from destruction by adult human digestive enzymes.

3.2 Why do we need Colostrum as adults?

Experience has shown that nature knows best in many cases of healing. But as we age, we notice it takes us a little longer to fight off a cold or flu, we become more vulnerable to disease, our energy and enthusiasm lessen, our skin loses its elasticity, and we gain unwanted weight and lose muscle tone. This is because after maturity, we gradually lose the natural immune and growth factors in our body. Aging, illness and death occur with the loss of immune and growth factors in our bodies. Medical science has shown in hundreds of published reports worldwide that these can possibly be replaced in the human body with bovine colostrum.

The past 20 years has witnessed the publication of over 2000 research papers strongly supportive of both colostrum and its numerous components. As one prestigious research institute stated...
"Bovine colostrum offers tremendous possibilities for providing unparalleled support for the immune system that may be the deciding factor in the body's war against illness."

Colostrum has antioxidant properties, natural anti-inflammatory properties and is a source of many vitamins, minerals, enzymes and amino acids. Bovine colostrum rebuilds the immune system, helps the body ward off foreign invaders, accelerates healing of all body tissue, increases bone and lean muscle mass and replenishes an aging system. Supplementation of colostrum enhances the efficiency of amino acid and carbohydrate fuel uptake by the intestine. More nutrients are made available for muscle cells and other vital tissues and organs. One of the reasons for the energy boost seen in most healthy

individuals who use colostrum as a food supplement is this ability of colostrum to improve nutrient availability.

“Colostrum stimulates the lymphoid tissue providing benefits in aged or immune-deficient people”. Researchers reported that colostrum stimulates maturation of B Lymphocytes (type of white blood cell) and primes them for production of antibodies, enhances growth and differentiation of white blood cells. Similar activity in cow and human colostrum can also activate Macrophages” ...Dr. M. Julius, McGill University,Montreal: Science News.“Bovine colostrum contains high levels of growth factors that promote normal cell growth and DNA synthesis” ...Drs. Oda, Shinnichi, et. al.; Comparative Biochemical Physiology.

“Drs. suggest that an important role for growth factors is in promoting wound healing. Accelerated healing is possible for treatment with trauma and surgical wounds” ...Drs. Bhora, et. al.; Journal. Surg. Res.

Colostrum has been used for the treatment of rheumatoid arthritis. Sabin, an anti-polio vaccine was prepared from bovine colostrum. It has been reported to be very safe and effective for its use in repair of tissues as well as for enhancing immunity.

Table 3.1: Antibody activities of Bovine colostrum collected during first 10 h post parturition

Antigen	Reciprocal Antibody Titers Contained
Escherichia coli	640
Escherichia coli J5	640
Pseudomonas aeruginosa	640
Klebsiella pneumoniae	640
Proteus vulgaris	80
Serratia marcescens HY	1280
Salmonella typhimurium	160
Staphylococcus aureus	640
Staphylococcus epidermidis	160
Staphylococcus pyogenes	160
Staphylococcus faecalis	160
Staphylococcus viridans	640
Streptococcus B	80
Candida albicans	320
Cryptosporidia oocysts	100
Campylobacter jejuni (outer surface antigens)	1280
Helicobacter pylori	640
Yersinia enterocolitica YOP1 (outer membrane proteins)	1280
Shiga-like toxin I	1600
Shiga-like toxin II	3200
E. coli heat unstable enterotoxin (LT)	100
Rotavirus	32

Hundreds of small peptides present in colostrum serve numerous purposes. Studies have documented the presence of number of bioactive peptides but no mention has been made of the use of these peptides fragments, their specific sequences or information regarding their isolation. These peptides are extremely sensitive to temperature, pH, stress and shear factors which posse several difficulties in their isolation and preserving their biological activity and method of collection of colostrum so as to deliver it to the required patient by maintaining its full biological activity.

3.3 What is in Colostrum?

Proline- rich Polypeptides (PRPs)

These are short chain proteins with a high concentration of the amino acid Proline. This bioactive protein has been shown to support the regulation of the thymus, the gland responsible for the normal development of immunologic function in the body. They are generally characterized by PRP1, PRP2, PRP3, and to a lesser level PRP4 and PRP5.

Proline-Rich Polypeptide (PRP): a hormone that regulates the thymus gland (bodies central command for the immune system), stimulating an under active immune system or downregulating an overactive immune system as seen in autoimmune disease (MS, rheumatoid arthritis, lupus, scleroderma, chronic fatigue syndrome, allergies, etc.).

It has been demonstrated to improve or eliminate symptomatology of both allergies and autoimmune diseases. PRP inhibits the overproduction of lymphocytes and T-cells and reduces the major symptoms of allergies and autoimmune disease: pain, swelling and inflammation.

PRP, in bovine colostrum, has the same ability to regulate activity of the immune system as hormones of the Thymus gland. It activates an underactive immune system, helping it move into action against disease-causing organisms. PRP also suppresses an overactive immune system, such as is often seen in the autoimmune diseases.

PRP is highly anti-inflammatory and also appears to act on T-cell precursors to produce helper T-cells and suppresser T-cells" ...**Drs. Staroscik, et. al., Molecular Immunology.** ..."PRP turns white blood cells into functionally active T cells. Results were shown in treatment of autoimmune disorders and cancer. An important Immune modulator stimulates an underactive immune system and tones down an overactive one"...**Drs. Janusz & Lisowski; Archives of Immunology**.

This term has been used in several different ways, proline-rich polypeptide or proliferin-related protein also abbr. PLF-RP. This secreted protein is related to the placental protein Proliferin. PRP mRNA is expressed at high levels in the fetal part of the placenta. Peak levels are seen at day 12 of gestation and after that levels decrease gradually until term. **Yamaguchi et al** show that PRP secretion by murine placental cells is affected by cAMP levels but not by TGF-alpha, IL1-alpha, EGF , TNF-alpha and IL6 . PRP has been shown to be a potent placental antiangiogenic hormone that prevents neovascularization.

Tumour cells engineered to express high levels of PRP show markedly reduced growth rates as tumours in mice. The protein also acts on human endothelial cells **(Bengtson and Linzer**).Regular et al have shown that the use of adenovirus vectors expressing PRP 11can lead to complete tumour rejection and prolonged survival in a high proportion of animals bearing transplanted murine B16F10 melanoma cells.

In mice, PRP has many regulatory effects on the humoral and cellular immune response, inducing the maturation and differentiation of murinenthymocytes, the formation of helper cells from PNAhigh thymocytes, and of cytotoxic T-cells from PNAlow thymocytes. Colostrinine appears to act as an inducer of cytokines, causing the production of IFN-beta and TNF-alpha in human peripheral blood

leukocytes and in whole blood cultures and also in murine resident peritoneal cells at concentration of 1-100 micrograms/ml in a dose-related manner.

Glycoproteins (Protease inhibitors)
A digestive factor that has been shown to help immune and growth factors survive the passage through the highly acidic digestive system.

Growth Factors
Growth hormone (GH), Insulin-like growth factor-I and II (IGF-1 and IGF-II), Epithelial growth factor (EgF),Fibroblast growth factor (FgF), Platelet-derived growth factor (PDGF),Transforming growth factors A & B (TgA and B)

Immune Factors
Immunoglobulins (A,D,E,G &M),Gamma Globulin, Cytokines: Interleukins 1,6,10; Interferon, G;lymphokines, Leukocytes, Lymphokines, Lactoferin, Proline- Rich-Polypeptides (PRP), Protease Inhibitors, Trypsin Inhibitors, Antibodies, Glycoproteins, Lactobacillus Bifidus Acidophilus, Oligo Polysaccharides, Glycoconjugates, Orotic Acid, secretory IgA, IgA specific helper, B Lactoglobulin, Lactalbumin,Albumin, Prealbumin, Alpha 1-Antitripsin, Alpha 1Fetoprotein, Alpha 2-Macroglobulin, Alpha 2- AP Glycoprotein, C3 & C4 Orosomucoids, Lyozyme, Lactoperoxidase, Thiocyanate, Peroxidase, Xanthine Oxidase, Vitamins A, B12, E, Sulfur.

The body's growth factors are capable of increasing T-cell production, accelerating healing, balancing blood glucose, reducing insulin need, increasing growth and repair of vital tissues while metabolizing fat for fuel.

Medical studies have shown the vital growth factors IgF-1, TgF A & B and nucleotides from bovine colostrum to be identical to human in composition and helps provide the raw materials to repair vital DNA and RNA in the body's cells. Further, by stimulating DNA formation it has been shown that they can help stimulate normal cell and tissue growth, regeneration and accelerated repair of aged or injured muscle, skin collagen, bone, cartilage, nerve tissues, heart muscle and new blood vessels for collateral coronary circulation.

These growth factors facilitate the healing of tissues damaged by ulcers, trauma, burns, surgery or inflammatory disease. Transforming Growth Factors A & B (TGF A & B) in bovine
Colostrum were involved in normal cellular activities such as cell proliferation, and tissue repair.

Also reported it promoted the synthesis and repair of DNA - the master code of the cell." ...July 1992 New England Journal of Medicine. Colostrum provides a good source of IgF-1 as a complementary therapy for successful weight loss and building of lean muscle. IgF-1 is required by the body to metabolize fat for energy through the Krebs cycle but with aging, less IgF-1 is produced in the body.

It helps stimulate the body to burn fat for fuel instead of the body's own muscle tissue in times of diet and fasting. High age is associated with reduced levels of growth hormones:GH and IgF-1. Induction of GH and IgF- 1 increase body weight through muscle growth of aged subjects" ...Drs. Ullman, Sommerland & Skottner, Dept. of Pathology and Pharmacology, Univ. of Gothenburg, Sahlgren Hospital & HabiVitrum AB, Stockholm, Sweden. Human trials in 1990 reported that IgF-1 stimulates glucose utilization.

It can help balance blood sugars (non-insulin diabetics and hypoglycemia). Inadequate levels of IgF-1 are associated with an increased incidence of Type II diabetes and difficulty in losing weight despite a proper nutritional intake and adequate exercise. Additionally, IgF-1 and GH in colostrum normalizes LDL-cholesterol while increasing HDL-cholesterol concentrations (the good cholesterol).

Genetically engineered versions of IGF-1 and GH are now marketed but they are found in high concentrations in colostrum. Biotechnology companies are currently selling IgF-1 for as much as $800 per 50 cc vial. GH is also very expensive. Even less expensive products marketed as growth hormone releasers (designed to help the body to manufacture their own HGH) are markedly more expensive than Colostrum. None of these expensive products contain any of the vast array of immune factors.

Drug manufacturers have tried to copy (genetically engineer) and market several of the individual components of colostrum, most notably interferon, gamma globulin, growth hormone, IgF-1 and protease inhibitors. Some of the following colostrum components may very well be next on the list of major breakthroughs by the pharmaceutical/nutraceutical industry: Immunoglobulins (A, D, E, G and M) - the most abundant of the immune factors found in colostrum; IgG neutralizes toxins and microbes in the lymph and circulatory system; IgM destroys bacteria while IgE and IgD are highly antiviral.

Colostrum and breast milk (from cows and humans) stimulates the newborns immune system; as yet, unidentified proteins speed the maturation of cultured B Lymphocytes (type of white blood cell) and primes them for production of antibodies. Clinical research by Dr. David Tyrell, in England, in 1980, revealed that a high percentage of the antibodies and immunoglobulins present in colostrum are believed not to be absorbed but remain in the intestinal tract where they attack disease causing organisms before they penetrate the body and cause disease.

The remainder are believed to be absorbed and distributed to assist in our internal defence processes. It is this combination of action that is believed to make colostrum so unique and effective as an oral supplement. Studies with human volunteers found that the preservation of the biological activity of IgG (Immunoglobulin), in the digestive secretions of adults receiving bovine colostrum orally, indicates passive enteral (intestinal) immunization for the prevention and treatment of acute intestinal diseases... Dr. L.B. Khazenson; Microbial & Epidemial Immunobiology.

Antibodies
Colostrum has been shown to contain specific antibodies that may help our body in its fight against specific diseases such as pneumonia, RVS, dysentery, candida, flu, and numerous other illnesses

Lactoferrin
An antiviral, anti-bacterial, anti-inflammatory, iron-binding protein with therapeutic effects in cancer, HIV, Cytomegalovirus, herpes, Chronic fatigue Syndrome, Candida albicans and other infections. Lactoferrin helps deprive bacteria of the iron they require to reproduce and releases iron into the red blood cells 14 enhancing oxygenation of tissues. Lactoferrin modulates cytokine release and its receptors have been found on most immune cells including lymphocytes, monocytes, macrophages and platelets... “Concentration of Lactoferrin and Transferrin in bovine colostrum was found necessary to transport iron into blood. Highest concentrations of both substances were found in the first milking after birth” ...Drs. Sanchez, et al, Biological Chemistry

Lactalbumin
Research indicates tremendous possibilities that lactalbumins can be highly effective against numerous forms of cancer and viruses. Colostrum lactalbumin has been found to be able to cause the selective death (paposes) of cancer cells, leaving the surrounding non-cancerous tissues unaffected.

Lactobacillus Bifidus Acidophilus
Friendly flora which is necessary for the digestion of food and in the reduction of the growth of harmful bacterial in the digestive system. Shown to effectively combat candida albicans.

Vitamins and Minerals
Colostrum is not a supplement. It is the whole food for the newborn. Its combination of vitamins and minerals are naturally occurring and in perfect combination. Vitamins - A, B12 and E are found in small amounts while traces of all others are also present in colostrum.

Sulfur
A mineral with multiple uses in metabolism and as part of many structural body proteins.

Leukocytes
Stimulate the production of interferon, which slows viral reproduction, and penetration of cell walls.

Enzymes
Lactoperoxidase-thiocyanate, peroxidase and Xanthine Oxidase oxidize bacteria through their ability to release hydrogen peroxide.

Lysozyme
A hydrolyzing agent and immune system booster capable of destroying bacteria and viruses on contact.

Trypsin Inhibitors and Protease Inhibitors
Prevent the destruction of immune and growth factors in colostrum from being broken down in the GI tract; they also prevent H. pylori from attaching to the walls of the stomach and can have a beneficial role in the treatment of peptic ulcers.

Lymphokines
Hormone-like peptides produced by activated lymphocytes which mediate the immune response.

Oligo Polysaccharides and Glycoconjugates
Attract and bind to pathogens (Strep., E. Coli), Salmonella, Cryptosporidia, Giardia, Entamoeba, Shigella, Clostridium Difficile Toxins A & B and Cholera) preventing them from attaching or entering the mucous membranes.

Orotic Acid
Stops the formation of pyrimidine nucleotides and prevents hemolytic anemia.

Neurotransmitters

Are endogenous signaling molecules such as Leptin in RECEPTOL® that alter the behaviour of neurons or effector cells. Neurotransmitter is used here in its most general sense, including not only messengers

that act directly to regulate ion channels, but also those that act through second messenger systems, and those that act at a distance from their site of release. Included are neuromodulators, neuroregulators, neuromediators, and neurohumors, whether or not acting at synapses.

Cytokines

Are any of several regulatory proteins, such as the interleukins and lymphokines, those are released by cells of the immune system and act as intercellular mediators in the generation of an immune response. Cytokines are produced in the human body by the actions of the PRP proteins. Two main cytokines that are produced by PRP include IFN-alpha and IFN-beta.

The function and applications of just these two cytokines are described in the literature below. Cytokine's Interlukin 1 & 6, Interferon Y and Lymphokines are shown to stimulate the lymph glands and are thought to be highly effective antiviral immune substance. Interleukins that regulate the duration and intensity of the immune response are responsible for cell to cell communication, boost T-cell activity and the production of immunoglobulins. Interleukin-10 is strongly anti-inflammatory, especially in arthritic joints.

The benefits of cytokines in the treatment of cancer was first popularized by the 1985 Steven Rosenberg Book, Quiet Strides in the War on Cancer. Since that time, the same cytokines found in colostrum (Interleukins 1, 6, 10, Interferon Gamma, Leukocytes and Lymphokines, tumor necrosis factor) have been the single most researched protocols in scientific research for the cure for cancer. Interlukin 1 & 6, Interferon Y and Lymphokines: Shown to stimulate the lymph glands and are thought to be highly effective antiviral immune substance.

Interleukins that regulate the duration and intensity of the immune response are responsible for cell to cell communication, boost T-cell activity and the production of immunoglobulins. Interleukin-10 is strongly anti-inflammatory, especially in arthritic joints. The term cytokine, or immune cytokines, was used initially to separate a group of immunomodulatory proteins, called also immunotransmitters, from other Growth factors that modulate the proliferation and bioactivities of non-immune cells.
However, this terminology suggesting a clear-cut distinction cannot be maintained and may not be meaningful altogether. Some cytokines are produced by a rather limited number of different cell types while others are produced by almost the entire spectrum of known cell types.

Today the term cytokine is used as a generic name for a diverse group of soluble proteins and peptides which act as humoral regulators at nano- to picomolar concentrations and which, either under normal or pathological conditions, modulate the functional activities of individual cells and tissues.

These proteins also mediate interactions between cells directly and regulate processes taking place in the extracellular environment (for some mechanistic concepts underlying cytokine actions see also: endocrine, paracrine, juxtacrine, retrocrine). Many growth factors and cytokines act as cellular survival factors by preventing programmed cell death (Apoptosis).

IFN-alpha (tumor necrosis factor-alpha)

Is a glycoprotein 17,000MW including 157 amino acids. It has immunomodulating effects on various immune effector cells i.e. Arthritis, Chrones Disease, skin lesions, has applications in reducing side effects in bone marrow transplantations, chemotherapy, etc. ALTERNATIVE NAMES: Cachectin, CF (cytotoxic factor), CTX (cytotoxin), DIF (differentiation inducing factor), EP (endogenous

pyrogens), Hemorrhagic factor, Macrophage-derived cytotoxic factor, J774-derived cytotoxic factor, MCF (macrophage cytotoxic factor), MCT (macrophage cytotoxin), PCF (peritoneal cytotoxic factor), RCF (Released cytotoxic factor). See also: individual entries for further information. The new nomenclature isTNFSF2 [TNF ligand superfamily member 2], based on homology with other members of the TNF ligand superfamily of proteins.

Human TNF-alpha is active on murine cells with a slightly reduced specific activity. In general, TNF-alpha and TNF-beta display similar spectra of biological activities in in vitro systems, although TNF-beta is often less potent or displays apparent partial agonist activity.

3.4 BIOLOGICAL ACTIVITIES

TNF-alpha shows a wide spectrum of biological activities. It causes cytolysis and cytostasis of many tumor cell lines in vitro. Sensitive cells die within hours after exposure to picomolar concentrations of the factor and this involves, at least in part, mitochondria-derived second messenger molecules serving as common mediators of TNF cytotoxic and gene-regulatory signaling pathways. The factor induces hemorrhagic necrosis of transplanted tumors.

Within hours after injection TNF-alpha leads to the destruction of small blood vessels within malignant tumors. The factor also enhances phagocytosis and cytotoxicity in neutrophilic granulocytes and also modulates the expression of many other proteins, including fos, myc, IL1 and IL6. The 26 kDa form of TNF is found predominantly on monocytes and T-cells after cell activation. It is also biologically active and mediates cell destruction by direct cell-to-cell contacts. In vivo TNF-alpha in combination with IL1 is responsible for many alterations of the endothelium.

It inhibits anticoagulatory mechanisms and promotes thrombotic processes and therefore plays an important role in pathological processes such as venous thromboses, arteriosclerosis, vasculitis, and disseminated intravasal coagulation. The expression of membrane thrombomodulin is decreased by TNF-alpha. TNF alpha is a potent chemoattractant for neutrophils and also increases their adherence to the endothelium.

The chemotactic properties of fMLP (Formyl-Met-Leu-Phe) for neutrophils are enhanced by TNF-alpha. TNF-alpha induces the synthesis of a number of chemoattractant cytokines, including IP-10 , JE , KC , in a cell-type and tissue-specific manner. Although TNF inhibits the growth of endothelial cells in vitro it is a potent promoter of angiogenesis in vivo. The angiogenic activity of TNF is significantly inhibited by IFN-gamma.

TNF-alpha is a growth factor for normal human diploid fibroblasts. It promotes the synthesis of collagenase and prostaglandin E2 in fibroblasts. It may function also as an autocrine growth modulator for human chronic lymphocytic leukemia cells in vivo and has been described to be an autocrine growth modulator for neuroblastoma cells. The autocrine growth-promoting activity is inhibited by IL4.

In resting macrophages TNF induces the synthesis of IL1 and prostaglandin E2. It also stimulates phagocytosis and the synthesis of superoxide dismutase in macrophages. TNF activates osteoclasts and

thus induces bone resorption. TNF-alpha inhibits the synthesis of lipoprotein lipase and thus suppresses lipogenetic metabolism in adipocytes.

In leukocyte and lymphocyte progenitors TNF stimulates the expression of class I and II HLA and differentiation antigens, and the production of IL1 , colony stimulating factors, IFN-gamma, arachidonic acid metabolism. It also stimulates the biosynthesis of collagenases in endothelial cells and synovial cells. IL6 suppresses the synthesis of IL1 induced by bacterial endotoxins and TNF, and the synthesis of TNF induced by endotoxins. The neurotransmitter SP (substance P; Tachykinins) induces the synthesis of TNF and IL1 in macrophages.

IL1, like IL6, stimulates the synthesis of ACTH (corticotropin) in the pituitary. Glucocorticoids synthesized in response to ACTH in turn inhibit the synthesis of IL6 , IL1 and TNF in vivo, thus establishing a negative feedback loop between the immune system and neuroendocrine functions. TNF promotes the proliferation of astroglia and microglia and therefore may be involved in pathological processes such as astrogliosis and demyelinisation. TNF-alpha enhances the proliferation of T-cells induced by various stimuli in the absence of IL2. Some subpopulations of T-cells only respond to IL2 in the presence of TNF-alpha. In The presence of IL2 TNF-alpha promotes the proliferation and differentiation of B-cells.

The functional capacities of skin Langerhans cells are also influenced by TNFalpha. These cells are not capable of initiating primary immune responses such as contact sensibilisation. They are converted into immunostimulatory dendritic cells by GM-CSF and also IL1. These cells therefore are a reservoir for immunologically immature lymphoid dendritic cells. The enhanced ability of maturated Langerhans cells to process antigens is significantly reduced by TNFalpha.

Although TNF-alpha is required also for normal immune responses the overexpression has severe pathological consequences. TNF-alpha is the major mediator of cachexia observed in tumor patients (hence its name: Cachectin). TNF is also responsible for some of the severe effects during Gram-negative sepsis.

TNF mediates part of the cell mediated immunity against obligate and facultative bacteria and parasites. It confers protection against Listeria monocytogenes infections and anti-TNF antibodies weaken the ability of mice to cope with these infections.

3.5 CLINICAL USE AND SIGNIFICANCE

In contrast to chemotherapeutic drugs TNF specifically attacks malignant cells. Extensive preclinical studies have documented a direct cytostatic and cytotoxic effect of TNF-alpha against subcutaneous human xenografts and lymph node metastases in nude mice, as well as a variety of immunomodulatory effects on various immune effector cells, including neutrophils, macrophages, and T-cells. Single- and multiple-dose phase I studies have confirmed that TNF can be administered safely to patients with advanced malignancies in a dose range associated with anticancer effect without concomitant serious toxicities such as shock and cachexia.

However, clinical trials on the whole have unfortunately so far failed to demonstrate significant improvements in cancer treatment, with TNF resistance and TNF induced systemic toxicity being two major limitations for the use of TNF as an antineoplastic agent in most cases. The combined use of

TNF and cytotoxic or immune modulatory agents, particularly IFN-gamma and possibly IL2, may be of advantage in the treatment of some tumors. In some cases intratumoral application of TNF has been found to be of advantage in tumor control.

Some mutant forms of TNF-beta with selective activity on the p55 receptor have been described recently. It has been shown that activation of the p55 receptor is sufficient to trigger cytotoxic activity towards transformed cells. Some of these mutants have been described to retain their antitumor activity in nude mice carrying transplanted human tumors. It is hoped that such mutant forms may induce less systemic toxicity in man. TNF can be used to increase the aggressiveness of lymphokine-activated killer cells (LAK cells).

There are some indications that inhibitors of TNF may be of advantage. Since TNF is found in the synovial fluid of patients suffering from arthritis, these inhibitors may be helpful in ameliorating the disease and this has been shown to be the case in animal models of severe collagen induced arthritis. Inhibitors may ameliorate also the severe consequences of Systemic inflammatory response syndrome.

TNF-alpha appears to be an important autocrine modulator promoting the survival of hairy cell leukemia cells. It may be important, therefore, in the pathogenesis of this disease.
Studies with an experimental fibrosarcoma metastasis model have shown that TNF induces significant enhancement of the number of metastases in the lung. It has been suggested that low doses of endogenous TNF or administration of TNF during cytokine therapy may enhance the metastatic potential of circulating tumor cells. The transduction of murine tumor cells with a functional TNF-alpha gene has been shown to lead to the rejection of the genetically modified cells by syngeneic hosts (for cancer vaccines see also: Cytokine gene transfer).

TNF-alpha has been shown also to protect hematopoietic progenitors against irradiation and cytotoxic agents, suggesting that it may have some potential therapeutic applications in aplasia induced by chemotherapy or bone marrow transplantation.

One case of severe therapy-resistant Morbus Crohn has been treated with monoclonal antibodies directed against TNF-alpha. Treatment has been reported to have resulted in a complete remission lasting for three months.

IFN-beta can be used for topic treatment of condylomata acuminata. It is also suitable for the prophylactic use following surgical removal of large condylomas. Some studies suggest that IFN-beta tends to prevent disease activity in patients with multiple sclerosis. IFN-beta in combination with IFN-alpha has been used in the treatment of chronic active hepatitis B and appears to be most promising if the disease has not lasted longer than 5 years. The antiviral activity of IFN-beta is demonstrated also in the treatment of severe childhood viral encephalitis. A combination treatment in combination with acyclovir is more effective than treatment with acyclovir alone.

IFN-beta is a lipophilic molecule that should be particularly useful for local tumor therapy due to its specific pharmacokinetics. It is hardly removed from the tumor tissues after intralesional administration and hence also shows little systemic side effects. Head and neck squamous carcinomas, mammary and cervical carcinomas, and also malignant melanomas respond well to treatment with IFNbeta. IFN-beta also appears to be very promising for the adjuvant therapy of malignant melanomas with a high potential for metastasis. Response rates have been reported to be improved by combining IFN-beta with antineoplastic agents or other cytokines.

In many instances a combination of the various interferons has been found to cause synergistic effects. The antiviral/antiproliferative/antitumor properties of IFN-beta is potentiated by febrile temperatures.

References:

1. Bengtson NW and Linzer DI Inhibition of tumor growth by the antiangiogenic placental hormone, proliferin-related protein. Molecular Endocrinology 14(12): 1934-43 (2000);
2. Linzer DI and Nathans D A new member of the prolactin-growth hormone gene family expressed in mouse placenta EMBO Journal 4(6): 1419-23 (1985);
3. Regulier E et al Adenovirus-mediated delivery of antiangiogenic genes as an antitumor approach. Cancer Gene Therapy 8(1): 45-54 (2001);
4. Yamaguchi M et al Cyclic adenosine 3',5'-monophosphate stimulation of placental proliferin and proliferin-related protein secretion. Endocrinology 136(5): 2040-6 (1995);
5. Yamaguchi M et al Selective inhibition of mouse placental lactogen II secretion by tumour necrosis factor-alpha. Journal of Endocrinology 143(1): 95-105 (1994)
6. Blach-Olszewska Z and Janusz M Stimulatory effect of ovine colostrinine (a proline-rich polypeptide) on interferons and tumor necrosis factor production by murine resident peritoneal cells. Arch. Immunol. Ther. Exp. Warsz. 45(1): 43-47 (1997);
7. Inglot AD et al Colostrinine: a proline-rich polypeptide from ovine colostrum is a modest cytokine inducer in human leukocytes. Arch. Immunol. Ther. Exp. Warsz. 44(4): 215-224 (1996)
8. Drs. Bocci, Bremen, Corradeschi, Luzzi and Paulesu; Journal Biology
9. Boesman – Finkelstein M, Finkelstein R, Lancet, 1989, 2:1336
10. Dicchtemuller W, Lissner R, J. Clin. Bio. Chem., 1990, 28:19-23
11. Aggarwal BB and Vilcek J (eds) Tumor necrosis factor: structure, function, and mechanism of action. Marcel Dekker Inc. 1992
12. Beutler B and Cerami A Tumor necrosis, cachexia, shock and inflammation: a common mediator. Annual Review of Biochemistry 57: 505-18 (1988);
13. Beutler B and Cerami A The biology of cachectin/TNF - a primary mediator of the host response. Annual Review of Immunology 7: 625-55 (1989)
14. Bock G (edt) Tumor necrosis factor and related cytotoxins. John Wiley and Sons, Chichester, Ciba Foundation Symp. 131,
15. Bodmer M et al Preclinical review of anti-tumor necrosis factor monoclonal antibodies. Crit. Care Med. 21: S441-6 (1993)
16. Bonavida B and Granger G (eds) Tumor necrosis factor: structure, mechanisms of action, role in disease and therapy. Karger, Basel 1990
17. Gifford GE and Duckworth DH Introduction to TNF and related lymphokines. Biotherapy 3: 103-11 (1991);
18. Strieter RM et al Role of tumor necrosis factor-alpha in disease states and inflammation. Crit. Care Med. 21: S447-63 (1993)
19. Tracey KJ and Cerami A Tumor necrosis factor: an updated review of its biology. Crit. Care Med. 21: S415-22 (1993)

References for Biological activities

1. Bonavida B Immunomodulatory effect of tumor necrosis factor. Biotherapy 3: 127-33 (1991);
2. Brouckaert P et al Tumor necrosis factor, its receptors and the connection with interleukin 1 and interleukin 6. Immunobiology 187: 317-29 (1993);
3. Camussi G et al The molecular action of tumor necrosis factor-alpha. European Journal of Biochemistry 202: 3-14 (1991);
4. Cordingley FT et al Tumor necrosis factor as an autocrine tumor growth factor for chronic B cell malignancies. Lancet I: 969-71 (1988);
5. Frater-Schröder M et al Tumor necrosis factor type a, a potent inhibitor of endothelial cell growth in vitro is angiogenic in vivo. Proceedings of the National Academy of Science (USA) 84: 5277-81 (1987);
6. Goillot E et al Tumor necrosis factor as an autocrine growth factor for neuroblastoma. Cancer Research 52: 3194-200 (1992);
7. Grunfeld C and Feingold KR The metabolic effects of tumor necrosis factor and other cytokines. Biotherapy 3: 143-58 (1991);
8. Larrick JW and Wright SC Cytotoxic mechanism of tumor necrosis factor-alpha FASEB Journal 4: 3215-32 (1990);
9. Larrick JW and Kunchel SL The role of tumor necrosis factor and interleukin in the immuno-inflammatory response. Pharm. Research 5: 129-39 (1988);
10. Last-Barney K et al Synergistic and overlapping activities of tumor necrosis factor-alpha and IL1. Journal of Immunology 141: 527-30 (1988);
11. Merrill JE Effects of Interleukin 1 and tumor necrosis factor alpha on astrocytes, microglia, oligodendrocytes, and glial precursors in vitro. Dev. Neurosci. 13: 1307 (1991);
12. Nacy CA et al Tumor necrosis factor-alpha: Central regulatory cytokine in the induction of macrophage antimicrobial activities. Pathobiology 59: 182-4 (1991);
13. Perez C et al A nonsecretable cell surface mutant of tumor necrosis factor (TNF) kills by cell-to-cell contact. Cell 63: 251-8 (1990);
14. Sato N et al Actions of TNF and IFN-gamma on angiogenesis in vitro. Journal of Investigative Dermatology 95: 85S-9S (1990);22
15. Schiller JH et al Tumor necrosis factor, but not other hematopoietic growth factors, prolongs the survival of hairy cell leukemia cells. Leukocyte Research 16:337-46 (1992);
16. Schulze-Osthoff K et al Depletion of the mitochondrial electron transport abrogates the cytotoxic and gene-inductive effects of TNF EMBO Journal 12:3095-3104 (1993);
17. Tartaglia LA et al The two different receptors for tumor necrosis factor mediate distinct cellular responses. Proceedings of the National Academy of Science (USA) 88: 9292-6 (1991)
18. Trinchieri G Effects of TNF and lymphotoxin on the hematopoietic system. Immunology Ser. 56: 289-313 (1992)

4. Receptol® Oral spray:

WHAT IS RECEPTOL®?

What is Radha 108

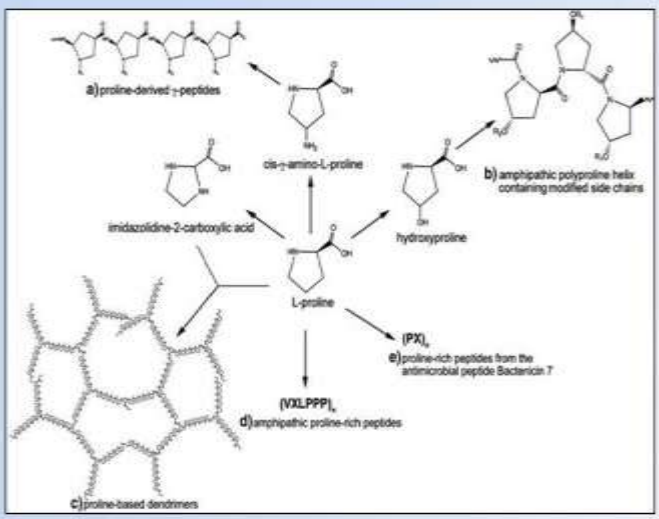
Radha 108 Active Pharmaceutical Ingredients (API)

- API in Radha 108 consist of Nano – Informational Peptides extracted from mammalian colostrum via Ultra Nano filtration Technology having sequence id 1-8 *(provided on next slide)* & Proline Rich Poly Peptides (PRPs)
- PRPs & Radha-108 are a class of nano informational peptide consisting of oligo-ribonucleotide attached to a peptide molecule that act as broad spectrum immuno-modulator & antiviral.
- Dosage - 3ml QDS via oral buccal spray (1 ml contains 0.03 grams of API Nanopeptides)

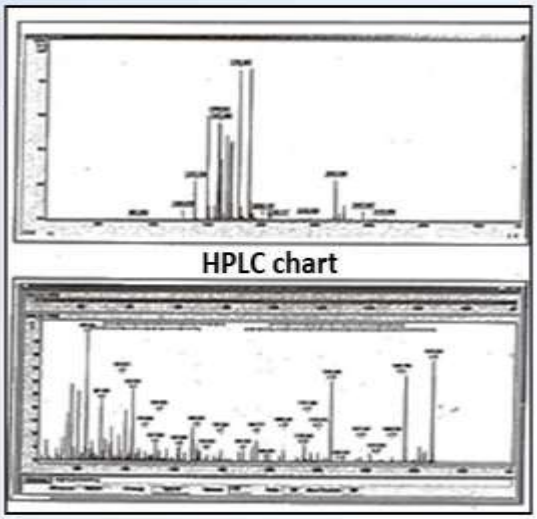
The 'Biggest' thing in Industry, just may be the 'Smallest' thing – Radha 108 Nanopeptides

Chemical structure of API

Proline Rich Polypeptides



Chemical Structure



HPLC chart

Mass Spectrum

RECEPTOL ® - Active pharmaceutical ingredients (API)

- Receptol® Oral Spray is an ultra-nano filtered extract of pure natural bovine colostrum consisting of low molecular weight API - Proline Rich Polypeptides (PRPs) & **Radha-108** peptide.
- PRPs & **Radha-108** are a class of nano informational peptide and consisting of oligo-ribonucleotide attached to a peptide molecule.
- Act as broad spectrum immuno-modulator & antiviral via increasing body's own immune system & prevents drug resistance with AR T/DOT therapy.
- Globally patented process using Nano-Biotechnology process.
- The 'Biggest thing right now in Industry, just may be the 'smallest thing - NANOPE PTIDES

Biochemistry of Proline Rich Polypeptides (PRPs)

Much of the efficacy of RECEPTOL® is attributable to effective delivery of the PRPs it contains: "PRPs, in bovine colostrum, have the same ability to regulate activity of the immune system as hormones of the thymus gland. It activates an under active immune system, helping it move into action against disease-causing organisms. PRPs also suppress an overactive immune system, such as is often seen in the autoimmune diseases. PRPs are highly anti-inflammatory and also appears to act on T-cell precursors to produce helper T-cells and suppresser T-cells" ...Drs. Staroscik, et. al., Molecular Immunology.

"PRPs turn white blood cells into functionally active T cells. Results were shown in treatment of auto-immune disorders and cancer. An important Immune modulator stimulates an under active immune system and tones down an overactive one"...Drs. Janusz & Lisowski; Archives of Immunology.

PRPs are cytokine modulators. Cytokines are a diverse group of soluble proteins and peptides which act as humoral regulators at nano- to picomolar concentrations and which, either under normal or pathological conditions, modulate the functional activities of individual cells and tissues. These proteins also mediate interactions between cells directly and regulate processes taking place in the extracellular environment. The cytokine's Interleukin 1 & 6, Interferon Y and Lymphokines have been shown to stimulate the lymph glands and are thought to be highly effective antiviral immune substances. Interleukins regulate the duration and intensity of the immune response and are responsible for cell to cell communication, boost T-cell activity and the production of immunoglobulins.

The cytokine IFN-beta is involved in the regulation of unspecific humoral immune responses and immune responses against viral infections. Extensive preclinical studies have documented a direct cytostatic and cytotoxic effect of the cytokine TNF-alpha against subcutaneous human xenografts and lymph node metastases in mice as well as a variety of immunomodulatory effects on various immune effector cells, including neutrophils, macrophages, and T-cells.

Following is a description of some of the biological activities of the IFN-beta and TNF-alpha cytokines:

IFN-beta (beta-interferon)
It is a glycoprotein with a 20,000MW including 166 amino acids. It is also known as Fibroblast interferon, Type-1 interferon, pH2-stable interferon, and R1-GI factor. IFN-beta is produced mainly by fibroblasts and some epithelial cell types.

IFN-beta is involved in the regulation of unspecific humoral immune responses and immune responses against viral infections. IFN-beta increases the expression of HLA class I antigens and blocks the expression of HLA class II antigens stimulated by IFN-gamma. IFN-beta stimulates the activity of NK-cells and hence also antibody-dependent cytotoxicity.

The activity of T suppressor cells elicited by several stimuli is stimulated also by IFN-beta. IFNbeta enhances the synthesis of the low affinity IgE receptor CD23. In activated monocytes, IFNbeta induces the synthesis of neopterin. It also enhances serum concentrations of Beta-2Microglobulin. IFN-beta selectively inhibits the expression of some mitochondrial genes. IFNbeta shows antiproliferative activity against a number of cell lines established from solid tumors.

IFN-beta can be used for topic treatment of condylomata acuminata. It is also suitable for the prophylactic use following surgical removal of large condylomas. Some studies suggest that IFN-beta tends to prevent disease activity in patients with multiple sclerosis.

IFN-beta in combination with IFN-alpha has been used in the treatment of chronic active hepatitis B and appears to be most promising if the disease has not lasted longer than 5 years. The antiviral activity of IFN-beta is demonstrated also in the treatment of severe childhood viral encephalitis.

IFN-beta is a lipophilic molecule that should be particularly useful for local tumor therapy due to its specific pharmacokinetics. It is hardly removed from the tumor tissues after intraregional administration and hence also shows little systemic side effects. Head and neck squamous carcinomas, mammary and cervical carcinomas, and also malignant melanomas respond well to treatment with IFN-beta. IFN-beta also appears to be very promising for the adjuvant therapy of malignant melanomas with a high potential for metastasis. Response rates have been reported to be improved by combining IFN-beta with antineoplastic agents or other cytokines.

In many instances a combination of the various interferons has been found to cause synergistic effects. The antiviral/anti proliferative/antitumor properties of IFN-beta are potentiated by febrile temperatures.

TNF-alpha (Tumor Necrosis Factor-Alpha)

TNF-alpha is a glycoprotein with a 17,000MW including 157 amino acids. It has immunomodulating effects on various immune effector cells. TNF-alpha shows a wide spectrum of biological activities. It causes cytolysis and cytostasis of many tumor cell lines in vitro. Sensitive cells die within hours after exposure to picomolar concentrations of the factor and this involves, at least in part, mitochondria-derived second messenger molecules serving as common mediators of TNF cytotoxic and gene-regulatory signaling pathways.

The factor induces hemorrhagic necrosis of transplanted tumors. Within hours after injection TNF-alpha leads to the destruction of small blood vessels within malignant tumors. The factor also enhances phagocytosis and cytotoxicity in neutrophilic granulocytes and also modulates the expression of many other proteins.

Radha108 (PRP) promotes differentiation of B cells, differentiation and maturation of macrophages and monocytes.Activates natural killer (NK) cells, cytotoxic cells of the innate immune system.Mitigates cell fusion and docks on HIV glycoprotein like Gp120, 180, 160 and 41 mimicking receptor on the cell

surface closing entry of viruses.Stimulates production of cytokines IL-1 to IL-11, TNF-α, INF–γ. Stimulates the maturation of immature thymocytes into either helper or suppressor T cells. Radha108 also functions as a molecular signaling device which works through receptors on target cell surfaces.

Radha108 series get absorbed in the blood through buccal mucosa and crosses BBB .Stimulates the maturation of immature thymocytes into either helper or suppressor T cells. Radha108 (PRP) promotes differentiation of B cells, differentiation and maturation of macrophages and monocytes. Activates natural killer (NK) cells, cytotoxic cells of the innate immune system.

Stimulates production of cytokines IL-1 to IL-11, TNF-α, INF–γ. Mitigates cell fusion and docks on HIV glycoprotein like Gp120, 180, 160 and 41 mimicking receptor on the cell surface closing spectrum entry of viruses. Radha108 also functions as a molecular signalling device which works through receptors on target cell surfaces.

Receptol®: 7 Key Profile Parameters qualifying as Drug

1. API/FP cGMP FACILITY:
   Receptol® Oral Spray contains low molecular weight PRPs including US Product Patented Radha108 sequences, manufactured from bovine colostrum through 10 &100kD ultra filters removing all microbes at class 100,000 GMP facility.

2. STRUCTURE & PHARMACODYNAMICS OF API:
   PRP like (Radha-108) are a class of nano-informational peptides consisting of oligoribonucleotides attached to a peptide molecule acting as broad spectrum anti-viral and new generation novel immuno-modulator building body's own immune system as per published data in peer reviewed international scientific and medical journals.

3. BATCH TO BATCH REPRODUCIBILITY:
   Batch to batch finished product analysis of Receptol indicates that product is reproducible using molecular weight exclusion ultra-filters.

4. PURITY:
   The ultra-filtration through 10 & 100kD ensures removal of high molecular weight proteins and isolates PRPs like (Radha108) sequences of 800-2000dalton molecular weight. The final filtration through 0.2µ biological filter ensures removal of biological impurities & provides pure product which is formulated as Receptol oral spray.

5. IMPURITIES:
   The colostrum whey, initial raw material, is subjected to pre-filtration through 0.45 & 0.3µ filters followed by molecular ultra-filters (10 & 100kD) & finally through 0.2µ biological filter to ensure removal of chemical & biological impurities.

6. PHARMACEUTICAL ACTION:
   As per pharmacodynamics Receptol acts as an anti-viral and novel immuno-modulator against HIV & associated recurrent infections.

7. SAFETY & EFFICACY:
   NIN study report validates Receptol safety with no acute & sub-acute toxicity through oral route & its efficacy human trials (Phase I, II & III) confirmed that Receptol is efficacious and safe for HIV as per NIN, Hyderabad study report.

RECEPTOL® Oral Spray is an invention by Biomix Network Ltd. Proline rich polypeptides (PRPs) including Radha108 sequences are isolated through nanotechnology filtration system from bovine colostrum and formulated in a liquid oral spray to easily administer through buccal mucosa for effective penetration and effect.

RECEPTOL® Global granted patents include two US Product patents for the treatment of AIDS and in SA, India and Singapore for treatment of 56 indications, including AIDS.

RECEPTOL® Oral Spray is an immuno-modulatory product. It acts through regulating thymus, which in turn, modulates the function of immunity cells of the body. It increases the level of Interleukins and Cytokines. It blocks receptors of the immunity cells and restricts the entry of virus. Hence, body's own immune system improves and avoids recurrent viral infections.

It was assessed as safe and effective for use in human population through precilinical and clinical trials of Phase I, Phase II and Phase III in India and abroad, in the treatment of HIV and other immune disorders.

RECEPTOL® Oral Spray is manufactured in a controlled environment by skilled and trained personnel. Final filtration of the product through biological 0.2µ filters ensures safe and microbial free product. Product Quality is ensured through stage-wise manufacturing and Quality Assurance controls.

GMP - World class facility

- **Radha108 Nano Peptide manufacturing plant is state of the art, nano biotech facility approved by TUV Nord Germany since 2012. GSK Consumer healthcare group UK & India due diligence done on product & the manufacturing facility**
- **Consistent raw material source : International quality from ISO/GMP certified, Amul, world's largest 75 year old dairy with stringent QC/QA checks & balances, right at the origin of Colostrum.**
- **Extraction of API, PRP (Radha108, Type of PRPs of molecular weight from 1800 to 500kDA) is done by Merck Millipore Molecular Exclusion Ultra filtration columns of 100 to 10 kDA at cGMP facility shown below.**

HOW RECEPTOL API RADHA 108 DISCOVERED?

In 1949 Dr. H. Sherwood Lawrence was working on the problem of tuberculosis which was a major health concern of the time. What he was trying to discover was if any component of the blood could convey a tubercular sensitivity from an exposed recovered donor to a naive recipient. Whole blood transfusions could be used but only between people of the same blood type. Lawrence first separated the blood's immune cells, the lymphocytes or white blood cells, from the whole blood. Then he broke open the lymphocytes and separated the contents of the cells into various size fractions. What he found was that a fraction of small molecules was able to transfer tuberculin sensitivity to a naive recipient. This is what Dr. Lawrence called Proline-Rich Polypeptides (PRPs) which are the active peptides in RECEPTOL®.

IS BLOOD ONLY SOURCE FOR RECEPTOL®?

Originally it was. It was not until the mid-1980 that two researchers came up with the idea that RECEPTOL® may also be present in colostrum. The confirmation of this discovery was awarded a patent in 1989. Cow (bovine) colostrum is now the best source of RECEPTOL with Global Patents awarded to Dr Pawan Saharan for his discovery of Radha 108 Sequence ID 1-8, which are a class of PRPs.

WHAT IS THE ACTUAL DEFINITION OF INFOPEPTIDES?

The term applies to a class of small proteins that circulate in the blood of mammals and accumulate or concentrate in their colostrum, in their milk, and in their blood sera. info peptides appear to convey information necessary for appropriate cellular function.

HOW DOES RECEPTOL® LIQUID COMPARE WITH WHOLE COLOSTRUM SUPPLEMENTS?

Comparing RECEPTOL® liquid to a whole colostrum supplement would be like comparing a precious metal to the ore from which it is derived.

CAN THESE INFOPEPTIDES BE AS EFFECTIVE FOR ADULTS AS FOR A NEWBORN INFANT?

Info peptides need to be processed to be effective for adults. The polypeptides from colostrum are not absorbable (or more properly, not "readable") by adults unless separated and broken up into smaller sizes. One company has successfully accomplished this goal, and refers to its product as RECEPTOL®.

CAN WE GET ENOUGH HUMAN COLOSTRUM TO PROVIDE ENOUGH OF THE INFOPEPTIDES?

Bovine colostrum - that is, from cows - provides infopeptides that are fully effective in humans. Good thing, otherwise their use would be prohibitively expensive.

BUT DOES THE BOVINE SOURCE OF INFOPEPTIDES REALLY WORK AS WELL AS HUMAN?

This answer is a very definite yes. Whereas bovine colostrum and lactoferrin are close but not precise matches of their human counterparts, infopeptides from cows may be even closer. Dr. Stephen Levine, a biochemist, says that these polypeptides are so important to animal survival that they may have come through the evolutionary process with virtually no change from species to species, much like vitamin C or melatonin. The clinical experience with bovine products is sufficiently compelling to imply that the bovine immune system is every bit as smart as the human one.

WHAT IS MEANT BY THE PHRASE, "NO CLEAR RELATIONSHIP BETWEEN DOSE AND BENEFIT"?

In the studies done to date, it has been noted that the administration of RECEPTOL® above the minimum levels necessary for response does not enhance or intensify the benefit.

WHAT DO THESE INFOPEPTIDES DO FOR ADULTS, ANYWAY?

Early studies suggest that Infopeptides are extremely effective as anti-inflammatory agents as well as immune enhancers.

5. What is Radha 108?

Summary of invention by Dr Pawan Saharan

One embodiment of the present invention provides for a formulation comprising peptides isolated from mammalian colostrum having sequences has recited in SEQ ID 1-8 here in after referred to as peptides of Radha 108 series, wherein the peptides function to modulate cell immunity and provide attachment inhibition for foreign antigen/viruses on cell surface receptors along with crossing BBB (blood brain barrier) and treating host of diseases in the brain.

In another embodiment, there is provided a method of treatment of immune related disorders including auto immune disorders the method comprising of administering a patient suffering from such disorders a therapeutically effective amount of formulation comprising the peptides of SEQ - ID 108.

In yet another embodiment there is provided a method of treatment of AIDS the method comprising administering a patient suffering from AIDS. A therapeutically effective amount of formulation comprising the peptides of SEQ-ID 1-8. The formulation can be provided in a liquid, powder gel and any other pharmaceutical delivery forms.

As per granted US patent claim,

A method for the treatment of Acquired Immune Deficiency Syndrome (AIDS) the method comprising administering to a patient suffering from such disorder a therapeutically effective amount of the do emulation comprising peptides of SEQ ID 1-8.

Radha108 is a class of Proline rich polypeptides (PRPs), natural, immunity enhancing component derived from bovine colostrum. Radha108 is essentially a class of peptides called Nano-peptides with molecular weight of 3500–10000 and Proline Rich Polypeptides (PRPs). Other naturally derived compounds present in the product include: Vitamin A, E, B1, B2, B5, B6, B12, B13, C, Folic acid, Sulphur and Beta-carotene.

Though some of the immunity enhancing properties of Proline-Rich Polypeptides were reported earlier the molecular mechanism and its synergistic action with low molecular weight Nanopetides were not known until Dr. Pawan Saharan, Chief Scientific Officer and Founder Director, Chaitanya Healthcare, India identified a series of Nanopeptides, also referred to as Nano- Information-Peptides from Bovine Colostrum.

Further study and confirmation of its therapeutic efficacy in a wide range of diseases/disorders was made possible only after these therapeutically effective ‘Nanopeptides’ were isolated in the pure and concentrated form by using sophisticated nanotechnology and filtration techniques by Biomix Network Ltd.

One of the exciting finding was the excellent efficacy and safety of these Nanopeptides (Radha108) in the treatment of HIV/AIDS. Clinical trials conducted in a major hospital in Mumbai have clearly shown that:

A. Receptol was immensely beneficial in:

a) Mitigating the symptoms like fever, diarrhoea, and nausea associated with AIDS
b) Increasing weight of the patients
c) Reducing the viral load
d) Increasing the CD4 count
e) Minimizing/eliminating associated opportunistic (viral, bacterial & fungal) infections

The observations on Receptol include:

B. The positive effects could be observed within a span of 12 weeks
C. No adverse effects observed even on prolonged usage
D. Can be used even as a monotherapy

5.1 Receptol® Mode of action

- The informational proteins (RADHA108) in RECEPTOL® are active in mitigating cell fusion
- RADHA108 series docks on glycoprotein receptor on the cell surface and thus closing doors and windows for viral entry into the immune cells.
- RADHA108 series get absorbed in the blood stream through buccal mucosa and crosses the Blood Brain Barrier (BBB).
- The levels of Interleukins & Cytokines are increased substantially.
- Supports regulation of thymus via producing functionally active NK cells
- RADHA108 augments cell-mediated immunity & activates T-cell precursors to produce helper & suppresser T-cells increasing CD4/8 counts.
- RADHA108 promotes growth & differentiation of stem cells in response to any disease

Fusion of HIV particles with human white blood cells, particularly CD4 cells occurs with the aid of glycoprotein epitopes on the viral wall. The informational proteins in Radha108 are active in mitigating cell fusion. Radha108 docks on HIV glycoprotein gp120 mimicking receptor on the cell surface and thus closing doors and windows for virus/antigen entry into the immune cells.

Receptol, a pure natural product having informational Nano peptides and Proline Rich Polypeptides (PRP), is an effective and safe in increasing weight, general well-being of patients, decrease in viral load and increase in CD4 cell count.

RECEPTOL® proteins directly support the Natural Killer (NK) cells of the immune system. Natural Killer Cells provide the front line of defence specially equipped to locate and kill disease cells. NK cells attach to the surfaces of foreign substances or their outer cell wall, and inject a chemical "grenade" (granule) into the interior. Once inside, the granules explode and destroy the foreign invader within five minutes. The NK cell itself remains intact and moves on to destroy the next immune attacker. Many doctors and clinics are finding RECEPTOL® helpful in promoting NK function and activity as well as supporting a healthy immune system for all patients. The immune system plays a great role in the quality of our health. Strong, active and optimally functioning NK cells promote optimal health and deter foreign substances from affecting immune function.

- Radha108 (PRP) promotes differentiation of B cells, differentiation and maturation of macrophages and monocytes.
- Activates natural killer (NK) cells, cytotoxic cells of the innate immune system
- Mitigates cell fusion and docks on HIV glycoprotein like Gp120, 180, 160 and 41 mimicking receptor on the cell surface closing entry of viruses.

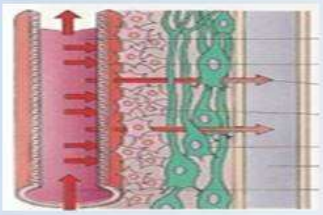
- Stimulates production of cytokines IL-1 to IL-11, TNF-α, INF–γ.
- Stimulates the maturation of immature thymocytes into either helper or suppressor T cells
- Radha108 also functions as a molecular signalling device which works through receptors on target cell surfaces.
- Radha108 series get absorbed in the blood through buccal mucosa and crosses BBB.
- Stimulates the maturation of immature thymocytes into either helper or suppressor T cells
- Radha108 (PRP) promotes differentiation of B cells, differentiation and maturation of macrophages and monocytes.
- Activates natural killer (NK) cells, cytotoxic cells of the innate immune system Stimulates production of cytokines IL-1 to IL-11, TNF-α, INF–γ.
- Mitigates cell fusion and docks on HIV glycoprotein like Gp120, 180, 160 and 41 mimicking receptor on the cell surface closing spectrum entry of viruses.
- Radha108 also functions as a molecular signalling device which works through receptors on target cell surfaces.

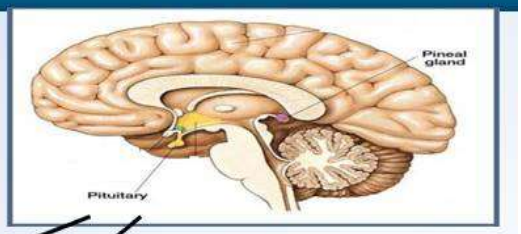
Radha 108 API containing SEQ ID1- 8 (With globally granted patent)

S. No.	Peptide Sequence	Spectral Count	Protein name
1	ELVPGVPRGTQL	27	DNA-binding protein inhibitor ID-3 **(MW – 1265.48)**
2	VAIIQHMIKKLR	24	Epstein-Barr virus induced gene 2 (Lymphocyte-specific G protein-coupled rec **(MW – 1449.86)**
3	LPQEVLNENLLRF	22	Alpha-S1-casein **(MW – 1584.84)**
4	RLNARMAELR	21	S-adenosylmethionine synthetase isoform type-1 **(MW – 1229.47)**
5	SSLQVLNMSHN	21	Toll-like receptor 4 **(MW – 1229.37)**
6	EYQELMNVK	20	Keratin, type II cytoskeletal 59 kDa, component IV (Fragment) **(MW – 1153.32)**
7	VDTLNDEINFLR	20	Keratin, type II cytoskeletal 7 **(MW – 1448.6)**
8	DGIVNENLAER	20	Ribonucleoside-diphosphate reductase small chain **(MW – 1229.31)**

Mode of action - Science behind Radha108 efficacy

PRPs get absorbed in the blood through buccal mucosa and crosses BBB →





- Radha108 (PRP) promotes differentiation of B cells, differentiation and maturation of macrophages and monocytes.
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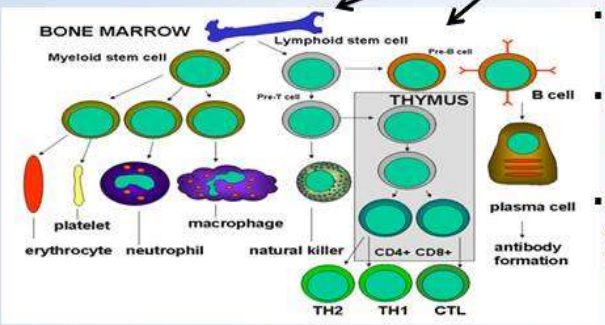


- Stimulates production of cytokines IL-1 to IL-11, TNF-α, INF–γ.
- Stimulates the maturation of immature thymocytes into either helper or suppressor T cells
- Radha108 also functions as a molecular signaling device which works through receptors on target cell surfaces

Radha 108 (PRP) competitive attachment inhibition against HIV virus on CD4 cell surface receptor (Scan EM below)

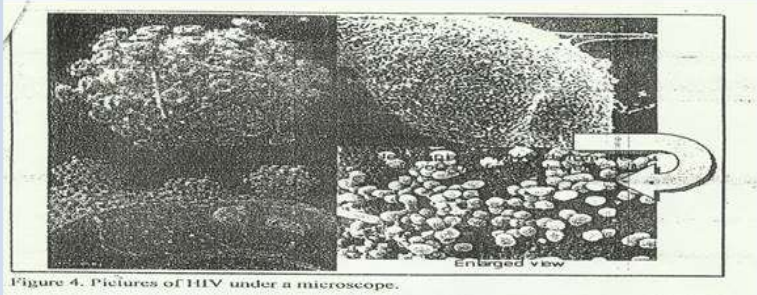


Figure 4. Pictures of HIV under a microscope.

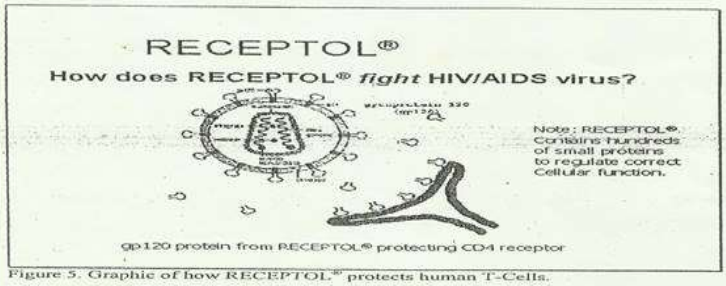
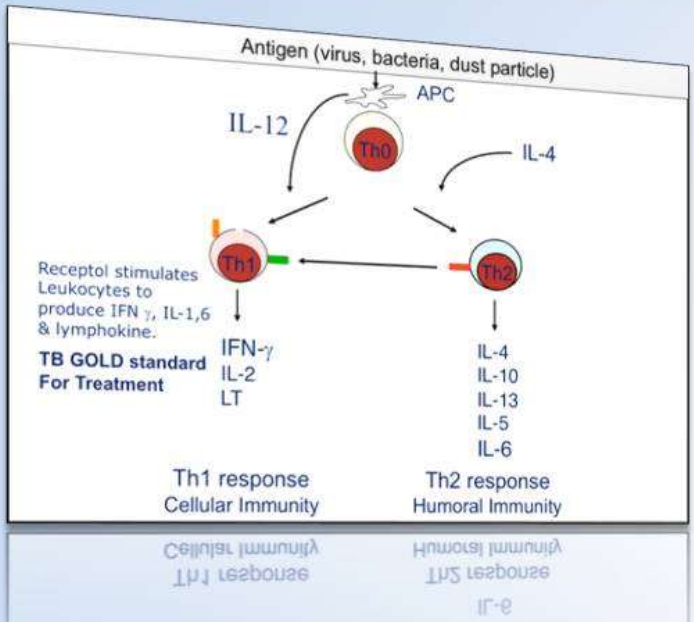


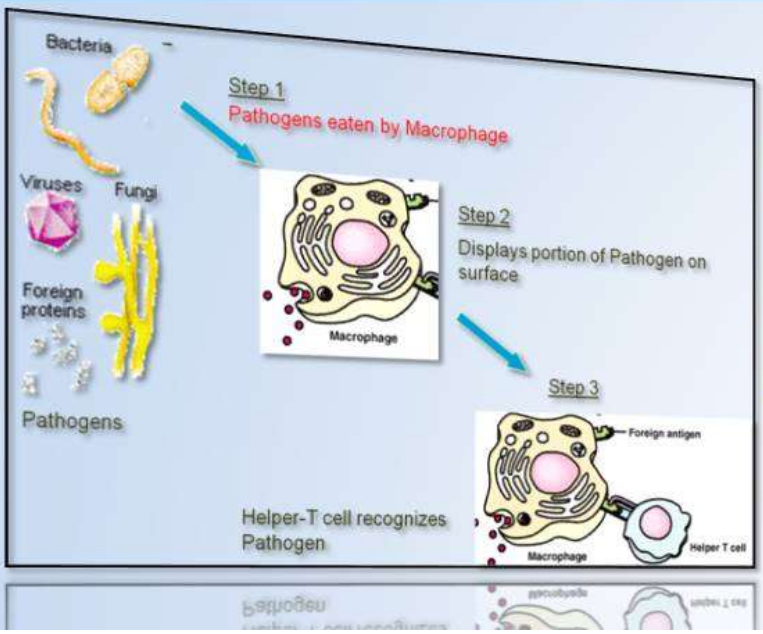
Figure 5. Graphic of how RECEPTOL® protects human T-Cells.

Mode of action



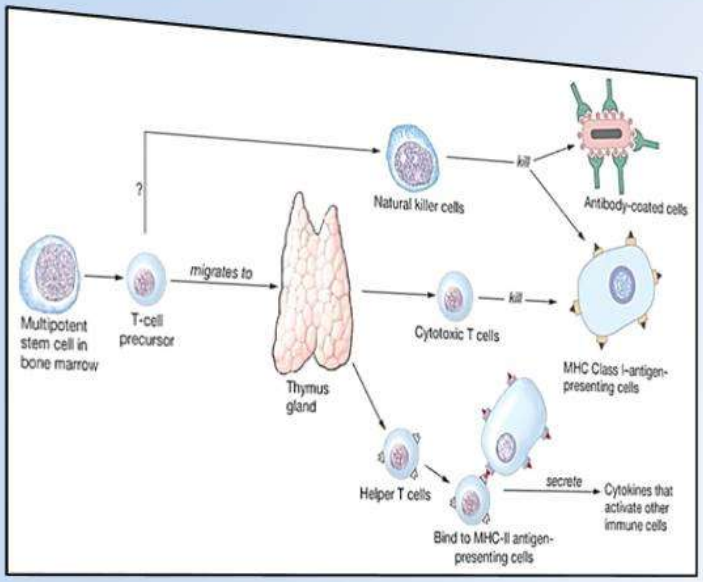
Mode of Action T Helper Cell Differentiation via Radha108 Nano Peptide®

Mode of action



Radha108 Nano Peptide plays role in differentiation and maturation of macrophages and monocytes

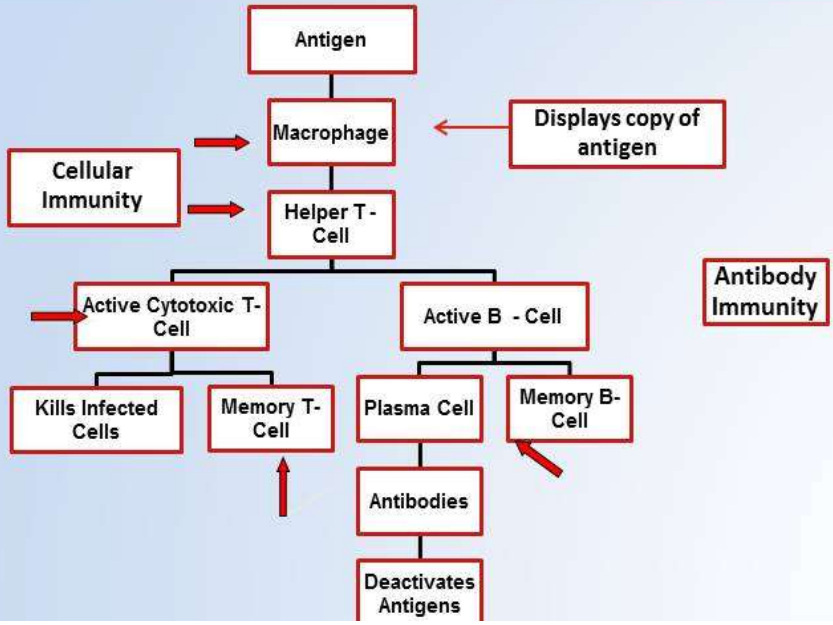
Mode of action



The activity of Natural Killer cells, cytotoxic cells of the innate immune system, was increased up to 5 times by Nanopeptides of Radha108 Nano Peptide

Mode of action

Radha 108 (⟶) Immune response summary



Radha 108 Nano Peptide Safety, Efficacy & Acceptability

On Immuno compromised HIV subjects used as the model

Preclinical Safety: as per **NIN** National Toxicology Panel

- **No Acute Toxicity & No Sub Chronic Toxicity**

Revalidation Phase III Indian Trials – Stand alone MONOTHERAPY with Radha 108 Nano Peptide sponsored by Government of India, MOH/NACO and Monitored by ICMR/NARI*

- **Study I (2006-07)** : By GoI on 50 Patients at LTMG Hospital Sion, Mumbai (Clinical trial registry No. : CTRI-2012-08-002931)
- **Study II (2007-08)** : By GoI on 51 Patients at LTMG Hospital, Sion, Mumbai (Clinical Trial registry No. : CTRI-2012-09-002959)

The study was fully controlled, conducted and sponsored , by Govt. of India, Biomix was facilitating the same & had no control on the specifications.

Safety and Efficacy Achieved by Global Trials:

Phase I : 12 cohort 30 days (completely safe) in Ohio, USA

Phase II : 30 cohort 90 days (highly effective with no side effects)in Nairobi – Kenya

Phase III : 60 cohort for 365 days (highly effective with no side effects) in Rwanda, Africa

6. Clinical Dossier for Pre-Clinical & Clinical Study

Toxicology study at National institute of nutrition (NIN)

Pre-Clinical safety study has been undertaken as per schedule Y of DCGI guideline under the supervision of Dr. B. Dinesh Kumar, Asst. Director (Study director) at **National Institute of Nutrition, Hyderabad**.

1.	Animal selected	SPRAGUE DAWLEY RATS (of both the sexes)
2.	Weight of the animal	150–180 gm (for both the studies)
3.	Age of the animal	4 to 6 weeks (for both the studies)
4.	Route of Administration	Oral

Acute toxicity

RESULTS
No pre-terminal deaths after administration of 50 times of intended therapeutic dose through oral route
All rats were found to be active and with normal body weight.
No Acute toxicity found.

** Indian council of medical research (ICMR)*

NIN Study : Sub acute data

No mortality was observed & product is safe

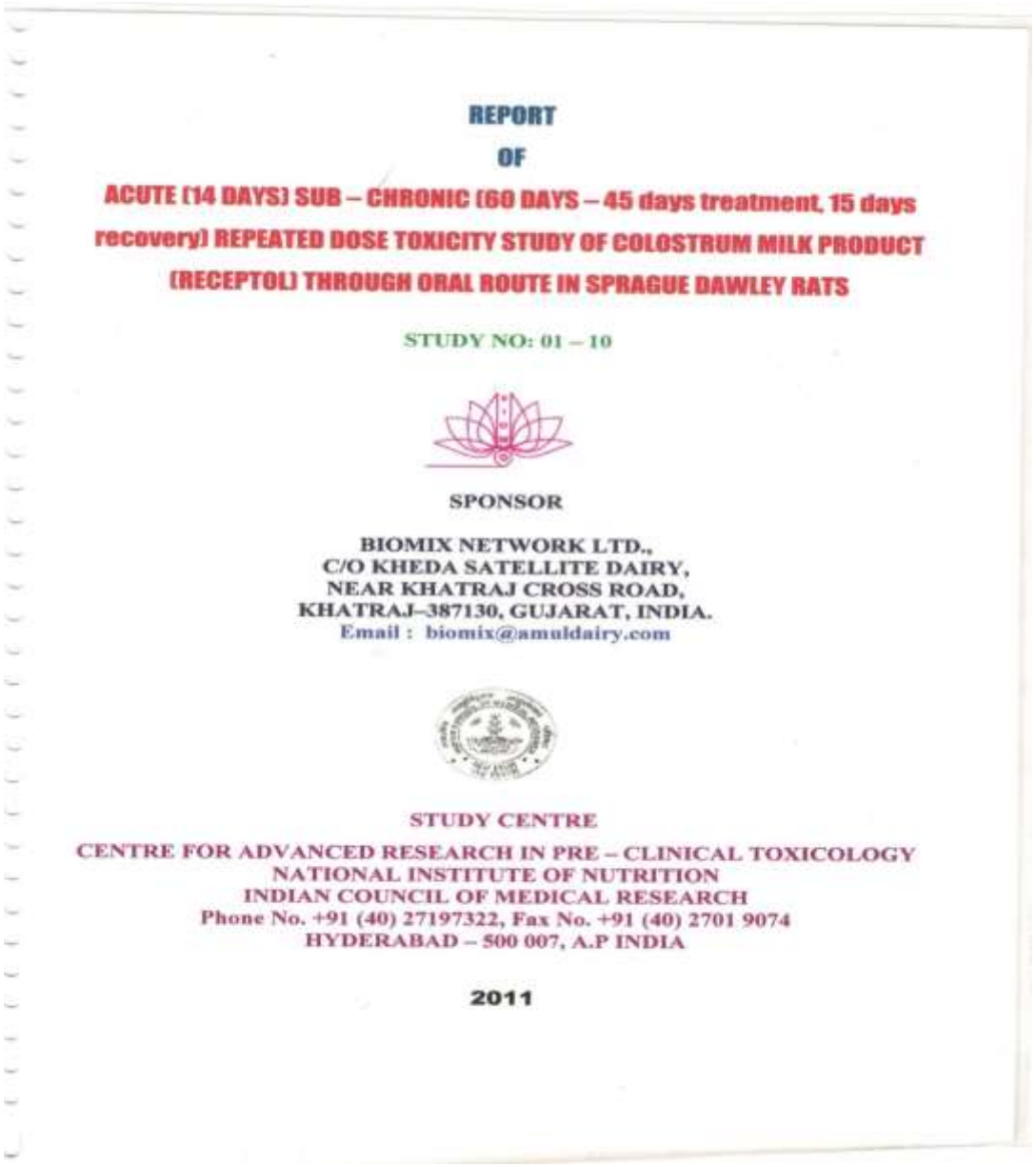
1.	No. of Rats used	48
2.	Categories	Vehicle control (VC), Therapeutic dose (TD – 1.08ml), Average dose (AD – 5XTD), (five times of TD) and High Dose (HD – 10XTD), (ten times of TD)
3.	Days of trial	45
4.	Period of Observation	Biweekly for live phase, cage side, physical and neurological parameters. At 48hrs and 15th day hematology and biochemistry profile along with gross necropsy and histopathology of major organs were evaluated.

RESULTS
No significant difference in physical activity and neurological activity between control and test groups throughout the study period.
No significant abnormalities in hematology , clinical chemistry profile in blood/serum samples.
No gross lesions were found in any organ and no significant difference in histopathology of various organs.
No sub chronic toxicity found

Clinical Dossier for Pre-Clinical & Clinical Study

6.1. ANIMAL TOXICOLOGY REPORT

(Study under Supervision of Dr. Dinesh Kumar Baradwaja at NIN – Hyderabad)



REPORT

OF

ACUTE (14 DAYS) SUB – CHRONIC (60 DAYS – 45 days treatment, 15 days recovery) REPEATED DOSE TOXICITY STUDY OF COLOSTRUM MILK PRODUCT (RECEPTOL) THROUGH ORAL ROUTE IN SPRAGUE DAWLEY RATS

STUDY NO: 01 – 10

SPONSOR

BIOMIX NETWORK LTD.,
C/O KHEDA SATELLITE DAIRY,
NEAR KHATRAJ CROSS ROAD,
KHATRAJ–387130, GUJARAT, INDIA.
Email : biomix@amuldairy.com

STUDY CENTRE

CENTRE FOR ADVANCED RESEARCH IN PRE – CLINICAL TOXICOLOGY
NATIONAL INSTITUTE OF NUTRITION
INDIAN COUNCIL OF MEDICAL RESEARCH
Phone No. +91 (40) 27197322, Fax No. +91 (40) 2701 9074
HYDERABAD – 500 007, A.P INDIA

2011

SIGNATURE PAGE

Study Director

Dr. B. Dinesh Kumar, PhD
National Institute of Nutrition

13/6/2011

Date

Director & Coordinator PCT

Dr. B. Sesikeran, MD
National Institute of Nutrition

डॉ. बी. सेसिकरण / Dr. B. SESIKERAN
DIRECTOR
National Institute of Nutrition
Indian Council of Medical Research
Jamai Osmania P.O. Hyderabad - 500 604

31/05/2011

Date

STUDY JUSTIFICATION

Colostrum milk is the most important food a newborn can receive from the mother soon after his/her birth. Colostrum is thick, yellowish milk that is secreted in the first few days after delivery. One factor that makes colostrum milk invaluable to the newborn is the high concentration of antibodies that are vital in warding off diseases in addition to calcium, protein, fat soluble vitamins, minerals etc.,

Biomix Pvt. Ltd has developed a new product "Receptol" which was derived from Bovine Lacteal source by Nano-biotechnology process, with an intention to promote it as an immuno–modulator for human consumption.

Since "Receptol" from Bovine Lacteal source has been processed by using cGMP practices, it is mandatory to generate Pre–clinical safety data as per the regulatory requirements.

1.1 QUALITY ASSURANCE STATEMENT

In accordance with the guidelines laid by the National Toxicology Panel, as management of the Institute as a Quality Assurance Officer (QAO) for the **STUDY No. 01– 10** entitled **"Pre –Clinical Toxicity Tests of Colostrum Milk Product (Receptol)"**, I visited different divisions involved in the study regularly and inspected the testing facilities and conduct of the investigations as per Standard Operating Procedures (SOPs) at different points of time during the study.

The Institutional Animal Ethics Committee approved the study [Append – VI (A & B)]. The report includes the methods and procedures followed by the investigators during the study. The results and inference were given on the basis of the raw data generated during the study.

During the audit of the records of various study investigations, I found that there were no deviations from the internal time schedule submitted by the investigators of the Pre–Clinical Toxicology Unit, FDTRC, and NIN to the best of my knowledge and belief, which would affect the integrity of the study except for minor amendment.

I visited the laboratories on the following dates, audited the records and the findings were reported to the management.

Audit Date	Phase audited	Date reported to Study Director	Date Reported to Management
18.12.2009	Receipt of test compound	18.12.2009	18.12.2009
21.04.2010	Receipt of test compound	21.04.2010	21.04.2010
29.04.2010	Receipt of test compound	29.04.2010	29.04.2010
03.12.2009	Protocol approval	03.12.2009	03.12.2009
ACUTE TOXICITY STUDY			
Rats – (Oral route – through gavage)			
Audit Date	**Phase audited**	**Date reported to Study Director**	**Date Reported to Management**
11.02.2010	Internal Time schedule approval	11.02.2010	11.02.2010
11.02.2010	As per S.O.P, Randomization and Caging of animals was done	11.02.2010	11.02.2010
15.02.2010, 02.03.2010	Inspection of experimental facility	15.02.2010, 02.03.2010	15.02.2010, 02.03.2010
02.03.2010	Euthanization of animals	02.03.2010	02.03.2010

SUB – CHRONIC TOXICITY STUDY			
Rats (Oral route – through gavage)			
Audit Date	**Phase audited**	**Date reported to Study Director**	**Date Reported to Management**
13.04.2010	Internal Time schedule approval	13.04.2010	13.04.2010
12.04.2010	Date of Receipt of animals	12.04.2010	12.04.2010
19.04.2010	Initial randomization	19.04.2010	19.04.2010
06.06.2010	Test compound exposure	06.06.2010	06.06.2010
03.05.2010, 31.05.2010 02.06.2010 & 04.06.2010	Random checking of Body weights and Inspection of experimental facility.	03.05.2010, 31.05.2010 02.06.2010 & 04.06.2010	03.05.2010, 31.05.2010 02.06.2010 & 04.06.2010
23.04.2010, 03.05.2010, 13.05.2010 & 04.06.2010	Monitoring of animals and Inspection of experimental facility	23.04.2010, 03.05.2010, 13.05.2010 & 04.06.2010	23.04.2010, 03.05.2010, 13.05.2010 & 04.06.2010
06.06.2010	Randomization (Mid term)	06.06.2010	06.06.2010
08.06.2010	Inspection of Euthanization Mid term	08.06.2010	08.06.2010
22.06.2010	Inspection of Euthanization final	22.06.2010	22.06.2010

Dr. D. Sreeramulu (QAO)

31st May 2011
Date

PRE – CLINICAL TOXICITY TESTS OF COLOSTRUM MILK PRODUCT (RECEPTOL)

1.3. ABSTRACT

1.3.1 Introduction: Biomix Pvt. Ltd., India has developed a colostrum milk product "Receptol" from Bovine Lacteal source by Nano-biotechnology process. Receptol as an oral liquid, with an intention to promote it as an Immuno–modulator.

The present (Acute & Sub Chronic) investigation is undertaken to evaluate pre–clinical safety profile of colostrum milk product "Receptol" administered by oral route in rats as per regulatory requirement.

1.3.2 Methodology: The present investigation involves **Acute and Sub–Chronic toxicity test** in Sprague Dawley rats.

In **acute toxicity** test, rats were exposed to fifty times of intended therapeutic dose (50XTD), to animals by oral route and observed for mortality.

Sub – Chronic toxicity test has been conducted in Sprague Dawley rats 48(24M+24F), which were equally divided into four groups viz., Vehicle control (VC), Therapeutic dose (TD), Average dose (AD), (five times of TD) and High Dose (HD), (ten times of TD) groups. The test compounds in varied doses were administered daily for 45 days orally through gavages. The rats were monitored bi–weekly for live phase, cage side, physical and neurological parameters. The hematology, and biochemistry, serum (IgG) profile along with gross necropsy and histopathology of major organs in animals were evaluated at 48hrs and 15th day post exposure to test compound.

1.3.3 Results: In acute toxicity test there were no pre–terminal deaths in rats observed after single administration of 50 times of intended therapeutic dose by oral route. All rats were found to be active with normal body weight.

In sub chronic toxicity test, There was no mortality in any group of animals exposed to vehicle control, test compound till end of the experiment There was no significant difference in body weight gains, live phase, physical activity and neurological activity between control and test groups throughout the study period. There were no significant abnormalities in hematology, IgG and clinical chemistry profile in blood / serum samples collected after 48hrs and 15th day of last exposure to test compound. At necropsy, no gross lesions were found in any organ collected from all group of animals. No significant

difference was observed in the histopathology of various organs between control and test groups.

1.3.4 Conclusion: In Acute toxicity test there was no mortality on single exposure of fifty times of the intended therapeutic dose in rats.

There was no abnormality in hematology, serum IgG and clinical chemistry profile in all groups. No abnormal changes in gross necropsy and histopathology of major organs were recorded which could be attributed to test compound administration.

4.0 STUDY PERSONNEL

4.1 PCT Coordinator

Dr. B. Sesikeran
Director, NIN

4.2 Scientific personnel

4.2.1	Dr. B. Dinesh Kumar, Ph.D. Scientist 'E'	Study Director
4.2.2	Dr. N.V. Giridharan, Ph.D Scientist 'F'	Study Investigator
4.2.3	Dr. P. Uday Kumar, M.D. Scientist 'E'	Pathologist
4.2.4	Dr. R. Hemalatha, M.D. Scientist 'E'	Study Investigator
4.2.5	Dr. SSYH Qadri, M.V.Sc. Scientist 'D'	Pathologist
4.2.6	Dr.N.Hari Shankar, Ph.D. Scientist 'C'	Study Investigator
4.2.7	Dr. M.V. Surekha (M.D) Scientist 'B'	Pathologist

4.3 Archives In–charge

Dr. SSYH Qadri, M.V.Sc.
Scientist 'D'

Technical Staff

Pre–Clinical Toxicology:

1. Mrs. D. Rama devi, M. Sc
2. Mr. V. Venu babu, M. Sc
3. Mr. S. Sharath babu, M. Sc
4. Mrs. G. Rama devi, M.Sc
5. Mr. R. Ramesh Kumar, M.Sc
6. Ms. K. Kusuma Kumari, M.Sc

Biochemistry:

1. Mrs. B. R. Annapurna, B.Sc. AIC (Chemistry)
2. Mrs. S. A. Brinda, B.Sc. AIC (Chemistry)

Histopathology:

1. Mrs. K. Sharadha, M.Sc
2. Mr. Armugham, S.S.C
3. Mr. M. Srinivas, M.Sc, P.G.D.M.L.T
4. Mrs. G. Sailaja, B.Sc
5. Mr. Khaja Ather Hussain, B.Sc (MLT)

6.1.1. RECEPTOL® – NIN Preclinical Study

Pre Clinical safety study of RECEPTOL has been undertaken as per schedule Y of DCGI guideline at **National Institute of Nutrition, Hyderabad**. The study involved Acute and Sub-Chronic test in Sprague Dawley rats.

STUDY DIRECTOR - Dr. B. Dinesh Kumar, Asst. Director

PCT COORDINATOR – Dr. B. Sesikeran, Director, NIN

Animal selected - SPRAGUE DAWLEY RATS of both the sexes

Weight of the animal - 150–180 gm (for both the studies).

Age of the animal – 4 to 6 weeks (for both the studies).

Route of Administration – Oral

Rationale for Selection of Species:

Rat's physiology is very similar to human being. A one-day old rat is physiologically similar to a six-month old baby (Fundamentals of Experimental Pharmacology, Dr.M.N.Ghosh).

1. Acute Toxicity :

In **Acute toxicity test**, rats were exposed to fifty times of intended therapeutic dose (50XTD), to animals by route and observed for mortality.

• **Acute toxicity** – rats exposed to 50 times (50XD) the intended Therapeutic dose for 14 days.

✓ No pre-terminal deaths after administration of 50 times of intended therapeutic dose through oral route.
✓ All rats were found to be active and with normal body weight.
✓ No Acute toxicity found.

NIN Study : Mortality of rat in acute toxicity

No mortality was observed & product is safe even after administration of 50 times dosage of product

S. No.	Unique Id.	Sex	Pre-terminal deaths	Activity*
1.	11541001	M	X	1
2.	11541002	M	X	1
3.	11541003	M	X	1
4.	11541004	M	X	1
5.	11541005	M	X	1
6.	11541006	M	X	1
7.	11542001	F	X	1
8.	11542002	F	X	1
9.	11542003	F	X	1
10.	11542004	F	X	1
11.	11542005	F	X	1
12.	11542006	F	X	1

* 1-Active, 2-Inactive, 3-Dead X-No death, Y-Dead, M-Male, F-Female

2. Sub- Chronic Toxicity:

In **Sub- Chronic toxicity test**, conducted on Sprague Dawley rats 48(24M+24F), which were equally divided into four groups viz., Vehicle control (VC), Therapeutic dose (TD), Average dose (AD) (five times of TD) and High Dose (10 times of TD) groups. The test compounds in varied doses were administered daily for 45 days orally through gavages. The rats were monitored biweekly for live phase, cage side, physical and neurological parameters. The hematology, and biochemistry, serum (IgG) profile along with gross necropsy and histopathology of major organs in animals were evaluated at 48hrs and 15th day post exposure to test compound.

Period of Observation – Biweekly for live phase, cage side, physical and neurological parameters. At 48hrs and 15th day hematology and biochemistry profile along with gross necropsy and histopathology of major organs were evaluated.

✓ No significant difference in physical activity and neurological activity between control and test groups throughout the study period.

✓ No significant abnormalities in hematology, clinical chemistry profile in blood/serum samples.

✓ No gross lesions were found in any organ and no significant difference in histopathology of various organs.

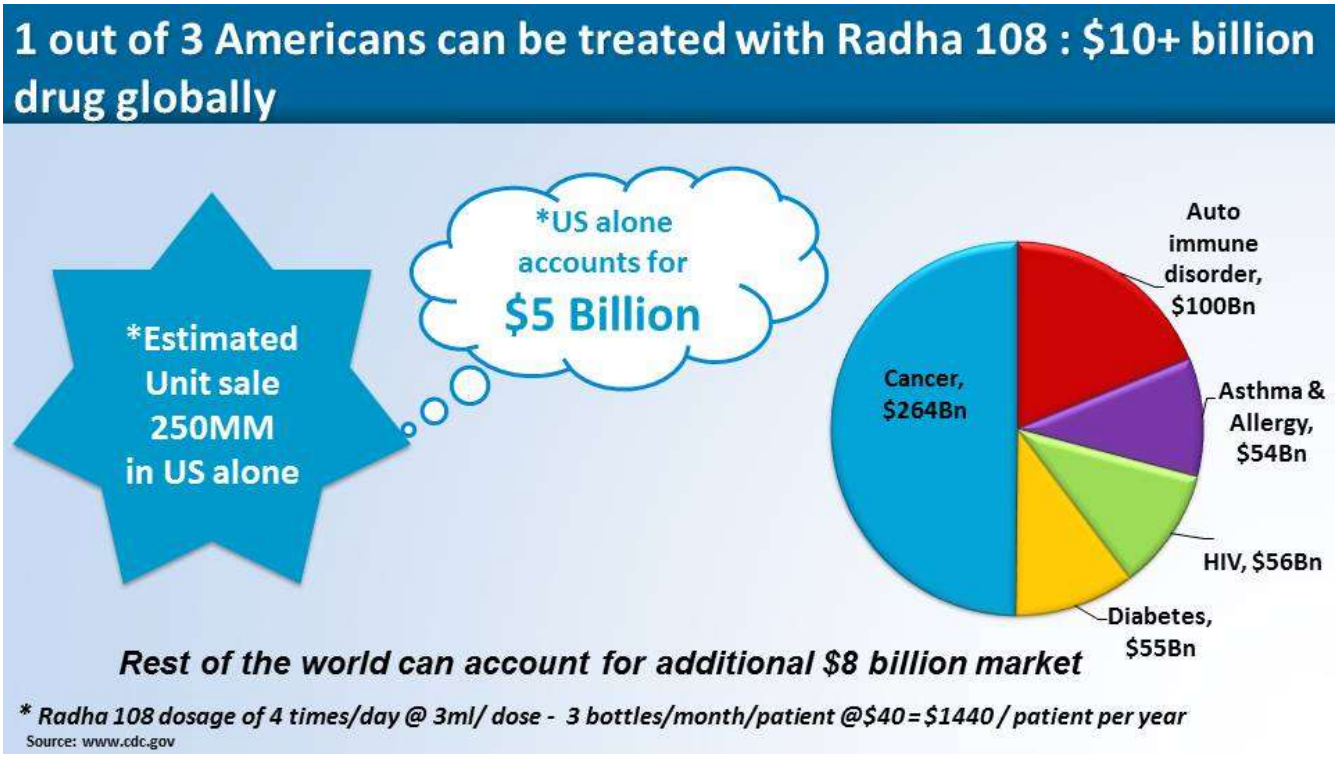
No sub chronic toxicity found.

NIN Study - Sub acute data : No sub chronic toxicity found

VC - Vehicle control TD -Therapeutic dose Average dose HD - High dose

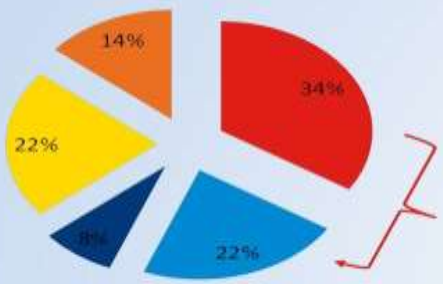
SR. NO.	DAYS OF OBSERVATION	VC		TD		AD (5XTD)		HD (10XTD)	
		M	F	M	F	M	F	M	F
1.	1	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
2.	2	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
3.	3	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
4.	4	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
5.	5	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
6.	6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
7.	7	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
8.	8	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
9	9	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
10.	10	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
11.	11	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
12.	12	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
13.	13	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
14	14	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
15.	15	0/6	0/6	0/6	0/6	0/6	0/6	0/6	1/5
16.	16	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/5
17.	17	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/5
18.	18	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/5
19.	19	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/5
20.	20	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/5
21.	21	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/5
22.	22	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/5
23.	23	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/5
24.	24	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/5
25.	25	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/5
26.	26	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/5
27.	27	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/5
28.	28	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/5
29.	29	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/5

6.2. RECEPTOL INTERNATIONAL CLINICAL STUDY



Radha 108 in NCDs : Rheumetoid Arthritis Study

Reporting Patients* : 63
Duration of Treatment : 6 months

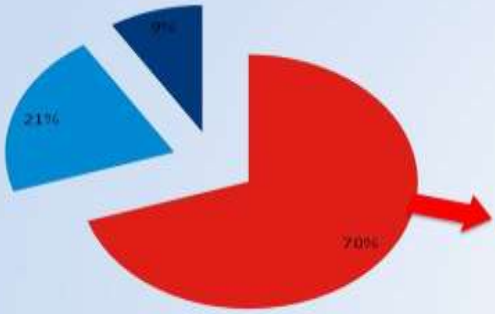


- Complete resolution of symptoms
- Significant benefits
- Some benefit
- Did not exhibit the same benefit
- Inconclusive

56% of patients found the product to be highly effective!

Radha 108 in NCDs : Fatigue Syndrome Study

Reporting Patients* : 108
Duration of Treatment : 6 months

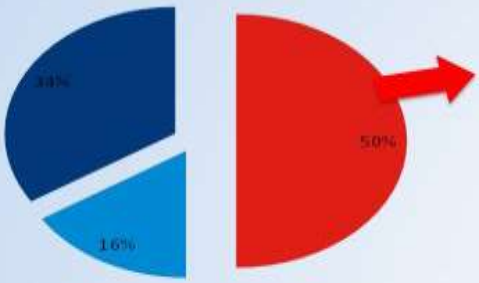


- Significant benefit
- Some Benefit
- Did not exibit the same benefit

70% of patients received significant benefits!

Radha 108 in NCDs : Endometriosis Study

Reporting Patients* : 106
Duration of Treatment : 6 months



Similarly for Endometriosis, **complete resolution** in most cases!

- Complete resolution of symptoms
- Some benefit
- Inconclusive

Asthma

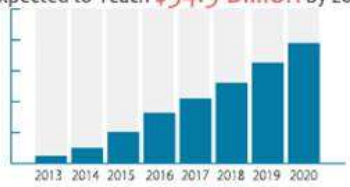
25MM alone in US

Asthma may affect as many as 334 million people.*

EXPECTED TO GROW BY MORE THAN 100MM BY 2025!

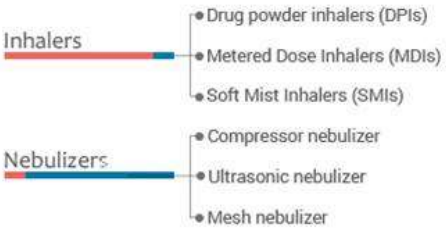
Global COPD and Asthma Devices Market

Global COPD and Asthma DevicesMarket is Expected to reach $34.3 Billion by 2020



Growing at a CAGR of 4.5 % (2014-2020)

Global COPD and Asthma Devices Market By Product Type



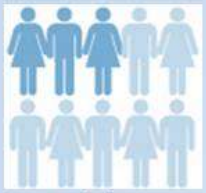
Global COPD and Asthma Devices Market By Geography

Asia-Pacific, North America,LAMEA

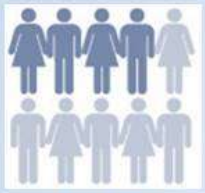
Europe Fastest Growing Segment at a CAGR 4.8% (2014-2020)

*Source: www.GlobalaAthmaReport.gov

Allergies & Asthma



Adults



Children

30% adults and **40%** of children worldwide are affected by allergies!

$25Billion is spent on Asthma drugs annually which has gone up by 50% since 2009!

*Source: www.GlobalaAthmaReport.gov

HIV is a major threat affecting ~40m people worldwide and the sales for HIV drugs are expected to increase steadily

1.2M only in US

36.9 MILLION

people worldwide are currently living with HIV/AIDS.

Source: www.aids.gov

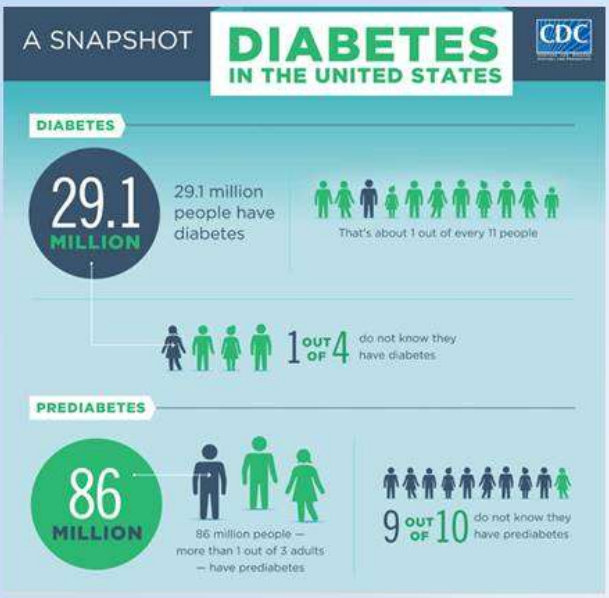
The vast majority of people living with HIV are in low- to middle-income countries, particularly in Sub-Saharan Africa.

2.6 MILLION CHILDREN

worldwide are living with HIV. Most of these children were infected by their HIV-positive mothers during pregnancy, childbirth or breastfeeding.

Forecast of HIV drug sales ($Billion)

Diabetes



246M worldwide are affected by Diabetes!

$55Billion is spent on annually which has gone up by 55% since 2012!

*Source: www.cdc.gov

RECEPTOL INTERNATIONAL CLINICAL STUDY
Clinical Study Report

Protocol No: BNL-001 (Phase – I Study)

6.2.1 A Single-Center, Interventional / Prospective Phase IStudy To Evaluate The Safety Of RECEPTOL® Oral Spray Used As A Stand-Alone Mono Therapy in HIV / AIDS Patients with multiple symptoms

- **TITLE PAGE**

STUDY TITLE	A Single-Center, Open Label, Phase I Study To Evaluate The Safety Of RECEPTOL® Oral Spray on Patients Infected with HIV
PROTOCOL CODE	BNL-001
NAME OF INVESTIGATIONAL PRODUCT TESTED	RECEPTOL® Oral Spray
DEVELOPMENT PHASE OF STUDY	Phase I
INDICATION STUDIED	HIV/AIDS
TRIAL DESIGN	A single-Center, open label, 30-days study in 12 subjects to determine safety of RECEPTOL® on patients with HIV / AIDS.
STUDY INITIATION DATE	February, 1996
STUDY COMPLETION DATE	April, 1996
SPONSOR	Biomix Network Limited Millennium Business Park, Unit No.303, Building 6, Sector-3, MIDC, Mahape, Navi Mumbai, Maharashtra – 400 709 INDIA Contact No: +91-9323000880
PARTICIPATING INSTITUTE	**PRINCIPAL INVESTIGATOR:** **Dr. Steve Mathews** **STUDY CENTER:** Infectious Disease Clinic, Dayton, Ohio,USA

❖ CONCLUSION:

The trial was conducted in 12 HIV patients with 30 days treatment and moderate control of product use. Results obtained from this trial were 10 out of 12 patients gained weight during the thirty-day trial period, of the 10 that gained weight, 7 (70%) gained an average of 6 lbs, 5 patients gained 6 lbs in one month, while 2 others gained 5.5 and 6.6 lbs respectively, the highest weight gain of 12 lbs was recorded for a patient who had been HIV positive since 1986 (10 years). 8 out of 10 patients had various levels of diarrhoea (mild, moderate or severe) at the beginning of the trial period. Out of the 8, 5 patients (62%) went from varying levels of diarrhoea severity to No diarrhoea symptoms. The 1 patient without weight gain experienced total elimination of severe chronic diarrhoea and a return to solid stool formation. 8 out of 12 patients had various levels of nausea at the beginning of the trial period. Of the 8, 5 patients (62%) went from varying levels of severity of nausea symptoms to No nausea. Of the remaining 3 patients, with some degree of nausea, 2 experienced a reduction in the severity of their symptoms. 9 out of 10 patients, who reported fatigue symptoms at the beginning of the trial, experienced an increase in their level of energy. 4 out of 12 had either a mild to moderate cough at the beginning of the trial. 2 of the 4 reported No cough at the end of the trial period. Of the remaining 2 patients, 1 reported a reduction in the severity of his cough. All 12 patients experienced an improvement in their overall symptoms assessment score. The average reduction approached 2/3 (63%).

Since 1996, several improvements in the process engineering were made to increase the efficacy of RECEPTOL®.

Clinical Study Report

Protocol No: BNL- 002 (Phase- II Study)

6.2.2 An Interventional / Prospective Phase II Accelerated Study To Determine The Efficacy & Safety Of RECEPTOL® Liquid Spray Used As A Stand-Alone Mono Therapy in HIV / AIDS Patients with multiple symptoms

- **TITLE PAGE**

STUDY TITLE	An Interventional / Prospective Phase II Accelerated Study To Determine The Efficacy & Safety Of RECEPTOL® Oral Spray Used as A Stand-Alone Mono Therapy in HIV / AIDS Patients with multiple symptoms
PROTOCOL CODE	BNL-002
NAME OF INVESTIGATIONAL PRODUCT TESTED	RECEPTOL® Oral Spray
DEVELOPMENT PHASE OF STUDY	Phase II
INDICATION STUDIED	HIV/AIDS
TRIAL DESIGN	A single arm, open label, 90 days study in 30 subjects to determine effect of treatment with RECEPTOL® on HIV Viral Load HIV / AIDS related clinical symptoms
STUDY INITIATION DATE	March, 2000
STUDY COMPLETION DATE	August, 2000
SPONSOR	Biomix Network Limited Millennium Business Park, Unit No.303, Building 6, Sector-3, M. I. D. C., Mahape, Navi Mumbai, Maharashtra - 400 709 INDIA. Contact: +91-9323000880
PARTICIPATING INSTITUTES	**PRINCIPAL INVESTIGATOR: Dr. Steve Mathews** **INVESTIGATOR: Drs.Peter Kiama,MD and Dr.Joshua Kimani, MD** **STUDY CENTER:** University of Nairobi, Kenya

❖ CONCLUSION:

This trial was conducted in 30 HIV patients with 90 days treatment and moderate control of product use. The objectives of this study were to demonstrate, under clinical conditions, the Efficacy and Safety of Info protein supplementation in patients known to have advanced disease (HIV/AIDS), compromised immune resources and limited access to conventional treatment. Positive clinical results were observed in the Nairobi patients. The results demonstrated that the product appeared to be free of side effects and generally well tolerated by the participants. Some signs, consistent with detoxification, were noted but resolved when the patients increased their water consumption. The product demonstrated significant value by reducing or resolving the symptoms of opportunistic infections most commonly associated with the dynamic of HIV/AIDS. Patients often experienced weight gains as part of an overall pattern of positive response.

Conclusion: Because of differences in size, cohort profile and length of evaluation period, the Nairobi study yielded a greater quantity of information that included positive clinical responses in three additional areas: hypertension, systemic lupus and tuberculosis. Several patients that had been bedridden for some time became ambulatory and were able to come to the clinic for continued participation in the study.

Clinical Study Report

Protocol No: BNL-003 (Phase –III Study)

6.2.3 An Interventional / Prospective Phase III Accelerated Study To Determine The Efficacy & Safety Of RECEPTOL® Liquid Spray Used As A Stand-Alone Mono Therapy in HIV / AIDS Patients with multiple symptoms

- **TITLE PAGE**

STUDY TITLE	An Interventional / Prospective Phase III Accelerated Study to Determine the Efficacy & Safety of RECEPTOL® Liquid Spray used as A Stand-Alone Mono Therapy in HIV / AIDS Patients with multiple symptoms
PROTOCOL CODE	BNL-003
NAME OF INVESTIGATIONAL PRODUCT TESTED	RECEPTOL® Oral Spray
DEVELOPMENT PHASE OF STUDY	Phase III
INDICATION STUDIED	HIV/AIDS
TRIAL DESIGN	A single arm, open label, 365 days study in 60 patients with advanced disease (HIV/AIDS), to determine the safety and effect of treatment with RECEPTOL® on clinical symptoms.
STUDY DATE	November 2002
SPONSOR	Biomix Network Limited Millennium Business Park, Unit No.303, Building 6, Sector-3, M. I. D. C., Mahape, Navi Mumbai, Maharashtra - 400 709 (India). Contact No: +91-9323000880
PARTICIPATING INSTITUTES	**PRINCIPAL INVESTIGATOR:** **Dr. Steve Mathews** **STUDY CENTER:** Rwanda, Africa

❖ CONCLUSION:

This trial was conducted in 60 HIV patients with 365 days treatment and moderate control of product use. The objectives of this study were to demonstrate, under clinical conditions, the Efficacy and Safety of Infoprotein supplementation in patients known to have advanced disease (HIV/AIDS). Cohorts were all symptomatic, ambulatory, compliant and native to Anti-Retroviral Therapy. Almost all patients showed reduction in HIV viral load and increase in CD4/CD8 cell count at the end of the study.All patients received RECEPTOL® every 6 hours for a period of 365 days. Positive clinical results were continually observed in the Rwanda patients. The results demonstrated that the product appeared to be free of side effects and generally well tolerated by the participants. Some signs, consistent with detoxification, were noted but resolved when the patients increased their water consumption. The product demonstrated significant value by reducing or resolving the symptoms of opportunistic infections most commonly associated with the dynamic of HIV/AIDS. Patients often experienced weight gains as part of an overall pattern of positive response. After 1 day of use there was a moderate level of relief of fever and diarrhoea. After 14 days of use all patients experienced relief of skin lesions, mouth thrush, fever, diarrhoea, tuberculosis. After 90 days of use all patients experienced relief of all symptoms. After 330 days all patients did not experience any negative symptoms.

Clinical Study Report

Protocol No: BNL-004 (Study I)

6.2.4 An Interventional / Prospective Phase III Accelerated Study To Determine The Efficacy & Safety Of RECEPTOL® Liquid Spray Used As A Stand-Alone MonoTherapy in HIV / AIDS Patients with multiple symptoms

- **TITLE PAGE**

STUDY TITLE	An Interventional / Prospective Phase III Accelerated Study TonDetermine The Efficacy & Safety Of RECEPTOL® Oral Spray Used As A Stand-Alone Mono Therapy In HIV / AIDS Patients with multiple symptoms
PROTOCOL CODE	BNL-004
NAME OF INVESTIGATIONAL PRODUCT TESTED	RECEPTOL® Oral Spray
DEVELOPMENT PHASE OF STUDY	Phase III
INDICATION STUDIED	HIV/AIDS and related communicable diseases
TRIAL DESIGN	A STAND-ALONE, single arm, open label, 12-week study in 50 subjects to determine efficacy & safety of treatment with RECEPTOL® on HIV viral load, Clinical & Physical Symptoms and Absolute CD4 cell counts in subjects with HIV / AIDS.
STUDY INITIATION DATE	October 15th, 2005
STUDY COMPLETION DATE	April 30th, 2006
SPONSORS	Ministry of Health; National AIDS Control Organisation (NACO), Government of India & Biomix Network Limited Millennium Business Park, Unit No.303, Building 6, Sector-3, MIDC, Mahape, Navi Mumbai, Maharashtra – 400 709 INDIA Contact No: +91-9323000880
PARTICIPATING INSTITUTES	**PRINCIPAL INVESTIGATOR:** Dr. G.C. Rajadhyaksha, MD Medicine, Associate Professor: Dept. of Medicine, LTM Medical College and LTMG Hospital, Sion. Mumbai – 400 022, INDIA

	STUDY CENTER: Lokmanya Tilak Municipal Medical College & General Hospital Sion, Mumbai – 400 022, INDIA. Phone No: 2407 6381, Fax No: 2407 6100 **CENTRAL LABORATORY:**Metropolis Health Services Pvt. Ltd. Laboratory (NABL & CAP-USA accredited) Kasibhai Navrangi, Shri Niketan 8, Grant Road, Mumbai – 400 007, INDIA.

❖ CONCLUSION:

• A total of 74 patients were enrolled in this study, out of which 2 patients did not fulfill the given inclusion criteria, 22 out of town patients dropped out from this study due to not being able to travel from their villages, Therefore, at the end of study, pre and post treatment data of 50 patients mentioning clinical symptoms and biochemical profile including HIV viral load and Absolute CD4 cell count were available for analysis.

• **Sample size for this stand alone monotherapy with RECEPTOL® only was calculated by following recommendations as per the End-Points used in any WHO study:**

1) Institutional Review Board of LTMMC & LTMG Sion Hospital consisting of Scientific Committee, Ethics Committee & Biostatistics Department of Sion Hospital

2) National Institute of Medical Statistics (Indian Council of Medical Research)

3) All India Institute of Medical Sciences (AIIMS) – Biostatistics Department

4) Ministry of Health & Family Welfare notification no. F-207 dated 12/01/05

• Out of the total of 50 subjects, 28 (56%) were Male and 22 (44%) were Female having average weight 50.48 kg with SD 10.97, average age 34.33 years with SD 8.87 with the range of 20-56 years.

• At the end of 12-Week Treatment (end of the study) with RECEPTOL® showed **significant change (reduction) in HIV viral load** based on PCR Diagnostic Test.

• At the end of 12-Weeks Treatment (end of the study) with RECEPTOL®, **median of HIV Viral load showed a significant change ($p<0.001$) from baseline** as evident in the **statistical analysis which was done by Dept. of Biostatistics, AIIMS.**

• At baseline, 88% of Patients had **Fatigue/Malaise** which became asymptomatic after 6th week of treatment with RECEPTOL®.

• HIV related **Diarrhea** was reduced in all patients from 5th Week onwards with significant reduction from 3rd Week

• **Nausea** disappeared from 5th Week onwards with significant fall from 3rd Week onwards. HIV related **Vomiting** had significant fall after 4th Week and all patients became asymptomatic after 7th Week onwards**.**

• Significant fall in **Fever** and related symptoms was observed in all HIV patients after 4^{th} week and became asymptomatic after 7th week onwards.

• HIV related **Cough** had a significant fall from 3rd week onwards and all patients became asymptomatic from 10th week onwards**.**

• HIV **related Tuberculosis patients became asymptomatic from 2nd week onwards.**

• HIV related **Disturbed Sleep** patients had a significant improvement after 2 weeks of treatment and became asymptomatic after 5th week.

• HIV related **Skin Rash** had a significant fall at the end of 2nd week and all patients reported no rashes from 4th week onwards.

• HIV related **Herpes Zoster** had a significant fall at the end of 3rd week and became asymptomatic in all patients after 4th week with the treatment RECEPTOL®.

• 11 weeks continued treatment with RECEPTOL® resulted in a significant increase in Absolute CD4 cell count with a reduction in HIV viral load. The results also showed a marked improvement in HIV Related Clinical Symptoms and Physical Findings and all patients were relieved of their symptoms by the treatment with RECEPTOL®.

• At the end of 12-Week Treatment (end of the study) with RECEPTOL®, median of **Absolute CD4 counts showed p<0.06 based on Flow Cytometry Analysis**. This is of borderline statistically significant.

• **All patients showed significant gain in Body Weight during 12 Week trial therapy With RECEPTOL® with an average gain of 4.73 kg, range of variation 3 - 7 kgs**.

• There was a marked improvement in HIV related clinical symptoms and many patients became asymptomatic at the end of 3 weeks therapy ($p < 0.05$).

• The 11 weeks trial treatment with **RECEPTOL® was well tolerated by all 50 patients and no patient experienced any Adverse or Serious Adverse Events.**

• The **overall results** obtained from this trial prove that continued treatment with RECEPTOL® Oral Spray for 12 consecutive weeks resulted in a **significant decrease in HIV viral load and increase in the Absolute CD4 cell count** along with a significant gain in body weight leading to relief of symptoms in all the 50 HIV/AIDS patients studied.

• As per the previous international studies of Phase I, II & III trials conducted in USA & Africa, RECEPTOL® showed similar clinical efficacy & safety in HIV Patients.

• Thus, RECEPTOL®, a natural Nano-Informational Peptides (RADHA1081-100) and Proline Rich Polypeptides (PRPs) derived from the Bovine Colostrum holds good promise for a safe and effective alternative treatment for HIV Patients across all age group.

Clinical Study Report

Protocol No: BNL-005 (Study II)

6.2.5 An Interventional / Prospective Phase III Accelerated Study To Determine The Efficacy and safety Of RECEPTOL® Liquid Spray Used As A Stand-Alone Mono Therapy in HIV / AIDS Patients With Multiple Symptoms

- **TITLE PAGE**

STUDY TITLE	An Interventional / Prospective Phase III accelerated Study To Determine The Efficacy and safety Of RECEPTOL® Oral SprayUsed As A Stand-Alone Mono Therapy In HIV / AIDS Patients With Multiple Symptoms
PROTOCOL CODE	BNL-005
NAME OF INVESTIGATIONAL PRODUCT TESTED	RECEPTOL® Oral Spray
DEVELOPMENT PHASE OF STUDY	Phase III
INDICATION STUDIED	HIV/AIDS and related communicable diseases
TRIAL DESIGN	A stand-alone, single arm, open label, 12-week study in 51 subjectsto determine effect of treatment with RECEPTOL® on HIV Viral Load, Clinical & Physical Symptoms and Absolute CD4/CD8 counts in subjects with HIV / AIDS.
STUDY INITIATION DATE	October, 2006
STUDY COMPLETION DATE	April, 2007
SPONSOR	Ministry of Health; National AIDS Control Organisation (NACO),Government of India & Biomix Network Limited Millennium Business Park, Unit No.303, Building 6, Sector-3, MIDC, Mahape, Navi Mumbai, Maharashtra – 400 709 INDIA Contact No: +91-9323000880

❖ CONCLUSION:

• A total of 51 patients diagnosed with HIV/AIDS were followed up during a 12 weeks continuous treatment period with RECEPTOL® liquid spray as a mono-therapy. All 51 patients completed the 12 week treatment without a single drop-out. Thus, at the end of the study, pre and post treatment data from all 51 patients on their clinical symptoms and biochemical profile including Absolute CD4 and CD8 cell counts and HIV viral load were available for analysis.

• **Sample size for this stand alone monotherapy with RECEPTOL® only was calculated by following recommendations as per the End-Points used in any WHO study:**

1) Institutional Review Board of LTMMC & LTMG Sion Hospital consisting of Scientific Committee, Ethics Committee & Biostatistics Department of LTMMC & LTMG Sion Hospital

2) ICMR (Indian Council of Medical Research, National Institute of Medical Statistics)

3) All India Institute of Medical Sciences (AIIMS) – Biostatistics Department

4) Ministry of Health & Family Welfare notification no. F-207 dated 12/01/05

• Of the 51 subjects studied, 21 (41.18%) were males and 30 (58.82%) females, with a mean body weight of 49.21 + 12.33 kg , and mean age of 33.35 + 9.14 years (range: 21-60 years).

• 12 weeks continued treatment with RECEPTOL® resulted in with a **significant reduction in HIV viral load.**

• The results also showed a **marked improvement in HIV Related Clinical Symptoms and Physical Findings** and all patients were relieved of their symptoms by the treatment with RECEPTOL®.

• At the end of the 12-Week Treatment Period (end of the study), majority of the patients showed reduced HIV viral load based on PCR Diagnostic Test. At the end of 12-Weeks Treatment (end of the study) with RECEPTOL®, **mean Viral Load showed a significant reduction ($p<0.001$) from baseline as evident in the statistical analysis**. These measurements were made at the Institute of Immuno-Hematology (IIH), ICMR centre, KEM Hospital, Mumbai at the beginning (baseline) and at the end of the 12 weeks trial treatment.

• Patients treated with RECEPTOL® therapy were relieved of their HIV related symptoms of Diarrhoea, Nausea and Vomiting, Fatigue/Malaise, Fever and Cough, Disturbed Sleep, Skin Rashes, Herpes Zoster, Paraesthesia, Hair Changes, Oral Thrush, Lymphadenopathy and Leukoplakia. There was a marked improvement in HIV related clinical symptoms and many patients became **asymptomatic at the end of 3 weeks therapy ($p < 0.001$)**. At baseline, all the patients exhibited symptoms of fatigue malaise. However, all were asymptomatic at the end of 4 weeks treatment with RECEPTOL®.

• HIV related **Diarrhoea and Nausea** was cured in all patients from 3rd week onwards with significant fall from 2nd week while a significant fall in HIV related Vomiting was seen in patients within 1st week of treatment with RECEPTOL®. All patients became asymptomatic form 3rd week onwards.

• There was a **significant fall in the incidence of Fever, Cough** and related symptoms in all patients at the end of 1st week of treatment and all became asymptomatic after 3rd week onwards with the therapy.

• While HIV related symptoms of **Disturbed Sleep and Skin Rash** had a significant fall after 2nd week of treatment and patients showed no signs of these symptoms after 3rd week of the therapy.

• Lastly, number of subjects with HIV related **Herpes Zoster** showed a significant reduction at the end of 1st week and became asymptomatic after 3rd week with the treatment RECEPTOL®.

• At the end of the 12-Week Treatment Period (end of the study), **mean CD4 and CD8 counts showed significant increase (p=0.042 & p=0.0080 respectively based on Flow Cytometry Analysis).**

• All patients showed a significant gain in Body Weight during the 12 Week trial therapy with RECEPTOL® with an **average gain of 4.68 ± 1.9 Kg** and range of variation from 2 to 9 kgs.

• The 12 weeks trial treatment with **RECEPTOL® was well tolerated by all 51 patients and no patient experienced any Adverse or Serious Adverse Events**.

• The overall results obtained from this trial prove that continued treatment with RECEPTOL® Oral Spray for 12 consecutive weeks resulted in a **significant decrease in HIV viral load & a significant increase in the Absolute CD4 and CD8 cell counts** along with a significant gain in body weight and to relief of symptoms in all the 51 HIV/AIDS patients studied. **As per the previous international studies of Phase I, II & III trials conducted in USA & Africa, RECEPTOL® showed good clinical results**. Also, this Phase III trial conducted in India at Sion Hospital, Mumbai showed positive efficacy and safety results.

• Thus, RECEPTOL®, a natural Nano-Informational Peptides (RADHA1081-100) and Proline Rich Polypeptides (PRPs) derived from the Bovine Colostrum holds good promise for a safe and effective alternative treatment for HIV Patients across all age group

6.3. Summary of pre- clinical & clinical trials

Summary: Safety & Efficacy data as per global study on Receptol®

KEY DIMENSIONS	PHASE I, II & III INTERNATIONAL TRIALS	STUDY I	STUDY II
Phase	Phase I – HIV trial, US Phase II – HIV trial, Nairobi, Kenya Phase III – HIV trial, Rwanda	Phase III validation trial by GOI on HIV patients, Standalone monotherapy	Phase III validation trial by GOI on HIV patients, Standalone monotherapy
No. of patients	Phase I – 12 cohorts Phase II – 30 cohorts Phase III – 60 cohorts	50 HIV seropositive patients	51 HIV seropositive patients
Duration	365/ 30 days	3 months	3 months
Compliance	Very good	Very good	Very good
Side effect	None	None	None
Weight gain	6 lbs average gain	4.73 kg per patient, $p<0.05$	$4.68 \pm 1,9$ kg per patient, $p<0.001$
Clinical symptoms	90 days relief from symptoms	Improved within 3 weeks from starting of therapy	Improved within 3 weeks from starting of therapy
CD4 cell count	Phase II: Average by 31	Average by 51, median CD4 cell count from 312 to 363 ($p = 0.06$)	On an average by 27 ($p = 0.042$)
HIV Viral load	Phase II: Mean HIV log viral load from 4.6 to 2.5	Mean HIV log viral load from 4.63 to 4.18 ($p = 0.001$)	Mean HIV log viral load from 4.41 to 4.02 ($p = 0.009$)

1. **Pre-clinical study (for acute and sub-chronic toxicity):** Carried out as per the International Conference on Harmonization (ICH) guideline at Nation Institute of Nutrition, Hyderabad.

2. **Phase I clinical trial:** Ohio, USA.

   The trial was conducted to evaluate the safety of Receptol® Oral Spray on 12 HIV patients for a period of 30 days.

- No adverse effects were reported during the study.
- Improvement was observed in HIV associated clinical symptoms.
- Week after week weight gain showed a positive response.

Table 1.1: Clinical improvement during Phase I - USA

Symptom	Number of patients with symptom N=12	Number of patients with elimination of symptoms N=12
Diarrhea	8	5
Fatigue	9	9
Nausea	8	5
Cough	4	2

3. **Phase II study:** Nairobi, Kenya.

   A t-Trial was conducted on 30 patients with HIV/AIDS, who received a 90 day treatment with Receptol® Oral Spray with an objective to demonstrate efficacy and safety under clinical conditions.

- Receptol® Oral Spray appeared to be safe and well tolerated.
- Significant viral load reduction in minimizing the infection associated with HIV/AIDS.
- Week after week weight gain showed a positive response.
- Marked reduction in symptoms
- Significant increase in CD4 count.

4. **Phase III study:** Rwanda, Africa

A t-Trial was conducted in 60 patients with HIV/AIDS, where patients received a 12 month treatment with Receptol® Oral Spray with an objective to study the efficacy and safety under clinical conditions.

- Patients were unaware of positive potential of drug so as to avoid any bias
- After day 1 moderate level of relief of diarrhea and fever
- Week after week weight gain showed a positive response.
- After 14 days, relief from skin lesion, mouth thrush, fever, diarrhea, tuberculosis symptoms.
- After 90 days relief of all symptoms with increase in absolute CD4 Counts and reduction in viral load
- No adverse effects observed over 12 months follow up even after 5 years of therapy, and an improvement in Quality of Life was noted.

5. **Phase III revalidation trial in Indian ethnic population:** At Mumbai

Study I – LTMMS Tertiary Care Sion Hospital, Mumbai on 50 patients who were HIV+

Absolute CD4 cell count & HIV Viral Load – tested at CAP, USA accredited Metropolis lab, Mumbai. Clinical & Physical symptoms study - at ART Center, Sion Hospital, Mumbai.

Objective: To evaluate safety & efficacy of Receptol®

Symptoms: HIV, Diarrhea, Fatigue/Malaise, Nausea, Cough.

Inclusion criteria – Absolute CD4 cell count greater than 100 cells/mm^3

Exclusion criteria – no pre- exposure to ART

Statistically significantly reduction in mean HIV log viral load ($p<0.001$)

- Marginal statistically significant increase in CD4 cell count ($p=0.06$)
- Clinical symptoms disappeared in 3 weeks of treatment in all patients ($p<0.05$)
- Statistically significant weekly weight gain in all patients ($p<0.001$)

Table 1.2: Summary of Study 1 data

Visit (Weeks)	No. of Subjects with Nausea	No. of Subjects with Vomiting	No. of Subjects with Fatigue/ Malaise	No. of Subjects with Diarrhea	No. of Subjects with Fever	No. of Subjects with Cough
1	8	7	44	9	12	14
2	3	2	32	5	3	10
3	2	2	26	1	6	6
4	1	1	17	1	1	3
6	0	1	1	0	0	1
8	0	0	1	0	0	2
10	0	0	1	0	0	0
12	0	0	0	0	0	0

Table 1.3: Summary CD4 count, baseline vs week 12

Sr. No.	CD4 count N=48	Baseline	After 12 Weeks	p-value
1.	Median	312.5	363.5	0.06
2.	25^{th} Percentile	275.5	294.2	
3.	75^{th} Percentile	430	435	

Table 1.4: Summary CD4 count, baseline vs week 12

Sr. No.	Parameter	Baseline	After 12 Weeks	p-value
1.	Log of HIV-1, RNA (N=34)	5.11(0.090)	4.103(1.32)	< 0.001
2.	Median	206057	25280	< 0.001
3.	25^{th} Percentile	62884	1665	
4.	75^{th} Percentile	508038	87511	

Study II – Sion Hospital, Mumbai on 51 AIDS Patients

Absolute CD4 cell count & HIV viral load – tested at Institute of Immuno Hematology (IIH), Indian Council of Medical Research (ICMR), King Edward Memorial (KEM) Hospital, Mumbai.

Inclusion criteria – Absolute CD4 cell count greater than 100 cells/$mm^3$and 100% symptomatic patients at baseline.

Exclusion criteria – No pre-exposure to ART

- The drop in the mean HIV log viral load was statistically significantly ($p<0.009$)
- Statistically significant increase in the CD4 cell count ($p< 0.042$)
- Clinical symptoms disappeared in 3 weeks of treatment in all patients ($p<0.001$)
- Statistically significant weekly weight gain in all patients ($p<0.001$)

Table 1.5: Indian re-validation phase III trials, Mumbai - Study II

Clinical Symptoms	N	At Baseline	Responders At Week-2
Diarrhea	51	51(100%)	12 (23.53%)
Nausea	51	51(100%)	3 (5.9%)
Vomiting	51	51(100%)	17 (33.3%)
Fever	51	51(100%)	13 (25.5%)
Cough	51	51(100%)	13 (25.5%)
Paraesthesia	51	51(100%)	16 (31.4%)
Disturbed Sleep	51	51(100%)	0 (0%)
Skin Rash	51	51(100%)	7 (13.7%)
Fatigue/Malaise	51	51 (100%)	51 (100%)
Herpes Zoster	51	51 (100%)	18 (35.3%)
Hair Changes	51	51 (100%)	16 (31.4%)
Leukoplakia	51	51 (100%)	5 (9.8%)
Oral Thrush	51	51 (100%)	51 (100%)

Table 1.6: CD4 Count, Baseline vs Week 12

Parameter	Baseline Mean ± SD	Week 12 Mean ± SD	Difference (Week 12-Baseline) Mean ± SD	P-value
CD4 Counts (cells/ mm)	317.16 ± 128.67	344.24 ± 165.79	+ 27.08 ± 92.47	0.042
CD8 Counts (cells / mm^3)	1037.06 ± 285.02	1139.75 ± 386.76	+102.69± 267.44	0.008

Published Peer reviewed first rate Journal References for Mode of Action of RECEPTOL® :

1. Landmark study: PRPs it's clinical applications,Steven J Block,MD,International journal of integrative medicine.(Article has 44 additional ref.)

2. Lawrence HS, Borkowsky W:Transfer factor:Current status and future prospects,Biotherapy9:1:5,1996.

3. Saharan P.Mammalian Colostrum derived Nanopeptides for broad spectrum viral and recurrent infection with a method of isolation thereof, US Granted product patent(#8518454 B2).

4. Granitov, VM et al…Usage of RECEPTOL® in treatment of HIV – Infected patients. Russian Journal of HIV AIDS and Related Problems 2002, 1, 79-80

5. World Health Organization. Progress on global access to HIV antiretroviral therapy: a report on "3 by 5" and beyond. 2006.

6. Brahmbhatt H, Kigozi G, Wabwire-Mangen F, Serwadda D, Lutalo T, Nalugoda F, Sewankambo N, Kiduggavu M, Wawer M, Gray R. Mortality in HIV-infected and 11 uninfected children of HIV-infected and uninfected mothers in rural Uganda. J Acquire Immune Defic Snyder 2006;41(4):504-8.

7. Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet 2004; 364(9441):1236-43.

8. Taha TE, Dallabetta GA, Canner JK, Chiphangwi JD, Liomba G, Hoover DR, Miotti PG. The effect of human immunodeficiency virus infection on birth weight and infant and child mortality in urban Malawi. Int J Epidemiol 1995; 24(5):102

9. Janusz M., Staroscik K., Zimeckt M., Wieczorek Z., Lisowski J., Aproline-rich polypeptide (PRP) with immunoregulatory properties isolated from ovine colostrums. Archivum immulologiac therapies experimentalis (Warszawa) 34(4): 427-436 (1986).

10. Wieczorec Z., Zimecki M., Spiegel K., Lisowski J., Janusz M., Differentiation of T-Cells from immature precursors: identification of a target cell for a proline-rich polypeptide (PRP) Archivum immunological therapies experimentalists (Warszawa) 37(3-4):313-322(1989).

11. Kubis A., Marcinkowska E., Janusz M., Lisowski J. Studies on mechanism of action of a proline-rich polypeptide complex (PRP): Effect on stage of cell differentiation peptides 26(11) : 2188-2192 (2005).

12. Modulation of 4HNE-mediated signaling by proline-rich polypeptides from ovine colostrums. Journal of Molecular Neuroscience 20(2):125-134 (2003).

13. Zibiocka A., Janusz M., Rybka K., Wirkus – Romanowska I. Kupryszewski G., Lisowski J. Cytoline inducing activity of a proline-rich polypeptide (PRP) from ovine colostrum and its active nanopeptide fragment analogs. European Cytokine Network 12(3) :462-467 (2001).

14. Fernadez- ortega C. Dubed M. Ruibal O. Vilarruba OL. Menendez de San Pedro JC. Navea L. Ojeda M. Arana MJ. Inhibition of in vitro HIV infection by dialyzable leucocyte extracts, Biotherapy 9(1-3)33-40 (1996).

15. Zimecki M,Staroscik K, Janusz M, Lisowski J, Wieczorek Z. The inhibitory activity of proline-rich polypeptide on the immune response to polyvinyl pyrrolidone (PVP). Arch Immunol Ther Exp (Warsz)1983;31(6):895-903.

16. Boldogh I, Liebenthal D, Hughes TK, Juelich TL, Georgiades JA, Kruzel ML, Stanton GJ. Modulation of 4HNE-mediated signaling by a proline-rich polypeptides from ovine colostrum. J Mol Neurosci. 2003;20(2):125-134.

17. Modulation of 4HNE-mediated signaling by proline-rich polypeptides from bovine colostrums. Journal of Molecular Neuroscience 20(2):125-134 (2003).

18. Fernadez- ortega C. Dubed M. Ruibal O. Vilarruba OL. Menendez de San Pedro JC. Navea L. Ojeda M. Arana MJ. Inhibition of in vitro HIV infection by dialyzable leucocyte extracts, Biotherapy 9(1-3)33-40 (1996).

19. Eggena MP, Barugahare B, Jones N, Okello M, Mutalya S, Kityo C, Mugyenyi P, Cao H. Depletion of regulatory T cells in HIV infection is associated with immune activation. J Immunol. 2005; 174(7):4407-4414.

20. Shi M, Hao S, Chan T, Xiang J. CD4+ T cells stimulate memory CD8+ T cell expansion via acquired pMHC I complexes and costimulatory molecules, and IL-2 secretion. J Leuco Biol, 2006; 80(6):1354-1363.

21. Fierlbeck G et al [Intralesional therapy of melanoma metastases with recombinant interferon-beta] Hautarzt. 43: 16-21 (1992);

22. Stuart-Harris RC et al The clinical application of the interferons: a review. NSW Therapeutic Assessment Group Med. Journal of Aust. 156: 869-72 (1992);

23. Gifford GE and Duckworth DH Introduction to TNF and related lymphokines. Biotherapy 3: 103-11 (1991);

24. Sato N et al Actions of TNF and IFN-gamma on angiogenesis in vitro. Journal of Investigative Dermatology 95: 85S-9S (1990)

25. Barnes, D. Debate over potential AIDS drug. Science, 237(4811), pages 128-130,July10,1987.

26. Brenneman, D. and others. Neuronal cell killing by the envelope protein of HIV and its prevention by vocative intestinal peptide. Nature, 335(6191), pages 639-642,October13,1988.

27. Brenneman, D. and others. Peptide T prevents gp120 induced neuronal cell death in vitro: relevance to AIDS dementia. Drug Development Research, volume15,pages361-369,1988.

28. Immunology, Immunopathology and Immunity, Sell S, Appleton and Lange: Stamford CT 1996.

29. Bishop GA., Haxhinasto SA., Slunz LL., Hostager BS. Antigen specific B-lymphocyte activation. Critical reviews in immunology 23(3): 159-197 (2003).

30. Claes – Henrik Floren S., Chinenye L., Elfstrand C., Hagman L. Thse. Coloplus a new product based on bovine colostrum alleviates HIV- asociated diarrhoea. Scandinavian journal of Gastroenterology 2006: 41-68 2-686.

31. Effects of oral dietary supplimentation with Ai/E$^{10®}$ upon Natural Killer (NK) cell activity in a healthy human population. Quantum Research, Inc., Scottsdate, Arizona, 2001.

32. An examination of Immune Response Modulation in Humans by Ai/E$^{10®}$ utilizing a double blind study. Immune Consultants, Inc., Tucson, Arizona, 2001.

33. Macroft A, Youle M, Moore A, et al. Reaseons for modification and discontinuation of antiretrovirals : results from a single center. AIDS, 2001; 15:185-94.

34. Fatenkeheur G, Romer K, Cramer P, et al. High rates of changes of first antiretroviral combination regimen in an unselected cohort of HIV 1 infected patients. 8th ECCAT Greece, 2001; abstract no. 50.

35. Raise E, Guerra L, Viza D, Pizza G, De Vinci C, Schiattone ML, Rocaccio L, Cicognani M, Gritti F. Preliminary results in HIV I infected patients with transfer factor (TF) and zidovudine (ZDV). Biotherapy. 1996;9(1-3):49-54.

36. Shi M, Hao S, Chan T, Xiang J. CD4+ T cells stimulate memory CD8+ T cell expansion via acquired pMHC I complexes and costimulatory molecules, and IL-2 secretion. J Leuco Biol, 2006; 80(6):1354-1363.

37. Razonable, Raymund, R., et.al. Division of Infectious Diseases and Internal Medicine, Mayo Clinic and Foundation, Selective Reactivation of Human Herpesvirus 6 variant A Occurs in Critically Ill Immunocompetent Hosts, The Journal of Infectious Diseases, January , 2002.

38. Dwyer JM. The use of antigen-specific RECEPTOL® in the management of infections with herpes viruses. In: Kirkpatrick CH, Burger DR and Lawrence HS eds. Immunobiology of RECEPTOL®. New York Academic Press 1983:233-243.

39. Viza D, Vich JM, Phillips J et al. Orally administered specific RECEPTOL® for the treatment of herpesvirus infections. Lymphok Res 1985;4:27-30.

40. Jones JF, Jeter WS, Fulginiti VA et al. Treatment of childhood combined Epstein-Barr virus/cytomegalovirus infection with oral bovine RECEPTOL®. Lancet 1981;2:122-124.

41. Ablashi DV, Levine PH, DeVinci C et al. Use of anti HHV-6 RECEPTOL® for the treatment of two patients with chronic fatigue syndrome (CFS). Two case reports. Biotherapy 1996;9:81-86.

42. Steele RW, Myers MG and Monroe VM. RECEPTOL® for the prevention of varicella-zoster infection in childhood. N Engl J Med 1980;303:355-359.

43. Lang I, Nekam H, Gergely P et al. Effect of in vivo and in vitro treatment with dialyzable leukocyte extracts on human natural killer cell activity. Clin Immunol and Immunopathol 1982;25:139-144.

44. Boucheix C, Phillips J, Pizza G et al. Activity of animal RECEPTOL® in man. Lancet 1977;1:198-199.

45. Fudenberg H and Pizza G. RECEPTOL® 1993: New frontiers. Progress in Drug Res 1994;42:309-400.

46. Arala-Chaves M, Ramos MTF and Rosado RMF. Evidence for prompt and intense constitution of cell-mediated immunity by means of RECEPTOL® in a case of complex immune deficiency. Cell. Immunol. 1974;12:160.

47. Ballow M and Good RA. Report of a patient with T-cell deficiency and normal B-cell function: a new immunodeficiency disease with response to RECEPTOL®. Cell. Immunol. 1975;19:219.

48. Jones JF, Pizza G, DeVinci C. Infectious mononucleosis: immunotherapy with EBV-specific RECEPTOL®. J Exp Pathol 1987;3:399-406.

49. Khan A, Hansen B, Hill NO et al. RECEPTOL® in the treatment of herpes simplex types 1 and 2. Dermatologica 1981;163:177-185.

50. Winkelman RK, DeRemee RA, Ritts RE Jr. Treatment of varicella-zoster pneumonia with RECEPTOL®. Cutis 1984;34:278-281.

51. Rozzo SJ and Kirkpatrick CH. Purification of RECEPTOLs. Mol Immunol 1992;29:167-182.

52. Pizza G, Viza D, Roda A et al. RECEPTOL® for the treatment of chronic active hepatitis. N Engl J Med 1979;300:1332.

53. Nkrumah F, Pizza G, Viza D et al. Regression of progressive lymphadenopathy in a young child with acute cytomegalovirus (CMV) infection following the administration with specific anti-CMV activity. Lymphok Res 1985;4:237-241.

54. Neequaye J, Viza D, Levine PH et al. Specific RECEPTOL® with activity against Epstein-Barr virus reduces late relapse in endemic Burkittâs lymphoma. Anticancer Res 1990;10:1183-1187.

55. Viza D, Vich JM, Phillips J et al. Specific RECEPTOL® protects mice against lethal challenge with herpes simplex virus. Cell Immun 1986;100:555-562.

56. Wilson GB, Poindexter C, Fort JD et al. De novo initiation of specific cell-mediated immune responsiveness in chickens by RECEPTOL® (specific immunity inducer) obtained from bovine colostrum and milk. ACTA Virol 1988;32:6-18.

57. Kirkpatrick CH, Hamad AR, and Morton LC. Murine RECEPTOLs: dose-response relationships and routes of administration. Cell Immunol 1995:164:203-206.

58. Viza D, Lefesvre A, Patrasco M et al. A preliminary report on three AIDS patients treated with anti-HIV specific RECEPTOL®. J Exp Path 1987;3:653-659.

59. Pizza G, DeVinci C, Palareti A et al. 25 years of clinical experience with RECEPTOLs. XI International Symposium on RECEPTOL®. March 1-4, 1999. Monterey, Mexico.

60. Barnes, D. Debate over potential AIDS drug. Science, 237(4811), pages 128-130,July10,1987.

61. Brenneman, D. and others. Neuronal cell killing by the envelope protein of HIV and its prevention by vasoactive intestinal peptide. Nature, 335(6191), pages639-642,October13,1988.

62. Brenneman, D. and others. Peptide T prevents gp120 induced neuronal cell death in vitro: relevance to AIDS dementia. Drug Development Research, volume15, pages361-369,1988.

63. Bridge, P. and others. Peptide T: Improvements in phase I trial of AIDS patients.Draft of letter submitted to Lancet, July 1989.

64. Kowalski, M. and others. Functional regions of the envelope glycoprotein of human immunodeficiency virus type 1. Science, 237 (4820), pages 1351-1355,1987.

65. Lasky and others. Delineation of a region of the human immunodeficiency virus type 1 gp120 glycoprotein critical for interaction with the CD4 receptor. Cell, volume 50 number 6, pages 975-985, 1987.

66. Nygren and others. 95- and 25-kDa fragments of the human immunodeficiency virus envelope glycoprotein gp120 bind to the CD4 receptor. Proceedings of the National Academy of Sciences U. S. A., volume 5number17,pages6543-6546,1988.

67. Pert, C., and others. Octapeptides deduced from the neuropeptide receptor-like pattern of antigen T4 in brain potently inhibit human immunodeficiency virus receptor binding and T-cell infectivity. Proceedings of the National Academy of Sciences U. S. A., volume 83, pages 9254-9258, December 1986.

68. Pert interview, Science Impact, pp. 6-7, June 1987.Ruff, M., and others. Peptide T[4-8] is core HIV envelope sequence required for CD4 receptor attachment.Lancet,2(8561),page751,Sept.26,1987.

69. Sodroski, J., and others. HIV envelope-CD4 interaction not inhibited by synthetic octapeptides. Lancet, 1(8547), pages 1428- 1429, June 20, 1987.

70. Wetterberg, L., and others. Treatment with peptide T in seven immunodepressed HIV infected patients. Draft of paper submitted to AIDS, Gower Academy Journal, London, June, 1988.

71. Wetterberg, L., and others. Peptide T in treatment of AIDS. The Lancet, 1(8525), page 159, Jan. 17, 1987.

72. Granitov, VM et al…Usage of RECEPTOL® in treatment of HIV – Infected patients. Russian Journal of HIV AIDS and Related Problems 2002, 1, 79-80.

73. World Health Organization. Progress on global access to HIV antiretroviral therapy: a report on "3 by 5" and beyond. 2006.

74. Lawrence HS, Borkowsky W: TRANSFER FACTOR: current status and future prospects. Biotherapy 9:1-5, 1996

75. Dr. Olle Hernell, At the University of Ulmea, Sweden; Science, www.nextdimension.org, 4 Aug 1999

76. Drs. Bocci, Bremen, Corradeschi, Luzzi and Paulesu; Journal Biology

77. Boesman – Finkelstein M, Finkelstein R, *Lancet*, 1989, 2:1336

78. Dicchtemuller W, Lissner R, *J. Clin. Bio. Chem.,* 1990, 28:19-23

79. Ogra SS, Ogra P.L., *J. Pediatr*, 1978, 92:546-549

80. Szaniszlo, P; German, P; Hajas, G; Saenz, D; Woodberry, M; Kruzel, M; Boldogh, I, *International Immunopharmacology* , 2009, **9** (2): 181–93.

81. Bacsi, A; Woodberry, M; Kruzel, M; Boldogh, I, *Neuropeptides*, *2007,* 41 (2): 93–101

7. Meta-Analysis Data

Meta-Analysis is a combine analysis of 25,000 subjects across HIV, Swine Flu, Allergy, Asthma, Rheumatoid arthritis, Endometriosis, NCD (Chronic Fatigue Syndrome showing increase in weight gain an Indication of overall wellness showing safety & Efficacy of Receptol.

Table: 1.1 Stand Alone Receptpol® Therapy in Global clinical studies

Sr.No.	Stand Alone Receptol Therapy in Global clinical studies	No. of Patients
1	Healthy people	10,000
2	HIV Patient in USA, Africa, India	5000
3	Swine Flu	5000
4	Other Indications like allergy, asthma, Rheumatoid Arthritis, Chronic Fatigue Syndrome, Endometriosis Study etc.	5000

7.1 An observational Study of Healthy Population with frequent recurrent infections & weight loss past history to determine the Efficacy & Safety Of RECEPTOL® Oral Spray Used as a Stand-Alone Mono Therapy:

7.1.1 Title

A STAND-ALONE, single arm, open label, 1 month study was conducted in 10,000 subjects to determine efficacy & safety of treatment with RECEPTOL® on weight changes in subjects with Healthy Population with frequent recurrent infections & weight loss past history .

7.1.2 OBJECTIVES

Primary Objective

To evaluate the efficacy of RECEPTOL® liquid in Healthy People in terms of weight gain as weight gain is the indication of overall wellness.

Secondary Objectives

To determine the effect of oral spray administration of RECEPTOL® liquid on overall Assessment of Efficacy and Safety/Tolerability of RECEPTOL®.

7.1.3 METHODOLOGY

• This trial was a 1-Month, Stand-Alone, single arm, open label study to evaluate the Efficacy and Safety/Tolerability of RECEPTOL® liquid in Healthy People.

• The potential subjects were screened after obtaining a written informed consent from (As per Schedule Y) the subject or LAR (Legally Acceptable Representative)/impartial witness.

• The study was designed to investigate efficacy of RECEPTOL® therapy in reducing Viral Load and clinical symptoms & change in body weight.

• The study subjects received RECEPTOL® liquid as a spray self-administered by patients on either side of the oral buccal surface 4 times daily at every 4 hour's interval. Each administration comprised of metered dose of 0.75 ml spray directly on the buccal mucosa.

• Subjects' body weight was monitored at every visit to determine the effect of RECEPTOL® therapy on change in the weight.

• The subjects were also assessed for clinical symptoms and physical findings which included Health Populatin with frequent recurrent infections related Fatigue/Malaise, Diarrhoea, Nausea, Vomiting, Fever, Cough, Parasthesia Sleep Disturbance, Skin Rash, Herpes Zoster, Lymphadenopathy, Hair changes, oral thrush, Leukoplakia, every visit to determine the effect of RECEPTOL® therapy on change in the weight. Liver enlargement, Spleen enlargement, Weight of patient and Tuberculosis.

• Physician and Patient Overall Assessment scale were used to evaluate the efficacy and safety/ tolerability of RECEPTOL® liquid at the end of the treatment.

7.1.4 STUDY PLAN

a) Study Design: Observational study

b) Population: 10,000 cases

c) Methods: This trial was a 1-Month, Stand-Alone, single arm study to evaluate the Efficacy and Safety/Tolerability of RECEPTOL® oral spray in Healthy subjects. The potential subjects were screened after obtaining a written informed consent from (As per Schedule Y) the subject or LAR (Legally Acceptable Representative)/impartial witness. The study was designed to investigate efficacy of RECEPTOL® therapy in change in body weight. The study subjects received RECEPTOL® as a spray self-administered by patients on either side of the oral buccal surface 4 times daily at every 4 hour's interval. Each administration consist a metered dose of 0.75 ml spray directly on the buccal mucosa. Body weight of subjects was monitored at every visit to determine the effect of RECEPTOL® therapy on change in the weight.

7.1.5 RESULT

Table 1.2:

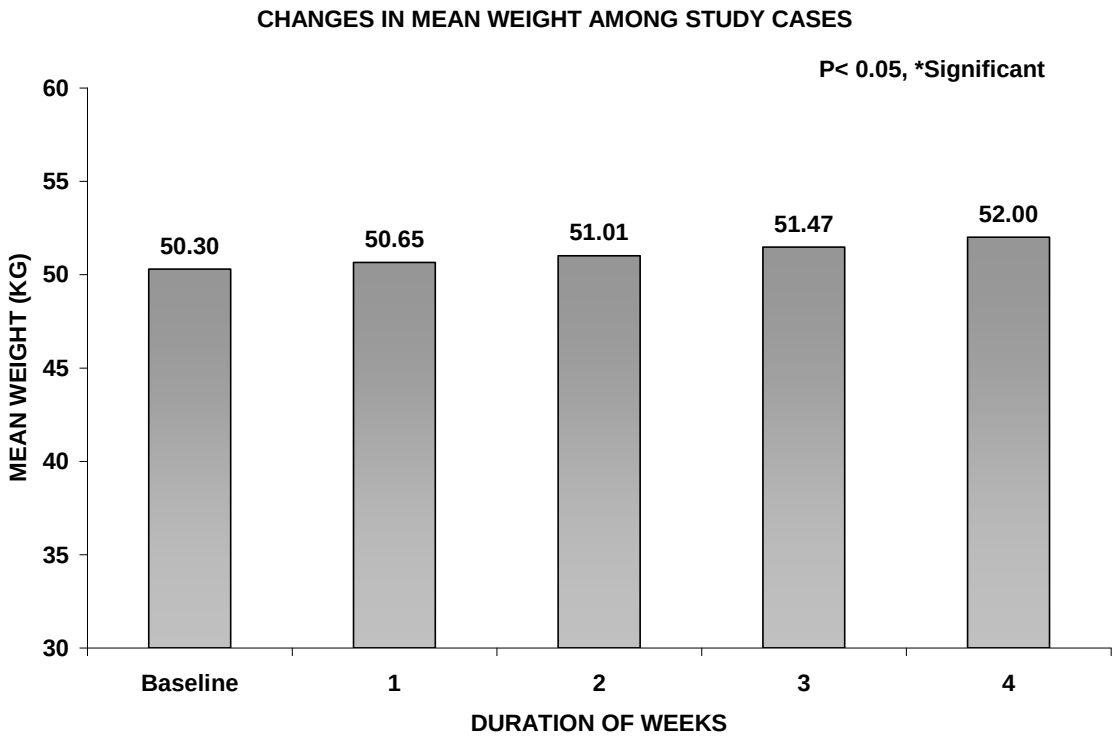
CHANGES IN MEAN WEIGHT AMONG STUDY CASES

Duration (Weeks)	**Mean weight ($\overline{X}$ ± SD) (N = 10000)**
Baseline	50.30 ± 10.02
1	50.65 ± 10.01
2	51.01 ± 09.96
3	51.47 ± 09.94
4	52.00 ± 09.96
Mean Diff. (Baseline – Wk1) (P value)	*00.35 ± 00.66 (0.001)
Mean Diff. (Baseline – Wk2) (P value)	*00.71 ± 01.24 (0.001)
Mean Diff. (Baseline – Wk3) (P value)	*01.17 ± 01.95 (0.001)
Mean Diff. (Baseline – Wk4) (P value)	*01.70 ± 02.15 (0.001)

By ANOVA * Significant

- As per this data mean weight at baseline was **50.30 kg.**
- After 1 week of treatment, mean weight showed a significant rise of **0.7%** from baseline.
- After 2 week of treatment, mean weight showed a significant rise of **1.4%** from baseline. Same trend was observed till the end of 4 weeks.

- **Figure 1.1:**



According to above figure, after RECEPTOL treatment mean weight significantly increases from week 2 onwards till end of treatment with respect to baseline

Table 1.3:

CHANGE IN MEAN WEIGHT AS PER GENDER

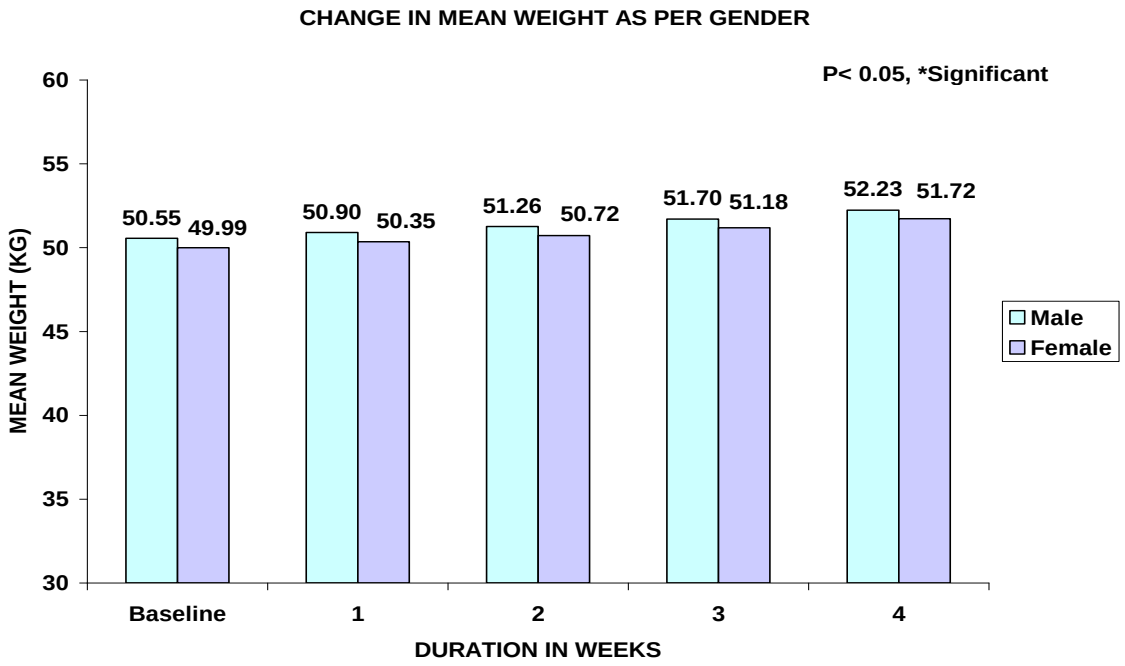
Duration (Weeks)	**Mean weight ($\overline{X}$ ± SD)**		**P Value**
	Male (N = 5462)	**Female (N = 4538)**	
Baseline	50.55 ± 10.00	49.99 ± 10.04	0.582 NS
1	50.90 ± 09.97	50.35 ± 10.05	
2	51.26 ± 09.93	50.72 ± 09.98	
3	51.70 ± 09.89	51.18 ± 09.98	
4	52.23 ± 09.95	51.72 ± 09.96	
Mean Diff. (Baseline – Wk1) (P value)	*00.35 ± 00.55 (0.001)	*00.36 ± 00.77 (0.001)	0.627 NS

Mean Diff. (Baseline – Wk2) (P value)	*00.71 ± 01.10 (0.001)	*00.73 ± 01.38 (0.001)	0.600 NS
Mean Diff. (Baseline – Wk3) (P value)	*01.15 ± 01.68 (0.001)	*01.19 ± 02.24 (0.001)	0.368 NS
Mean Diff. (Baseline – Wk4) (P value)	*01.68 ± 02.33 (0.001)	*01.73 ± 01.91 (0.001)	0.175 NS

By ANOVA * Significant NS = Not Significant

- Above data states that mean weight at baseline was **50.55kg** in males which was comparable to **49.99kg** in females and the difference was not significant.
- After 1 week of treatment, mean weight showed a significant increase of **0.7%** among male and female each from baseline. If compared the increase was same among both the Group and difference was not significant.
- Same trend was observed till the end of 4 weeks.

Figure 1.2:



Above figure shows that after treatment with RECEPTOL, there is a significant change in weight in both the genders from baseline till end of treatment.

7.1.6 CONCLUSION

This observation study reveals that after RECEPTOL® oral spray therapy, mean weight of study cases showed significant increase from baseline till end of treatment and these changes were observed in both the genders.

Hence, these results showed that RECEPTOL ®oral spray is very effective and safe to use in healthy population with frequent recurrent infections and weight loss cases to increase the weight and overall wellness.

7.2 An observational Study on HIV positive patients to determine the Efficacy & Safety Of RECEPTOL® Oral Spray Used as a Stand-Alone Mono Therapy

7.2.1 Title

A STAND-ALONE, single arm, open label, 6 month study was conducted on 5000 subjects to determine efficacy & safety of treatment with RECEPTOL® on weight changes in subjects with HIV / AIDS.

7.2.2 OBJECTIVES

Primary Objective

To evaluate the efficacy of RECEPTOL® liquid in HIV/AIDS patients in terms of weight gain as weight gain is the indication of overall wellness.

Secondary Objectives

To determine the effect of oral spray administration of RECEPTOL® liquid on:

- Absolute CD4 cell count
- Overall Assessment of Efficacy and Safety/Tolerability of the RECEPTOL®.

7.2.3 METHODOLOGY

- This trial was a 6-Month, Stand-Alone, single arm, open label study to evaluate the Efficacy and Safety/Tolerability of RECEPTOL® liquid in HIV/ AIDS patients.

- The potential subjects were screened after obtaining a written informed consent from (As per Schedule Y) the subject or LAR (Legally Acceptable Representative)/impartial witness.

- The study was designed to investigate efficacy of RECEPTOL® therapy in reducing Viral Load and clinical symptoms & increase in Absolute CD4 cell count & change in body weight.

- The study subjects received RECEPTOL® liquid as a spray self-administered by patients on either side of the oral buccal surface 4 times daily at every 4 hour's interval. Each administration consist a metered dose of 0.75 ml spray directly on the buccal mucosa.

- Subjects' body weight was monitored at every visit to determine the effect of RECEPTOL® therapy on change in the weight.

• The subjects were also assessed for clinical symptoms and physical findings which included HIV related Fatigue/Malaise, Diarrhoea, Nausea, Vomiting, Fever, Cough, Paraesthesia Sleep Disturbance, Skin Rash, Herpes Zoster, Lymphadenopathy, Hair changes, oral thrush, Leukoplakia, Liver enlargement, Spleen enlargement, Weight of patient and Tuberculosis.

• Physician and Patient Overall Assessment scale were used to evaluate the efficacy and Safety/ tolerability of RECEPTOL® liquid at the end of the treatment.

7.2.4 STUDY PLAN

a) Study Design: Observational study

b) Population: 5000 cases

c) Methods: This trial was a 6-Month, Stand-Alone, single arm, open label study to evaluate the Efficacy and Safety/Tolerability of RECEPTOL® oral spray in HIV/ AIDS patients in terms of weight gain. The potential subjects were screened after obtaining a written informed consent from (As per Schedule Y) the subject or LAR (Legally Acceptable Representative)/impartial witness. The study was designed to investigate efficacy of RECEPTOL® therapy in terms of change in body weight. The study subjects received RECEPTOL® as a spray self-administered by patients on either side of the oral buccal surface 4 times daily at every 4 hour's interval. Each administration consist a metered dose of 0.75 ml spray directly on the buccal mucosa. Body weight of subjects was monitored at every visit to determine the effect of RECEPTOL® therapy on change in the weight.

7.2.5 RESULT

Table 1.4:

CHANGES IN MEAN WEIGHT AMONG STUDY CASES

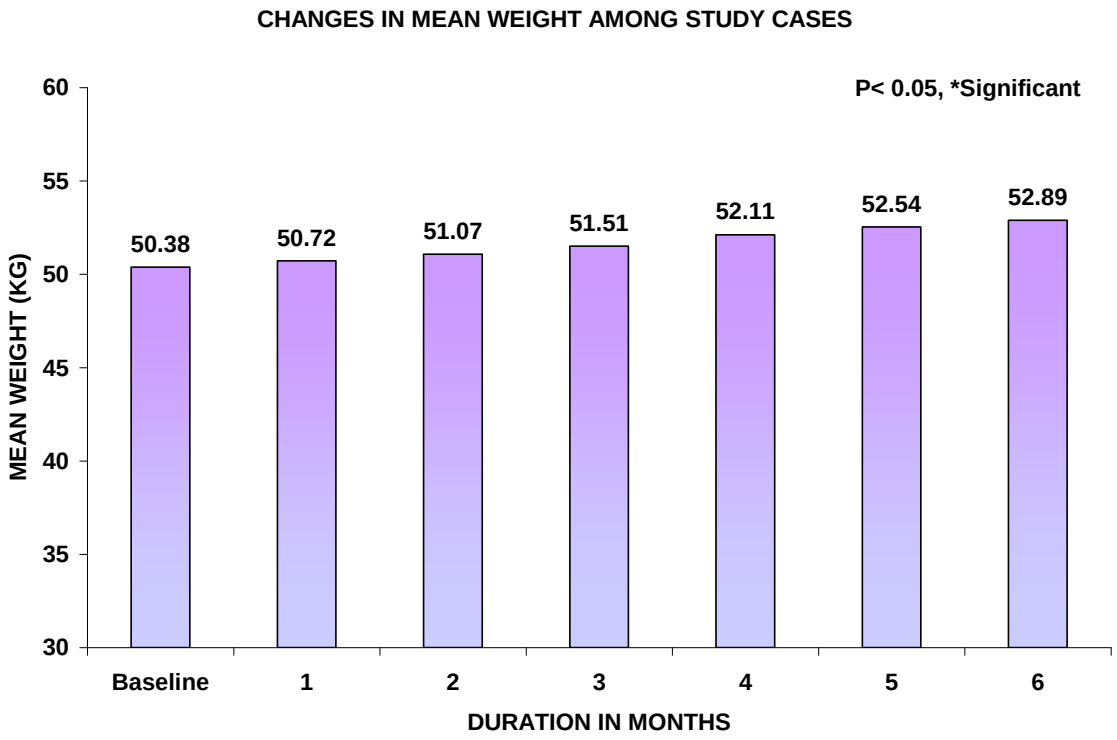
Duration (Months)	**Mean weight ($\bar{X}$ ± SD) (N = 5000)**
Baseline	50.38 ± 09.89
1	50.72 ± 09.88
2	51.07 ± 09.82
3	51.51 ± 09.79
4	52.11 ± 09.75
5	52.54 ± 09.76
6	52.89 ± 09.77
Mean Diff. (Baseline – 1 month) (P value)	*00.34 ± 00.57 (0.001)

Mean Diff. (Baseline – 2 months) (P value)	*00.69 ± 00.91 (0.001)
Mean Diff. (Baseline – 3 months) (P value)	*01.13 ± 01.39 (0.001)
Mean Diff. (Baseline – 4 months) (P value)	*01.73 ± 01.71 (0.001)
Mean Diff. (Baseline – 5 months) (P value)	*02.16 ± 01.76 (0.001)
Mean Diff. (Baseline – 6 months) (P value)	*02.51 ± 02.07 (0.001)

By ANOVA * Significant

- As per this data mean weight at baseline was **50.38kg.**
- After 1 month of treatment, mean weight showed a significant rise of **0.7%** from baseline.
- After 2 months of treatment, mean weight showed a significant rise of **1.4%** from baseline. Same trend was observed till the end of 6 months.

- **Figure:1.3**



According to above figure, mean weight increased after treatment of Receptol from baseline up to 6 months

Table 1.5:

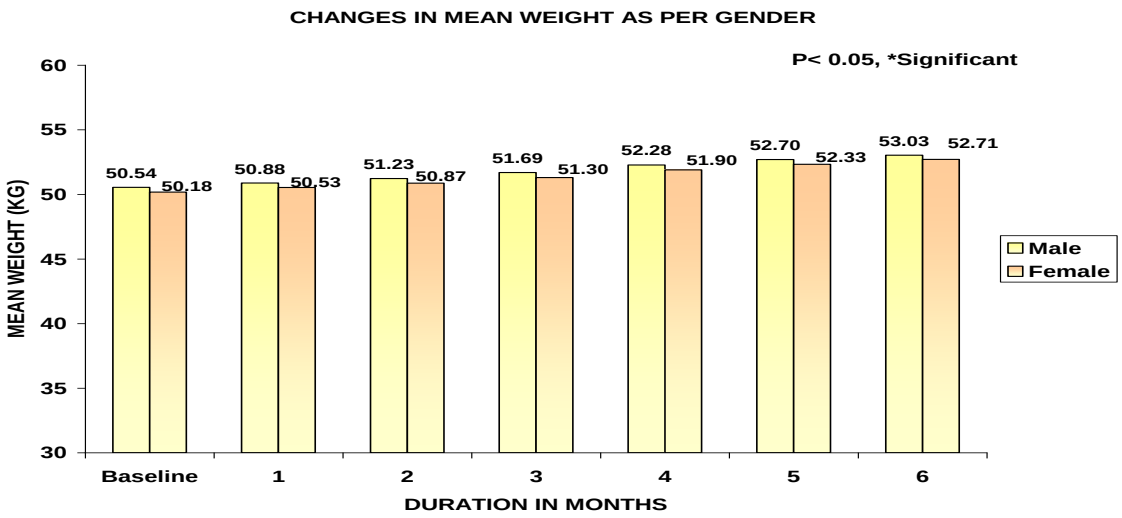
CHANGES IN MEAN WEIGHT AS PER GENDER

Duration (Months)	Mean weight ($\bar{X}$ ± SD)		P Value
	Male (N = 2745)	Female (N = 2255)	
Baseline	50.54 ± 09.90	50.18 ± 09.88	0.201 NS
1	50.88 ± 09.89	50.53 ± 09.87	
2	51.23 ± 09.82	50.87 ± 09.81	
3	51.69 ± 09.80	51.30 ± 09.77	
4	52.28 ± 09.76	51.90 ± 09.74	
5	52.70 ± 09.77	52.33 ± 09.75	
6	53.03 ± 09.79	52.71 ± 09.75	
Mean Diff. (Baseline – 1 month) (P value)	*00.34 ± 00.62 (0.001)	*00.35 ± 00.49 (0.001)	0.524 NS
Mean Diff. (Baseline – 2 months) (P value)	*00.69 ± 00.85 (0.001)	*00.69 ± 00.98 (0.001)	0.703 NS
Mean Diff. (Baseline – 3 months) (P value)	*01.15 ± 01.10 (0.001)	*01.12 ± 01.67 (0.001)	0.625 NS
Mean Diff. (Baseline – 4 months) (P value)	*01.74 ± 01.56 (0.001)	*01.72 ± 01.88 (0.001)	0.686 NS
Mean Diff. (Baseline – 5 months) (P value)	*02.16 ± 01.62 (0.001)	*02.15 ± 01.93 (0.001)	0.844 NS
Mean Diff. (Baseline – 6 months) (P value)	*02.49 ± 02.17 (0.001)	*02.53 ± 01.96 (0.001)	0.494 NS

By ANOVA * Significant NS = Not Significant

- This analysis indicates that mean weight at baseline was **50.54kg** in males which was comparable to **50.18kg** in females and the difference was not significant.
- After 1 month of treatment, mean weight showed a significant increase of **0.7%** among male and female each from baseline. If compared the increase was same among both the Group and difference was not significant.
- Same trend was observed till the end of 6 months.

Figure 1.4:



There was change in weight among male and female from baseline to end of treatment.

7.2.6. CONCLUSION:

The results of this observational study reveals that after RECEPTOL® Oral Spray therapy, mean weight of study cases showed significant increase from baseline to end of treatment and that change were observed in both the genders.

Hence we can conclude that, RECEPTOL® Oral Spray is very effective and safe in HIV/AIDS cases to increase the weight and overall wellness.

7.3 An observational Study of Swine Flu like symptoms observed at Mumbai International Airport during 2009-2010 Swine Flu pandemic to determine the Efficacy & Safety Of RECEPTOL® Oral Spray Used as a Stand-Alone Mono Therapy

7.3.1 Title

An observational Study in 5000 subjects to determine efficacy & safety of treatment with RECEPTOL® on weight changes in subjects with Swine Flu.

7.3.2 OBJECTIVES

Primary Objective

To evaluate the efficacy of RECEPTOL® liquid in Swine Flu patients in terms of weight gain as weight gain is the indication of overall wellness.

Secondary Objectives
To determine the effect of oral spray administration of RECEPTOL® liquid on:
• Overall Assessment of Efficacy and Safety/Tolerability of the RECEPTOL®

7.3.3 METHODOLOGY

• This trial was a 1-Month, An observational Study of Swine Flu to evaluate the Efficacy and Safety/Tolerability of RECEPTOL® liquid in HIV/ AIDS patients.

• The potential subjects were screened after obtaining a written informed consent from (As per Schedule Y) the subject or LAR (Legally Acceptable Representative)/impartial witness.

• The study was designed to investigate efficacy of RECEPTOL® therapy in reducing Viral Load and clinical symptoms & change in body weight.

• The study subjects received RECEPTOL® liquid as a spray self-administered by patients on either side of the oral buccal surface 4 times daily at every 4 hour's interval. Each administration consist a metered dose of 0.75 ml spray directly on the buccal mucosa.

• Subjects' body weight was monitored at every visit to determine the effect of RECEPTOL® therapy on change in the weight.

• The subjects were also assessed for clinical symptoms and physical findings which included Swine Flu related Fatigue/Malaise, Diarrhoea, Nausea, Vomiting, Fever, Cough, Parasthesia Sleep Disturbance, Skin Rash, Herpes Zoster, Lymphadenopathy, Hair changes, oral thrush, Leukoplakia, Liver enlargement, Spleen enlargement, Weight of patient and Tuberculosis.

• Physician and Patient Overall Assessment scale were used to evaluate the efficacy and safety/ tolerability of RECEPTOL® liquid at the end of the treatment.

7.3.4 STUDY PLAN

a) Study Design: Observational study

b) Population: 5000 cases

c) Methods: The trial was a 1-Month, observational Study of Swine Flu like symptoms observed at Mumbai International Airport during 2009-2010 Swine Flu pandemic to determine the Efficacy & Safety Of RECEPTOL® Oral Spray Used As a Stand-Alone Mono Therapy. The potential subjects were screened after obtaining a written informed consent from (As per Schedule Y) the subject or LAR (Legally Acceptable Representative)/impartial witness. The study was designed to investigate efficacy of RECEPTOL® therapy for change in body weight. The study subjects received RECEPTOL® as a spray self-administered by patients on either side of the oral buccal surface 4 times daily at every 4 hour's interval. Each administration consist a metered dose of 0.75 ml spray directly on the buccal mucosa. Subjects' body weights were monitored at every visit to determine the effect of RECEPTOL® therapy on change in the weight.

7.3.5 RESULT

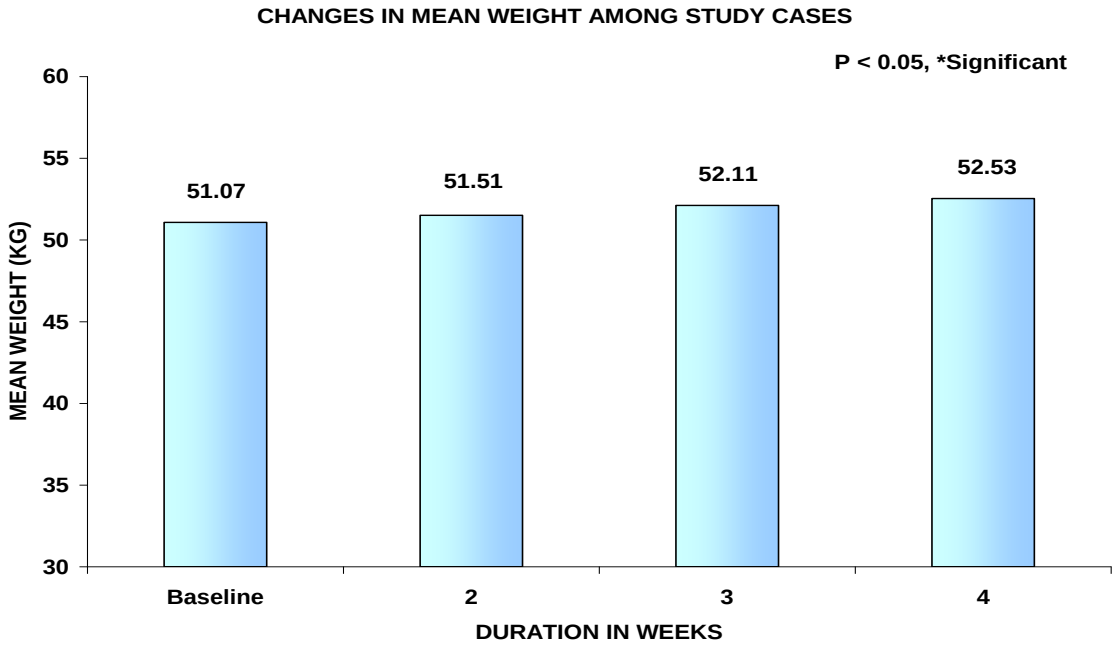
Table 1.6: CHANGES IN MEAN WEIGHT AMONG STUDY CASES

Duration (Weeks)	**Mean weight ($\overline{X} \pm$ SD) (N = 5000)**
Baseline	51.07 ± 9.82
2	*51.51 ± 9.79
3	*52.11 ± 9.75
4	*52.53 ± 9.76

By ANOVA P < 0.05, * Significant

- As per this data mean weight at baseline was **51.07kg.**
- At the end of 2nd week, mean weight showed significant change from baseline i.e. mean change of 1.44 kg.
- At the end of 4th week mean weight increased significantly that is 1.46 kg from baseline.

- **Figure 1.5:**



According to above figure, after RECEPTOL treatment mean weight significantly increases from week 2 onwards till end of treatment from baseline

Table 1.7:

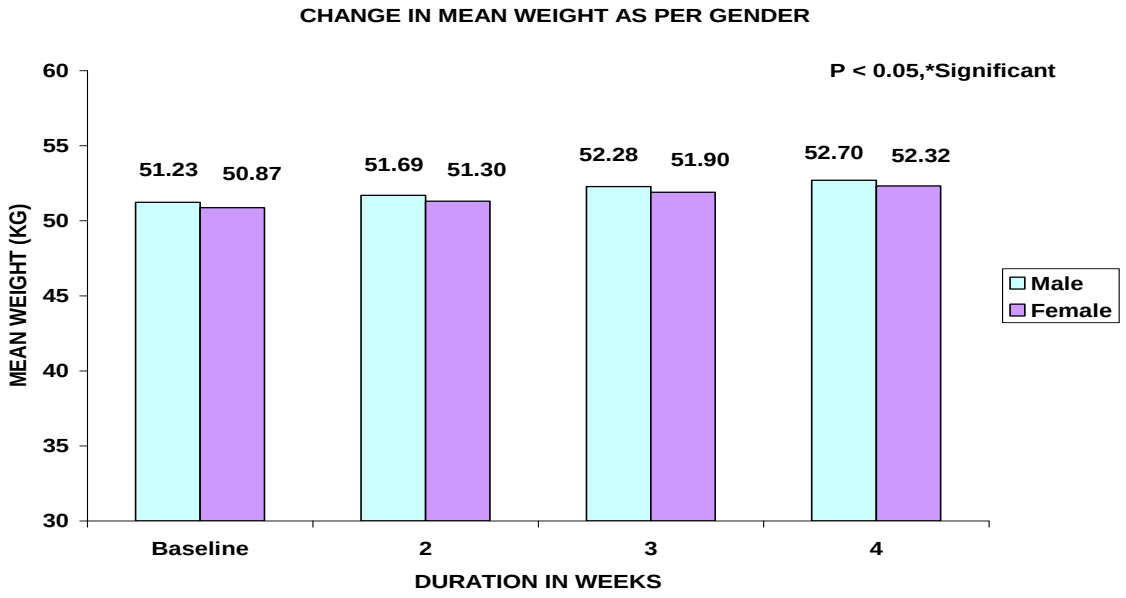
CHANGE IN MEAN WEIGHT AS PER GENDER

Duration (Weeks)	Mean weight ($\bar{X} \pm SD$)	
	Male (N = 2745)	Female (N = 2255)
Baseline	51.23 ± 9.82	50.87 ± 9.81
2	*51.69 ± 9.80	*51.30 ± 9.77
3	*52.28 ± 9.76	*51.90 ± 9.74
4	*52.70 ± 9.77	*52.32 ± 9.74

By ANOVA *P < 0.05, Significant

According to above data at baseline, mean weight was **51.23kg** among male cases which was comparable with **50.87kg** among female and the difference was not statistically significant. After 2nd week onwards mean weight showed increase in both the groups from baseline till the end of treatment.

Figure 1.6:



Above figure showed after treatment of RECEPTOL, there was significant change in weight among both the gender from baseline to end of treatment.

7.3.6. CONCLUSION

This observation study reveals that after RECEPTOL Oral Spray therapy, mean weight of study cases showed significant increase from baseline to end of treatment and these weight gain changes were observed in both the genders.

Hence these results showed that RECEPTOL oral spray is very effective and safe in Swine Flu cases to increase the weight and overall wellness.

7.4 An observational Study of Other Indications like Allergy, Asthma, Arthritis, Diarrhoea, Fever, Fatigue-malaise, Anaemia, Endometriosis etc. for Efficacy & Safety Of RECEPTOL® Oral Spray Used As a Stand-Alone Mono Therapy

7.4.1 Title

A STAND-ALONE, single arm, open label, 1 month study in 5,000 subjects to determine efficacy & safety of treatment with RECEPTOL® on weight changes in subjects with Indications like Allergy, Asthma, Arthritis, Diarrhea, Fever, Fatigue-malaise, Anemia, Endometriosis etc.

7.4.2 OBJECTIVES

Primary Objective
To evaluate the efficacy of RECEPTOL® liquid in Healthy People in terms of weight gain as weight gain is the indication of overall wellness.

Secondary Objectives
To determine the effect of oral spray administration of RECEPTOL® liquid on:
• Overall Assessment of Efficacy and Safety/Tolerability of the RECEPTOL®.

7.4.3 METHODOLOGY

• This trial was a 1-Month, Stand-Alone, single arm, open label study to evaluate the Efficacy and Safety/Tolerability of RECEPTOL® liquid in Healthy People.

• The potential subjects were screened after obtaining a written informed consent from (As per Schedule Y) the subject or LAR (Legally Acceptable Representative)/impartial witness.

• The study was designed to investigate efficacy of RECEPTOL® therapy in reducing Viral Load and clinical symptoms & change in body weight.

• The study subjects received RECEPTOL® liquid as a spray self-administered by patients on either side of the oral buccal surface 4 times daily at every 4 hour's interval. Each administration consist a metered dose of 0.75 ml spray directly on the buccal mucosa.

• Subjects' body weight was monitored at every visit to determine the effect of RECEPTOL® therapy on change in the weight.

• The subjects were also assessed for clinical symptoms and physical findings which included Health Populatin with frequent recurrent infections related Fatigue/Malaise, Diarrhoea, Nausea, Vomiting, Fever, Cough, Parasthesia Sleep Disturbance, Skin Rash, Herpes Zoster, Lymphadenopathy, Hair changes, oral thrush, Leukoplakia, Liver enlargement, Spleen enlargement, Weight of patient and Tuberculosis.

• Physician and Patient Overall Assessment scale were used to evaluate the efficacy and safety/ tolerability of RECEPTOL® liquid at the end of the treatment.

7.4.4 STUDY PLAN

a) Study Design: Observational study

b) Population: 5000 cases

c) Methods: This trial was a 1-Month, Stand-Alone, single arm, open label study to evaluate the Efficacy and Safety/Tolerability of RECEPTOL® oral spray in Healthy People. The potential subjects were screened after obtaining a written informed consent from (As per Schedule Y) the subject or LAR (Legally Acceptable Representative)/impartial witness. The study was designed to investigate efficacy of RECEPTOL® therapy in change in body weight. The study subjects received RECEPTOL® as a spray self-administered by patients on either side of the oral buccal surface 4 times daily at every 4 hour's interval. Each administration consist a metered dose of 0.75 ml spray directly on the buccal mucosa. Body weight of subjects was monitored at every visit to determine the effect of RECEPTOL® therapy on change in the weight. The subjects were also assessed for clinical symptoms and physical findings which included Healthy Population with frequent recurrent infections related to Fatigue/Malaise, Diarrhoea, Nausea, Vomiting, Fever, Cough, Parasthesia Sleep Disturbance, Skin Rash, Herpes Zoster, Lymphadenopathy, Hair changes, oral thrush, Leukoplakia, Liver enlargement, Spleen enlargement, Weight of patient and Tuberculosis.

7.4.5. RESULT

Table 1.8:

CHANGES IN MEAN WEIGHT AMONG STUDY CASES

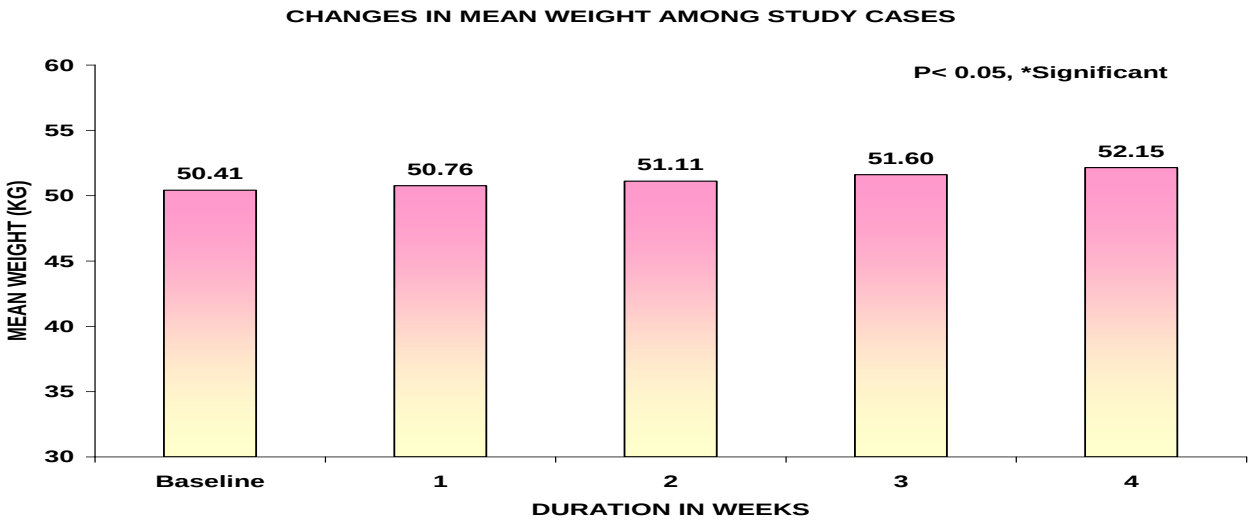
Duration (Weeks)	**Mean weight ($\bar{X}$ ± SD) (N = 5000)**
Baseline	50.41 ± 10.03
1	50.76 ± 10.01
2	51.11 ± 09.94
3	51.60 ± 09.91
4	52.15 ± 09.91
Mean Diff. (Baseline – Wk1) (P value)	*00.35 ± 00.57 (0.001)

Mean Diff. (Baseline – Wk2) (P value)	*00.70 ± 01.05 (0.001)
Mean Diff. (Baseline – Wk3) (P value)	*01.19 ± 01.77 (0.001)
Mean Diff. (Baseline – Wk4) (P value)	*01.74 ± 01.95 (0.001)

By ANOVA * Significant

- This analysis states that mean weight at baseline was **50.41kg.**
- After 1 week of treatment, mean weight showed a significant rise of **0.7%** from baseline.
- After 2 week of treatment, mean weight showed a significant rise of **1.4%** from baseline. Same trend was observed till the end of 4 weeks.

- **Figure 1.7:**



According to above figure, after RECEPTOL treatment mean weight significantly increases from week 2 onwards till end of treatment with respect to baseline

Table 1.9:

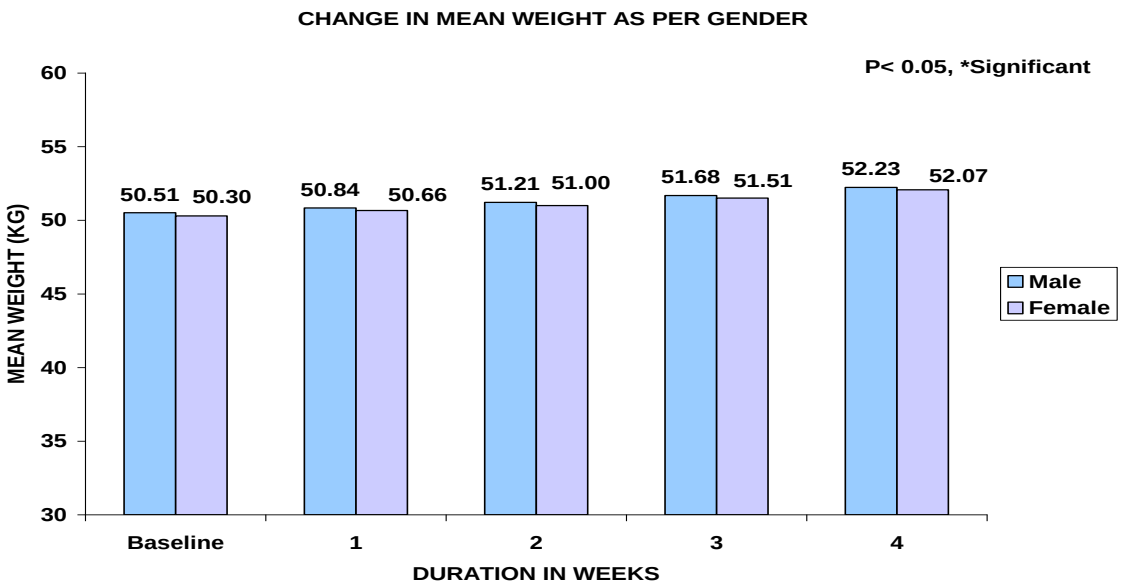
CHANGE IN MEAN WEIGHT AS PER GENDER

Duration (Weeks)	Mean weight ($\overline{X} \pm SD$)		P Value
	Male (N = 2693)	Female (N = 2307)	
Baseline	50.51 ± 09.96	50.30 ± 10.11	0.461 NS
1	50.84 ± 09.93	50.66 ± 10.10	
2	51.21 ± 09.88	51.00 ± 10.02	
3	51.68 ± 09.84	51.51 ± 10.00	
4	52.23 ± 09.87	52.07 ± 09.95	
Mean Diff. (Baseline – Wk1) (P value)	*00.33 ± 00.57 (0.001)	*00.36 ± 00.57 (0.001)	0.077 NS
Mean Diff. (Baseline – Wk2) (P value)	*00.70 ± 00.86 (0.001)	*00.70 ± 01.24 (0.001)	0.866 NS
Mean Diff. (Baseline – Wk3) (P value)	*01.17 ± 01.39 (0.001)	*01.21 ± 02.13 (0.001)	0.475 NS
Mean Diff. (Baseline – Wk4) (P value)	*01.72 ± 02.13 (0.001)	*01.77 ± 01.72 (0.001)	0.327 NS

By ANOVA * Significant NS = Not Significant

- This analysis reveals that mean weight at baseline was **50.51kg** in males which was comparable to **50.33kg** in females and the difference was not significant.
- After 1 week of treatment, mean weight showed a significant increase of **0.7%** among male and female each from baseline. If compared the increase was same among both the Group and difference was not significant.
- Same trend was observed till the end of 4 weeks.

Figure 1.8:



Above figure showed after treatment with RECEPTOL, there was significant change in weight among both the genders from baseline up to the end of treatment.

7.4.6. CONCLUSION

This observation study reveals that after RECEPTOL Oral Spray therapy, mean weight of study cases showed significant increase from baseline to end of treatment and that change were in both the genders.

Hence these results showed that RECEPTOL oral spray is very effective and safe among cases with other indications like Allergy, Asthma, Arthritis, Diarrhoea, Fever, Fatigue-Malaise, Anaemia, Endometriosis etc. to increase the weight and for overall wellness.

7.5 An Interventional / Prospective Phase III (1 Year Duration) Accelerated Study to Determine the Efficacy & Safety of RECEPTOL® Liquid Spray used as A Stand-Alone Mono Therapy in HIV / AIDS Patients with multiple symptoms

7.5.1 Title

An Interventional / Prospective Phase III (1 Year Duration) Accelerated Study to Determine the Efficacy & Safety of RECEPTOL® Liquid Spray used as A Stand-Alone Mono Therapy in HIV / AIDS Patients with multiple symptoms

7.5.2 OBJECTIVES

Primary Objective

To evaluate the efficacy of RECEPTOL® liquid in HIV/AIDS patients in terms of reduction in HIV viral load and HIV/AIDS related clinical symptoms.

Secondary Objectives

To determine the effect of oral spray administration of RECEPTOL® liquid on:

- Change in Body Weight of patients
- Absolute CD4 & CD8 cell count

Overall Assessment of Efficacy and Safety/Tolerability of RECEPTOL®.

7.5.3 METHODOLOGY

- This trial was a 365 days, single arm, open label study to evaluate the Efficacy and Safety of RECEPTOL® liquid in patients with advanced disease (HIV/AIDS).
- The study was designed to investigate efficacy of RECEPTOL® therapy in reducing Viral Load and increasing the absolute CD4 and CD8 counts.
- The study subjects received RECEPTOL® liquid as a spray self-administered by patients on either side of the oral buccal surface every 6 hours for a period of 365 days.

7.5.4 STUDY PLAN

a) Study Design: An interventional / Prospective study

b) Population: 60 cases

c) Methods: This trial was a 12-Months, Stand-Alone, single arm, open label study to evaluate the Efficacy of Receptol liquid spray in HIV/ AIDS patients. The potential subjects were screened after obtaining a written informed consent from (As per Schedule Y) the subject or LAR (Legally Acceptable Representative)/impartial witness. The study was designed to investigate efficacy of Receptol liquid therapy to increase in Absolute CD4 cell count & change in body weight. The study subjects received Receptol as a spray self-administered by patients on either side of the oral buccal surface 4 times daily at every 4 hour's interval. Each administration consist a metered dose of 0.75 ml spray directly on the buccal mucosa. Subjects' body weight was monitored at every visit to determine the effect of Receptol liquid therapy on change in the weight and CD4 count.

7.5.5 RESULT

Table 1.10:

PROFILE OF MEAN CD4 COUNTS AMONG STUDY CASES

Duration (months)	Mean CD4 count ($\overline{X}$ ± SD) (N = 60)
Baseline	265.95 ± 151.63
1	310.33 ± 151.60
2	371.40 ± 158.38
3	428.55 ± 163.92
4	479.55 ± 172.81
5	541.48 ± 192.57
6	588.70 ± 196.49
7	641.28 ± 212.33
8	691.15 ± 226.13
9	742.28 ± 243.50
10	796.58 ± 257.41
11	859.33 ± 272.31
12	955.58 ± 298.27

Above table reveals that mean CD4 count was **265.95** at baseline.

Table 1.11:

CHANGES IN MEAN CD4 COUNTS AMONG STUDY CASES

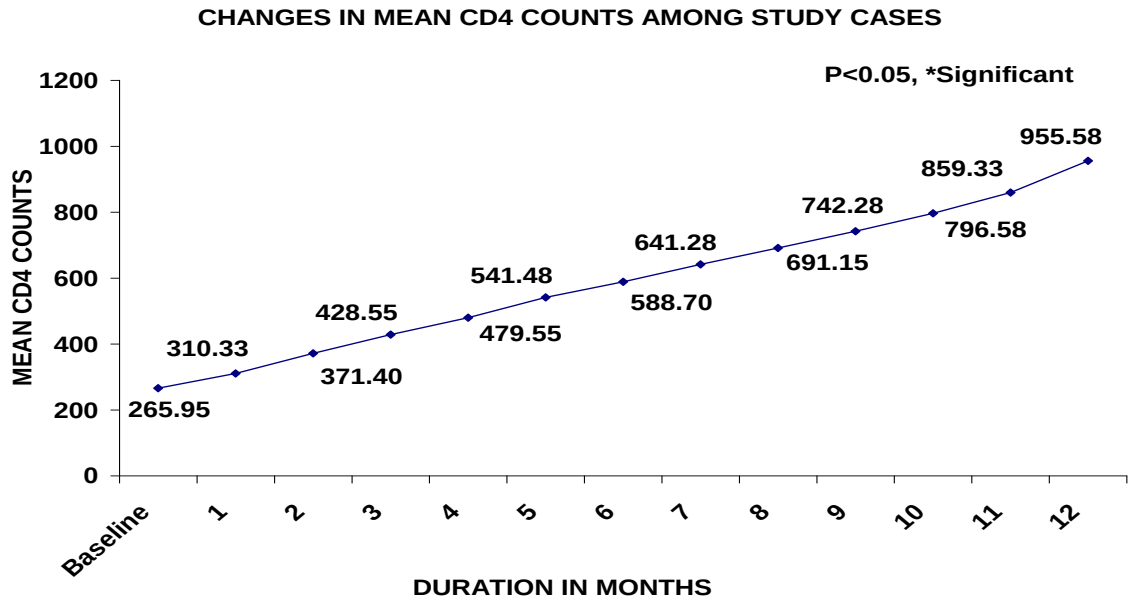
Duration (months)	**Mean CD4 counts ($\overline{X}$ ± SD) (N = 60)**
Diff (Baseline – 1) (P value)	*044.38 ± 041.09 (0.001)
Diff (Baseline – 2) (P value)	*105.45 ± 080.47 (0.001)
Diff (Baseline – 3) (P value)	*162.60 ± 106.78 (0.001)
Diff (Baseline – 4) (P value)	*213.60 ± 128.38 (0.001)

Diff (Baseline – 5) (P value)	*275.53 ± 162.29 (0.001)
Diff (Baseline – 6) (P value)	*322.75 ± 177.10 (0.001)
Diff (Baseline – 7) (P value)	*375.33 ± 200.20 (0.001)
Diff (Baseline – 8) (P value)	*425.20 ± 219.85 (0.001)
Diff (Baseline – 9) (P value)	*476.33 ± 241.64 (0.001)
Diff (Baseline – 10) (P value)	*530.63 ± 260.67 (0.001)
Diff (Baseline – 11) (P value)	*593.38 ± 278.82 (0.001)
Diff (Baseline – 12) (P value)	*689.63 ± 311.98 (0.001)

By ANOVA *Significant

- After 1 month of treatment, mean CD4 count showed a significant rise of **16.7%** from baseline.
- Same trend was observed at the end of 12 months of treatment.

Figure 1.9:



As per this figure, mean CD4 count significantly increased after treatment of Receptol liquid spray from 1 month onwards till end of treatment from baseline.

Table 1.12:

PROFILE OF MEAN WEIGHT AMONG STUDY CASES

Duration (months)	Mean Weight (kg) ($\overline{X} \pm SD$) (N = 60)
Baseline	53.13 ± 9.55
1	53.75 ± 9.51
2	54.47 ± 9.50
3	55.28 ± 9.54
4	56.28 ± 9.26
5	56.66 ± 9.57
6	57.37 ± 9.59
7	58.10 ± 9.75
8	58.79 ± 9.70
9	59.58 ± 9.82
10	60.27 ± 9.73
11	61.11 ± 9.83
12	62.11 ± 9.75

According to this data, mean weight was **53.13 kg** at baseline.

Table 1.13:

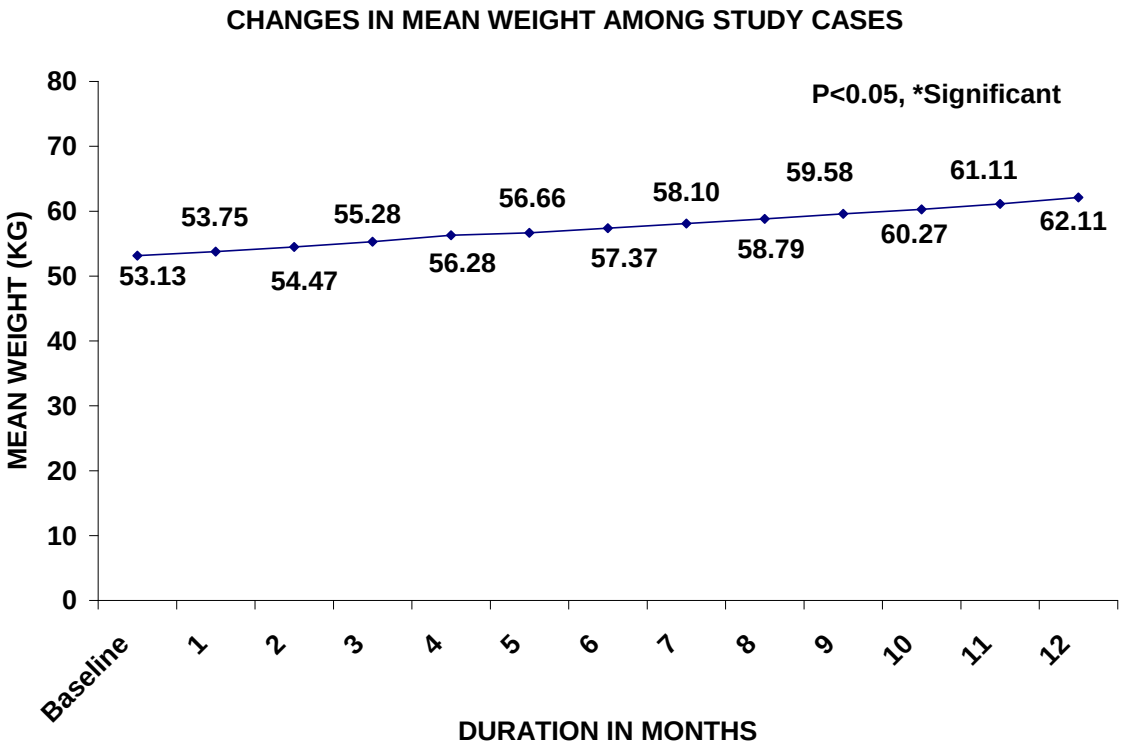
CHANGES IN MEAN WEIGHT AMONG STUDY CASES

Duration (months)	**Mean Weight (kg) ($\bar{X}$ ± SD) (N = 60)**
Diff (Baseline – 1) (P value)	0.62 ± 0.48
Diff (Baseline – 2) (P value)	1.34 ± 0.75
Diff (Baseline – 3) (P value)	2.15 ± 0.94
Diff (Baseline – 4) (P value)	2.83 ± 1.16
Diff (Baseline – 5) (P value)	3.53 ± 1.37
Diff (Baseline – 6) (P value)	4.24 ± 1.58
Diff (Baseline – 7) (P value)	4.97 ± 1.77
Diff (Baseline – 8) (P value)	5.66 ± 1.99
Diff (Baseline – 9) (P value)	6.45 ± 2.12
Diff (Baseline – 10) (P value)	7.13 ± 2.19
Diff (Baseline – 11) (P value)	7.97 ± 2.48
Diff (Baseline – 12) (P value)	8.97 ± 2.81

By ANOVA *Significant

- After 1 month of treatment, mean Weight showed a significant rise of **1.2%** from baseline.
- Same trend was observed at the end of 12 months of treatment.

Figure 1.10:



The above figure indicates that mean weight significantly increased after treatment of Receptol liquid spray from 1 month onwards till end of treatment from baseline

7.5.6. CONCLUSION:

The results of this an interventional / Prospective study reveals that after RECEPTOL Oral Spray therapy, average CD4 count and mean weight of study cases showed significant increase from baseline to end of treatment.

Hence we can conclude that, RECEPTOL is very effective and safe among HIV/AIDS cases to increase the weight and overall wellness.

7.6 An Interventional / Prospective Phase III (12 week duration) Accelerated Study To Determine The Efficacy and safety Of RECEPTOL® Liquid Spray Used As A Stand-Alone Mono Therapy in HIV / AIDS Patients With Multiple Symptoms

7.6.1. Title

An Interventional / Prospective Phase III (12 week duration) Accelerated Study to Determine the Efficacy and safety Of RECEPTOL® Liquid Spray Used As A Stand-Alone Mono Therapy in HIV / AIDS Patients With Multiple Symptoms

7.6.2 OBJECTIVES

Primary Objective

To evaluate the efficacy of RECEPTOL® liquid in HIV/AIDS patients in terms of reduction in HIV viral load and HIV/AIDS related clinical symptoms.

Secondary Objectives

To determine the effect of oral spray administration of RECEPTOL® liquid on:

- Change in Body Weight of patients
- Absolute CD4 cell count
- Overall Assessment of Efficacy and Safety/Tolerability of the RECEPTOL®.

7.6.3 METHODOLOGY

- This trial was a 12-week, Stand-Alone, single arm, open label study to evaluate the Efficacy and Safety/Tolerability of RECEPTOL® liquid in HIV/ AIDS patients.

- The potential subjects were screened after obtaining a written informed consent from (As per Schedule Y) the subject or LAR (Legally Acceptable Representative)/impartial witness.

- The study was designed to investigate efficacy of RECEPTOL® therapy in reducing Viral Load and clinical symptoms & increase in Absolute CD4 cell count & change in body weight.

- The study subjects received RECEPTOL® liquid as a spray self-administered by patients on either side of the oral buccal surface 6 times daily at every 4 hour's interval. Each administration consist a metered dose of 0.75 ml spray directly on the buccal mucosa.
- Subjects' body weight was monitored at every visit to determine the effect of RECEPTOL® therapy on change in the weight.

- The subjects were also assessed for clinical symptoms and physical findings which included HIV related Fatigue/Malaise, Diarrhea, Nausea, Vomiting, Fever, Cough, Parasthesia Sleep Disturbance, Skin Rash, Herpes Zoster, Lymphadenopathy, Hair changes, oral thrush, Leukoplakia, Liver enlargement, Spleen enlargement, Weight of patient and Tuberculosis.

- Physician and Patient Overall Assessment scale were used to evaluate the efficacy and safety/ tolerability of RECEPTOL® liquid at the end of the treatment.

7.6.4 STUDY PLAN

a) Study Design: An interventional / Prospective study

b) Population: 101 cases

c) Methods: This trial was a 12-week, stand-alone, single arm, open label study to evaluate the Efficacy of Receptol liquid spray in HIV/ AIDS patients. The potential subjects were screened after obtaining a written informed consent (As per Schedule Y) from the subject or LAR (Legally Acceptable Representative)/impartial witness. The study was designed to investigate efficacy of Receptol liquid therapy to increase in Absolute CD4 cell count & change in body weight. The study subjects received Receptol liquid as a spray self-administered by patients on either side of the oral buccal surface 6 times daily at every 4 hour's interval. Each administration consist a metered dose of 0.75 ml spray directly on the buccal mucosa. Subjects' body weight was monitored at every visit to determine the effect of Receptol liquid therapy on change in the weight.

7.6.5 RESULT

Table 1.14:

DEMOGRAPHIC DATA

Parameters	
No. of cases	**101**
Age (yrs) Mean SD Range	 33.91 09.24 21.00 – 60.00 yrs
Sex (%) Male Female	 44 (43.6) 57 (56.4)

- In this study, the age of the cases was ranging from **21.00 – 60.00 yrs** with average age being **33.91 yrs**.
- **43.6%** of the cases were male and **56.4%** of the cases were female.

Table 1.15:

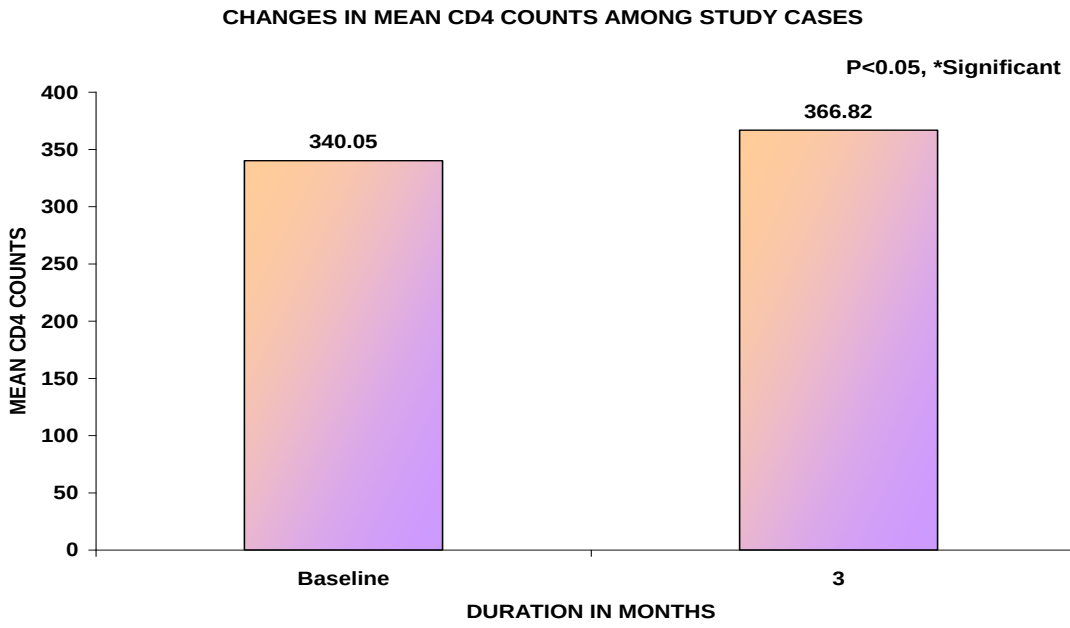
CHANGES IN MEAN CD4 COUNTS AMONG STUDY CASES

Duration (months)	Mean CD4 counts ($\overline{X}$ ± SD) (N = 101)	Median (Range)
Baseline	340.05 ± 161.10	307.00 (127.00 – 1156.00)
3	366.82 ± 181.90	333.00 (076.00 – 1234.00)
Diff (Baseline – 3 months) (P value)	*026.77 ± 119.73 (0.026)	-

By Student t test *Significant

This data reveals that at baseline median CD4 count was **307.0** After 3 months of treatment, median CD4 count (333.0) showed a significant rise of **7.9%** from baseline in average CD count.

Figure 1.11:



As per this figure, mean CD4 count significantly Increased after treatment with Receptol Liquid Spray from baseline to 3 months.

Table 1.16:

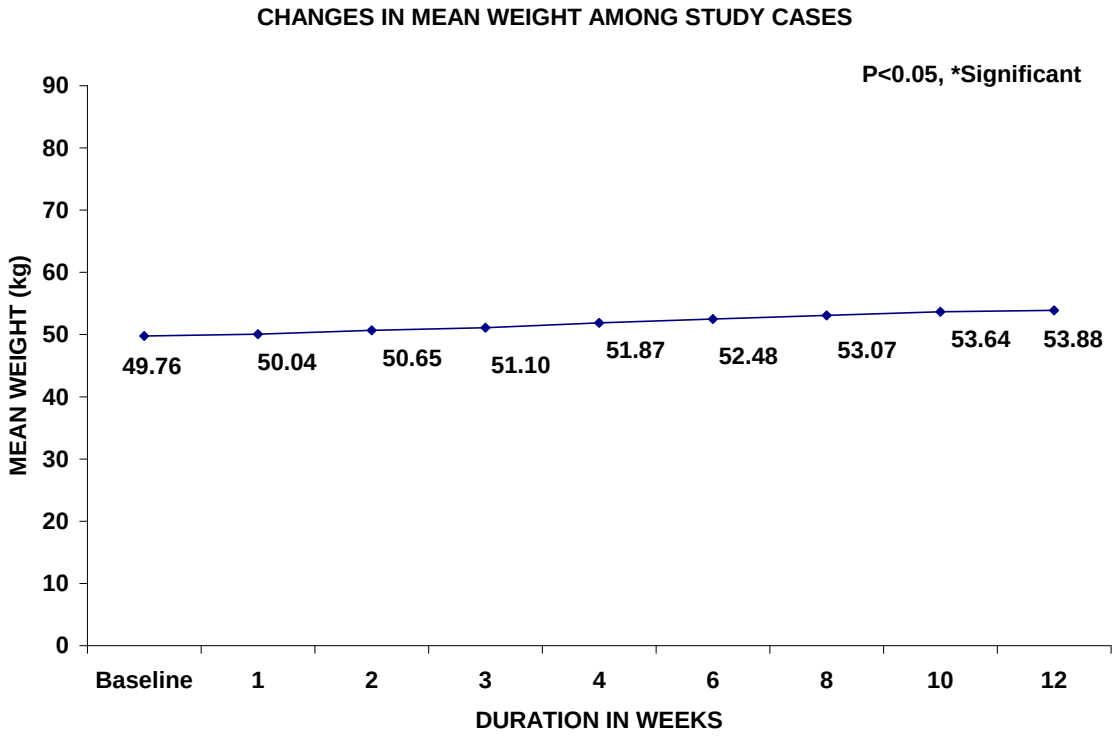
CHANGES IN MEAN WEIGHT AMONG STUDY CASES

Duration (week)	**Mean weight (kg) ($\overline{X}$ ± SD) (N = 101)**
Baseline	49.76 ± 12.33
1	50.04 ± 12.30
2	50.65 ± 12.20
3	51.10 ± 12.28
4	51.87 ± 12.18
6	52.48 ± 12.41
8	53.07 ± 12.33
10	53.64 ± 12.21
12	53.88 ± 12.16
Diff (Baseline – 1 wk)	*0.28 ± 0.67 (0.001)
Diff (Baseline – 2 wk)	*0.88 ± 1.07 (0.001)
Diff (Baseline – 3 wk)	*1.33 ± 2.33 (0.001)
Diff (Baseline – 4 wk)	*2.10 ± 1.66 (0.001)
Diff (Baseline – 6 wk)	*2.71 ± 8.38 (0.001)
Diff (Baseline – 8 wk)	*3.31 ± 2.05 (0.001)
Diff (Baseline – 10 wk)	*3.87 ± 2.16 (0.001)
Diff (Baseline – 12 wk)	*4.11 ± 2.09 (0.001)

By Student t test *Significant

- As per above data, mean weight was **49.76 kg** at baseline.
- After 1 week of treatment, mean weight showed a significant increased of **0.6%** from baseline.
- Same trend was observed at the end of week 12.

Figure 1.12:



According to above figure, mean weight significantly increased after treatment with Receptol liquid spray from week 1 onwards till end of treatment from baseline

7.6.6 CONCLUSION:

The results of this an interventional / Prospective study reveals that after RECEPTOL Oral spray therapy , average CD4 count and mean weight of study cases showed significant increase from baseline to end of treatment.

Hence we can conclude that, RECEPTOL is very effective and safe among HIV/AIDS cases to increase the weight and overall wellness.

8. Difference between Colostrum and Biomix Oral Spray (Receptol®), Liquid and Powder

Sr. No.	Colostrum	Biomix Oral Spray (Receptol®) and Biomix Liquid and Powder
1	Colostrum is a pre-milk substance produced from mother's breast of mammals during the first 24hours of lactation.	Biomix Oral Spray (Receptol®), Biomix Liquid and Biomix Powder are formulation containing nano-informative peptides isolated from mammalian colostrum having sequences SEQ-ID1-8 referred as Radha 108 series.
2	The peptides present in Colostrum are extremely sensitive to temperature, pH, stress and shear factors which pose several difficulties in their isolation and preserving their biological activity including method of collection of colostrum.	The unique manufacturing process of Biomix Oral Spray (Receptol®), Biomix Liquid and Biomix Powder ensures preservation of Biological active nano-peptides. These nano-peptides function to modulate cell immunity and provide attachment inhibition for foreign antigen/viruses on cell surface receptors. Due to low molecular weight these peptides easily cross BBB and treat host of diseases.
3	High temperature more than 100 degree C is used for the processing of colostrum which inactivates the Nanopeptides which are very important component for Immunity	In our patented process, Biomix Oral Spray (Receptol®) as well as powder is prepared at lower than 70 degree C temperature and at much low shear factor to protect physical and Biological activity of Nanopeptides
4	Colostrum contains only Immuno-globulin which has only short term immunity and does not treat or cure any serious diseases.	Biomix Oral Spray (Receptol®) as well as powder treat and prevent long term Immunity including 56 diseases listed in US Patent and 108 diseases in Europe and Asia including Singapore.
5	Colostrum is 100% pure bovine colostrum collected within 24 hours which contains fat, casein , SNF and Lactose	Biomix Oral Spray (Receptol®), Biomix Liquid and Biomix Powder are unique colostrum products specially prepared by removing fat. It is high quality colostrum product.
6	Colostrum typically provides 15% IgG by total dry weight	While Biomix Powder concentrated by the removal of fat, casein and Lactose provides a minimum of 40% IgG by total dry weight
7	Colostrum appears to be safe. But long term use may induce mild side effects such as an anxiety, logorrhea and insomnia and subsided spontaneously with a short period of time (3-4 days)	Biomix Oral Spray (Receptol®), Biomix Liquid and Biomix Powder are assessed as safe and effective for use in human population.

8	Colostrum has antioxidant properties, natural anti inflammatory properties and is source of many vitamins, minerals, enzymes and amino acids.	Biomix Oral Spray (Receptol®) and Biomix liquid are the class of peptides called Nano-Informational Peptides and Proline-Rich Polypeptides(PRPs)-RADHA1081-100, consisting of oligo-ribonucleotide attached to a peptide molecule. PRP is highly anti- inflammatory and also appears to action T-cell precursors to produce helper T- cells and suppressers T-cells.

8.1 Comparison of Biomix Oral Spray (Receptol®), Biomix Liquid and Biomix Powder with colostrum:

The generic Colostrum products are very less active as compared to the Biomix product as Biomix Product is available in different delivery systems like, Oral Spray, Liquid, Powder and Mouth melting strips which increases the bioavailability of active substances like Info-peptides, Radha 108 and PRP due to its unique patented manufacturing process.

Apart from it, Biomix Product has been approved under the Ayush with claims as under,

1) Build body's own immunity
2) Broad spectrum immune-modulator and anti-viral as Immunity booster
3) Clinically proven to keep sickness away
4) Total protection with 108 immunity supercharges and dependable immune power of Bovine Colostrum

In Generic Colostrum, all the above claims can't be proved as all the active ingredients are either in low concentration or in inactive form.

Biomix Product possesses following Immunity (+) Booster:

- Unique Nutraceutical that has shown Immune Boosting and rejuvenation results with feeling of overall wellness with prevention from many communicable ailments during International Scientific clinical studies in US, Africa and India"
- Packed with Radha108 immunity super chargers
- Reducing common infections like those of the stomach, nose and throat
- Health supplement proven to help keep sickness away. Improves Quality of Life.
- Receptol® is a scientifically proven pure natural product to keep sickness away via building body's own immune system through its broad spectrum immune modulator and anti-viral action.

9.0 Receptol® Indications (U.S. Patent No. 9,249,188 on February 02, 2016)

The RECEPTOL® oral spray consisting of Radha 108 Nanopeptides, which stimulates body's own immune system as a broadspectrum immunomodulator & antiviral to fight against several diseases listed in the following 5 groups & prevents communicable infections.

9.1 GROUPS: I

9.1.1. RECEPTOL® & Tuberculosis

About Tuberculosis

Tuberculosis is a chronic or acute bacterial infection caused by a rod-shaped bacterium, Mycobacterium tuberculosis. The organism primarily attacks the lungs, but may also affect the kidneys, bones, lymph nodes and central nervous system. Children and people with weakened immune systems are the most susceptible to the disease, with one-half of all untreated cases being fatal.

Tuberculosis is transmitted from person to person, usually via moisture droplets containing the bacterium. When an individual with active tuberculosis coughs, sneezes or speaks, small droplets containing 2-3 bacteria surrounded by a layer of moisture are released into the air and, if another person inhales these droplets, the bacteria may lodge in their lungs and multiply. The bacteria can also be transmitted through an open wound and, thus, are of concern to healthcare workers. Tuberculosis has also been reported in people who have received tattoos and in individuals who have been circumcised with non-sterile instruments.

If a person does contract the infection, the disease will develop in two stages.

Primary Stage:

In the first, or primary, stage, there are no noticeable symptoms and the disease is not contagious. White blood cells, primarily macrophages, ingest the bacteria and transport them to the lymph nodes where they may be either inhibited or destroyed or they may multiply.

If the bacteria are inhibited, white blood cells develop a wall around the inactive bacteria and form a mass, known as a granuloma or tubercle.

Secondary Stage:

In the secondary, or active, stage of the disease, the formerly dormant bacteria multiply in the lungs and may spread to other organs via the bloodstream. Tubercles continue to develop in the lung, allowing fluid or air to collect between the lungs and the lining of the lungs, and progressively destroying lung tissue. At this stage of the disease, the infected individual may cough blood or phlegm and carriers of the organism can infect others.

Symptoms of Tuberculosis:

The symptoms of tuberculosis range from no symptoms (latent tuberculosis) to symptoms of active disease. In fact, you may not even be aware that you have a latent TB infection until it's revealed through a skin test, perhaps during a routine checkup.
If you have active TB disease, you may have these symptoms:

- Overall sensation of feeling unwell
- Cough, possibly with bloody mucus
- Fatigue
- Shortness of breath
- Weight loss
- Slight fever
- Night sweats
- Pain in the chest

How RECEPTOL® Oral Spray helps with Tuberculosis

Scientific studies have shown that insulin-like growth factor (IGF-1), a major component of RECEPTOL®, and the IGF super family of proteins can restore and maintain a fully functional thymus, even in adults. In addition, RECEPTOL® contains the alpha and beta chains of the hormone thymosin that act independently and in concert to regulate the functions of the thymus.
Further, the Proline-rich peptide (PRP), also called thymulin, in RECEPTOL® is known to down-regulate the immune system and keep the response to a foreign substance under control. Other studies have shown that including only small amounts of RECEPTOL® in the daily diet of adult animals significantly enhances the ability of their white blood cells to respond to infection and destroy invading bacteria and viruses.

RECEPTOL® is an amazing resource of substances necessary to strengthen and support the immune system, potentiate the development and repair of cells and tissues; and assure the effective and efficient metabolism of nutrients.

"The Label claims are based on global studies on API: PRPs (Radha108 as class of PRPs being part of it) for which we have sent and up loaded claims on various indications based on published data in first rate Medical Journals. BMJ has accepted our two articles and two more are likely to be in leading Science Journal like NATURE by end of 2014 since our Global Medical Advisory Board has recommended to wait for follow up of patients who tried the product over 6 to 7 years a go and still have not shown any sign of disease reappearance, indicating that all Hibernation Viruses (crossing a window period of 8 years), including HIV have been stopped its reproduction leading to a possible claim for treatment & cure of AIDS & other major immune disorders, for which we have just received an approval for new US Product Patent as well".

References

1. Saharan P, Singh T. Efficacy and Safety/Tolerability clinical trial of RECEPTOL®: New Nanobiotechnology based Immunomodulator in RHEUMATOID ARTHRITIS therapy.Unpublished Patented data (2005-2006).

2. Khan A. Non-specificity of transfer factor. Annals of Allergy 38(5):320-322 (1977)

3. Immunology, Immunopathology and Immunity. Sell S. Appleton and Lange: Stamford CT 1996.

4. Andrew D, Aspinall R; Age-associated thymic atrophy is linked to a decline in IL-7 x 1996.

5. Aspinal R, Andrew D, Pido-Lopez J; Age associated changes in thymopoesis, Springer Semin Immunopathol 2002; 24(1): 87-101.

6. Binz K, et al; Repopulation of the atrophied thymus in diabetic rats by insulin-like growth factor-1, Proc Nat Acad Sci 1990; 87(10):3690-4.

7. Burgess W, et al; The immune-endocrine loop during aging: role of growth hormone and Insulin-like growth factor-1, Neuro-immunomodulation 1999; 6(1-2):56-68.

8. Clark R, et al; Insulin-like growth factor-1 stimulation of lymphopoesis, J Clin Invest 1993; 92(2): 540-8.

9. Fry TJ, Mackall CL; Current concepts of thymic aging, Springer Semin Immunopathol 2002; 92(2): 540-8.

10. Geffner M; Effects of growth hormone and insulin-like growth factor-1 on T- and B- Lymphocytes and immune function, Acta Pediatr 1997; 423:76-9.

11.Anon. Regulation (EC) No 853/2004 of the European Parliament and of the Council of 29 April 2004 laying down specific hygiene rules for food of animal origin. Official Journal of The European Communities L226. 2004. pp. 22–82. 25 June 2004 (including successive Amendments and corrigenda)

12. Anon. Pasteurisation: health risks from unpasteurised milk. [Internet] In Farm Industry Leaflets, Food Safety Authority of Ireland, Dublin;

13. Anon. Zoonotic tuberculosis and food safety. [Internet] Food Safety Authority of Ireland, Dublin; 2008.

14.Baker MG, Lopez LD, Cannon MC. et al. Continuing Mycobacterium bovistransmission from animals to humans in New Zealand. Epidemiology & Infection. 2006;134:1068–107315. Buckley J, McRory F, Mahony P. On farm study of consumption of unpasteurized milk.

15. Ancell CD, Phipps J, Young L; Thymosin alpha-1, Am J Health Sys Pharm 2001; 58(10): 879-85.

16. Andrew D, Aspinall R; Age-associated thymic atrophy is linked to a decline in IL-7 production, Exp Gerontol 2002; 37(2-3):455-63.

17. Aspinal R, Andrew D, Pido-Lopez J; Age associated changes in thymopoesis, Springer Semin Immunopathol 2002; 24(1): 87-101.

18. Binz K, et al; Repopulation of the atrophied thymus in diabetic rats by insulin-like growth factor-1, Proc Nat Acad Sci 1990; 87(10):3690-4.

19. Burgess W, et al; The immune-endocrine loop during aging: role of growth hormone and insulin-like growth factor-1, Neuro-immunomodulation 1999; 6(1-2):56-68.

20. Clark R, et al; Insulin-like growth factor-1 stimulation of lymphopoesis, J Clin Invest 1993; 92(2): 540-8.
21. Fry TJ, Mackall CL; Current concepts of thymic aging, Springer Semin Immunopathol 2002; 24(1): 7-22.

22.Geffner M; Effects of growth hormone and insulin-like growth factor-1 on T- and B-lymphocytes and immune function, Acta Pediatr 1997; 423:76-9.

23. Grimberg A, Cohen P; Role of insulin-like growth factors and their binding proteins in growth control and carcinogenesis, J Cell Physiol 2000; 183(1): 1-9.

24. Hwa V, Oh Y, Rosenfeld RG; The insulin-like growth factor binding protein (IGFBP) superfamily, Endocrin Rev 1999; 20(6): 761-87.

25. LeRoith D, Insulin-like growth factor receptors and binding proteins, Clin Endocrinol Metab 1996; **10**(1): 49-73.

26.Liu JL, LeRoith D; Insulin-like growth factor I is essential for post-natal growth in response to growth hormone, Endocrinology 1999; **140**(11): 5178-84. Skotiner V; Anabolic and tissue repair functions of recombinant insulin-like growth factors, Acta Pediat Scand 1990; **376**: S63-6.

27. Spagnoli A, Rosenfeld RG; The mechanisms by which growth hormone brings about growth. The relative contributions of growth hormone and insulin-like growth factors, Endocrinol Metab Clin North Am 1996; **10**(3): 615-31.

28. Herrera-Rodríguez SE, Gordiano-Hidalgo MA, López-Rincón G, Bojorquez-Narváez L, Padilla-Ramírez FJ, Pereira-Suárez AL, Flores-Valdez MA, Estrada-Chávez C.

29. Serrano-Moreno BA, Romero TA, Arriaga C, Torres RA, Pereira-Suárez AL, García-Salazar JA, Estrada-Chávez C. Zoonoses Public Health. 2008 Jun;55(5):258-66. doi: 10.1111/j.1863-2378.2008.01125.x.

30. Allen IC, McElvania-TeKippe E, Wilson JE, Lich JD, Arthur JC, Sullivan JT, Braunstein M, Ting JP. PLoS One. 2013;8(4):e60842. doi: 10.1371/journal.pone.0060842. Epub 2013 Apr 5.

31. Linde CM, Hoffner SE, Refai E, Andersson M. J Antimicrob Chemother. 2001 May;47(5):575-80. In vitro activity of PR-39, a proline-arginine-rich peptide, against susceptible and multi-drug-resistant Mycobacterium tuberculosis.

32. Runti G, Lopez Ruiz Mdel C, Stoilova T, Hussain R, Jennions M, Choudhury HG, Benincasa M, Gennaro R, Beis K, Scocchi M. J Bacteriol. 2013 Dec;195(23):5343-51. doi: 10.1128/JB.00818-13. Epub 2013 Sep 27.

33. Linde CM, Hoffner SE, Refai E, Andersson M. J Antimicrob Chemother. 2001 May;47(5):575-80.

34. An MJ, Cheon JH, Kim SW, Park JJ, Moon CM, Han SY, Kim ES, Kim TI, Kim WH. Nutr Res. 2009 Apr;29(4):275-80. doi: 10.1016/j.nutres.2009.03.011

9.1.2. RECEPTOL® & HIV

How RECEPTOL® Oral Spray helps in HIV

RECEPTOL® Safety, Efficacy & Acceptability

Receptol has been used with positive results in more than 20,500 patients globally for HIV, Tuberculosis, immunological diseases since its invention.

Preclinical Safety: as per **NIN** National Toxicology Panel

- **No Acute Toxicity & No Sub Chronic Toxicity**

Revalidation Phase III Indian Trials – Stand alone MONOTHERAPY with Receptol sponsored by Government of India, MOH/NACO and Monitored by ICMR/NARI*

- **Study I (2006-07)** : By GoI on 50 Patients at LTMG Hospital Sion, Mumbai (Clinical trial registry No. : CTRI-2012-08-002931)
- **Study II (2007-08)** : By GoI on 51 Patients at LTMG Hospital, Sion, Mumbai (Clinical Trial registry No. : CTRI-2012-09-002959)

•The study was fully controlled, conducted and sponsored , by Govt. of India, Biomix was facilitating the same & had no control on the specifications.

Safety and Efficacy Achieved by Global Trials:

Phase I : 12 cohort 30 days (completely safe) in Ohio, USA

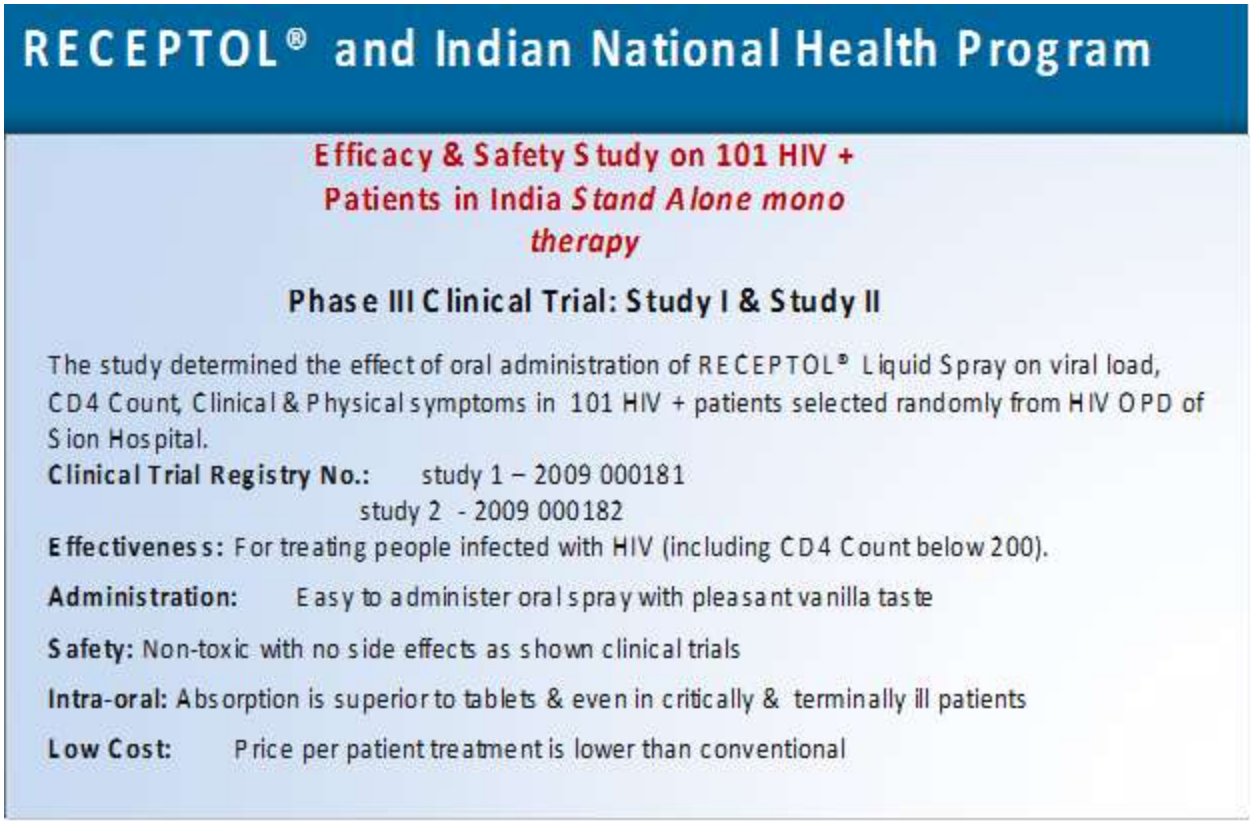
Phase II : 30 cohort 90 days (highly effective with no side effects)in Nairobi – Kenya

Phase III : 60 cohort for 365 days (highly effective with no side effects) in Rwanda, Africa

Safety & Efficacy data as per global study on Receptol®

KEY DIMENSIONS	PHASE I, II & III INTERNATIONAL TRIALS	INDIA PHASE III STUDY I	INDIA PHASE III STUDY II
Phase	Phase I – HIV trial, US Phase II – HIV trial, Nairobi, Kenya Phase III – HIV trial, Rwanda	Phase III validation trial by GOI on HIV patients, Standalone monotherapy	Phase III validation trial by GOI on HIV patients, Standalone monotherapy
No. of patients	Phase I – 12 cohorts Phase II – 30 cohorts Phase III – 60 cohorts	50 HIV seropositive patients	51 HIV seropositive patients
Duration	365/30 days	3 months	3 months
Compliance	Very good	Very good	Very good
Side effect	None	None	None
Weight gain	6 lbs average gain	4.73 kg per patient, p<0.05	4.68 ±1,9 kg per patient, p<0.001
Clinical symptoms	90 days relief from symptoms	Improved within 3 weeks from starting of therapy	Improved within 3 weeks from starting of therapy
CD4 cell count	Phase II: Average by 31	Average by 51, median CD4 cell count from 312 to 363 (p = 0.06)	On an average by 27 (p = 0.042)
HIV Viral load*	Phase II: Mean HIV log viral load from 4.6 to 2.5	Mean HIV log viral load from 4.63 to 4.18 (p = 0.001)	Mean HIV log viral load from 4.41 to 4.02 (p = 0.009)

Significant decrease in 3 months therapy documented in global and phase III trial in India. Viral load becomes undetectable after a period of 3 month in 20% patients and in all subjects in one year period for followed up patients over 5 years, in some cases up to 8years.

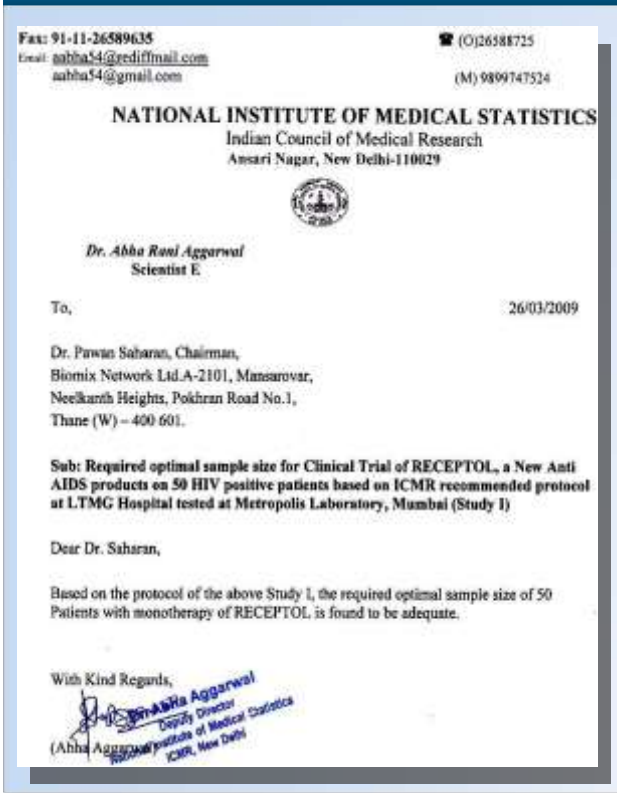


Sample size for phase III India study I & study II

- Based on the protocol of study I & study II, the sample size of 50 patients and 51 patients respectively with stand-alone mono therapy of RECEPTOL® for each study was found to be adequate by :
  - LTMMC & LTMG Hospital, Sion IRB (Ethics & Scientific Committee)
  - National Institute Of Medical Statistics, ICMR, New Delhi
  - Department of Health & Family Welfare Jan 12, 2005 Notification Based On Meeting with HFM, Secretary Heath, DGHS, DCGI, DG-ICMR.
  - NACO Research Committee Approval for Said Studies October 2005.
  - Report of Department of Biostatistics, AIIMS July 27, 2007.

Optimal sample size

Study 1



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Dr. Abha Rani Aggarwal
Scientist E

To, 26/03/2009

Dr. Pawan Saharan, Chairman,
Biomix Network Ltd.A-2101, Mansarovar,
Neelkanth Heights, Pokhran Road No.1,
Thane (W) – 400 601.

Sub: Required optimal sample size for Clinical Trial of RECEPTOL, a New Anti AIDS products on 50 HIV positive patients based on ICMR recommended protocol at LTMG Hospital tested at Metropolis Laboratory, Mumbai (Study I)

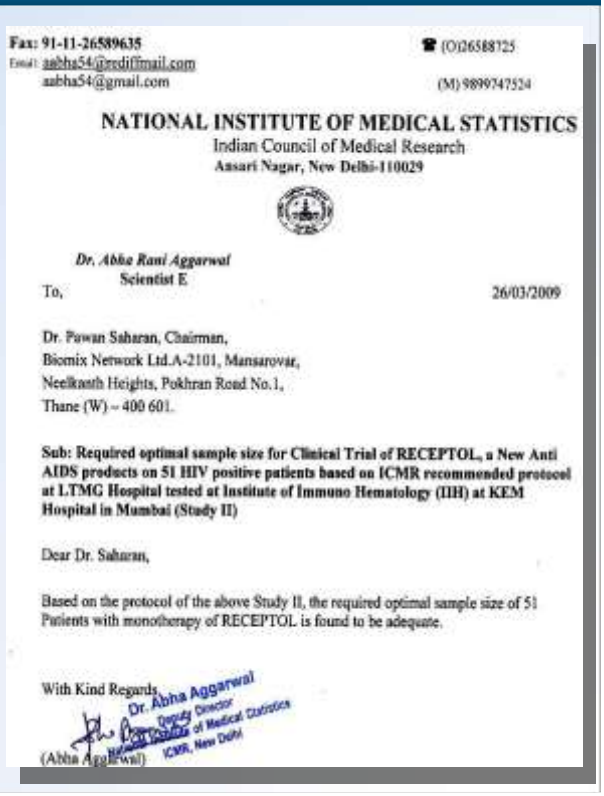
Dear Dr. Saharan,

Based on the protocol of the above Study I, the required optimal sample size of 50 Patients with monotherapy of RECEPTOL is found to be adequate.

With Kind Regards,

(Abha Aggarwal)

Study 2



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To, 26/03/2009

Dr. Pawan Saharan, Chairman,
Biomix Network Ltd.A-2101, Mansarovar,
Neelkanth Heights, Pokhran Road No.1,
Thane (W) – 400 601.

Sub: Required optimal sample size for Clinical Trial of RECEPTOL, a New Anti AIDS products on 51 HIV positive patients based on ICMR recommended protocol at LTMG Hospital tested at Institute of Immuno Hematology (IIH) at KEM Hospital in Mumbai (Study II)

Dear Dr. Saharan,

Based on the protocol of the above Study II, the required optimal sample size of 51 Patients with monotherapy of RECEPTOL is found to be adequate.

With Kind Regards,

(Abha Aggarwal)

RECEPTOL® Mono-therapy snapshot

Stand alone Mono-therapy Safety and Efficacy in HIV+ AIDS Patients:

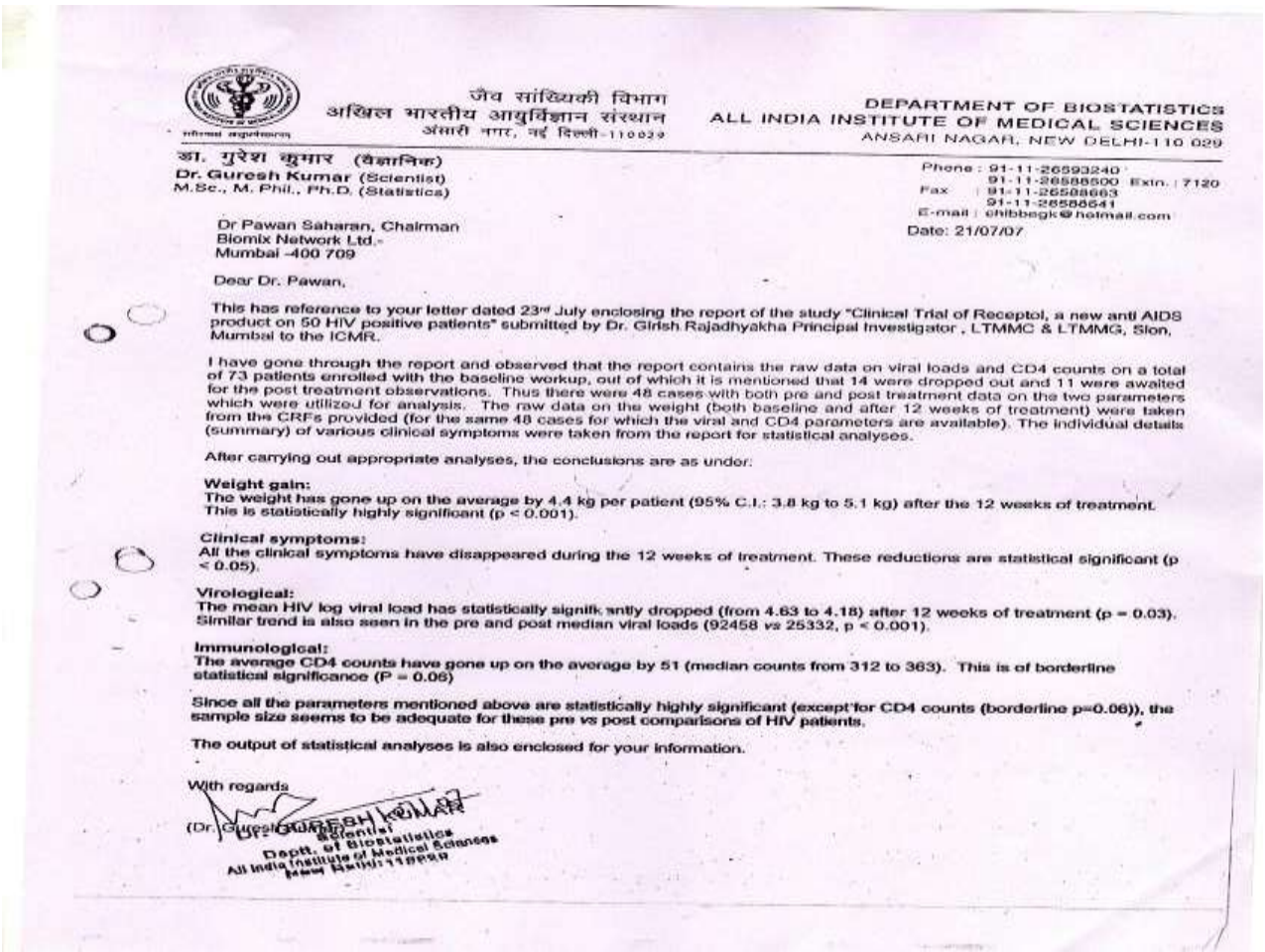
- Study I – Sion Hospital, Mumbai on 50 HIV+ Patients
  - Absolute CD4 cell count & HIV Viral Load – tested at NABL accredited Metropolis lab, Mumbai
  - Clinical & Physical symptoms study - at ART Center, OPD Center, Sion Hospital, Mumbai
  - Inclusion criteria – absolute CD4 cell count greater than 100 cells/mm3
  - Exclusion criteria – no pre- exposure to ART
  - Mean HIV log viral load has statistically significantly dropped ($p < 0.001$)
  - Statistically significant increase in CD4 cell count ($p = 0.06$)
  - Clinical symptoms disappeared in 3 weeks of treatment in All Patients ($p<0.05$)
  - Statistically significant weekly weight gain in All Patients ($p<0.001$).

Summary of study 1 data (Mumbai, India phase III)

Visit (Weeks)	No. of Subjects with Nausea	No. of Subjects with Vomiting	No. of Subjects with Fatigue/ Malaise	No. of Subjects with Diarrhea	No. of Subjects with Fever	No. of Subjects with Cough
1	8	7	44	9	12	14
2	3	2	32	5	3	10
3	2	2	26	1	6	6
4	1	1	17	1	1	3
6	0	1	1	0	0	1
8	0	0	1	0	0	2
10	0	0	1	0	0	0
12	0	0	0	0	0	0

Sr. No.	CD4 count N=48	Before	After 12 Weeks	p-value
1.	Median	312.5	363.5	0.06
2.	25th Percentile	275.5	294.2	
3.	75th Percentile	430	435	

Sr. No.	Parameter	Before	After 12 Weeks	p-value
1.	Log of HIV-1, RNA (N=34)	5.11(0.090)	4.103(1.32)	< 0.001
2.	Median	206057	25280	< 0.001
3.	25th Percentile	62884	1665	
4.	75th Percentile	508038	87511	



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Date: 21/07/07

Dr Pawan Saharan, Chairman
Biomix Network Ltd.
Mumbai -400 709

Dear Dr. Pawan,

This has reference to your letter dated 23rd July enclosing the report of the study "Clinical Trial of Receptol, a new anti AIDS product on 50 HIV positive patients" submitted by Dr. Girish Rajadhyakha Principal Investigator , LTMMC & LTMMG, Sion, Mumbai to the ICMR.

I have gone through the report and observed that the report contains the raw data on viral loads and CD4 counts on a total of 73 patients enrolled with the baseline workup, out of which it is mentioned that 14 were dropped out and 11 were awaited for the post treatment observations. Thus there were 48 cases with both pre and post treatment data on the two parameters which were utilized for analysis. The raw data on the weight (both baseline and after 12 weeks of treatment) were taken from the CRFs provided (for the same 48 cases for which the viral and CD4 parameters are available). The individual details (summary) of various clinical symptoms were taken from the report for statistical analyses.

After carrying out appropriate analyses, the conclusions are as under:

Weight gain:
The weight has gone up on the average by 4.4 kg per patient (95% C.I.: 3.8 kg to 5.1 kg) after the 12 weeks of treatment. This is statistically highly significant ($p < 0.001$).

Clinical symptoms:
All the clinical symptoms have disappeared during the 12 weeks of treatment. These reductions are statistical significant ($p < 0.05$).

Virological:
The mean HIV log viral load has statistically significantly dropped (from 4.63 to 4.18) after 12 weeks of treatment ($p = 0.03$). Similar trend is also seen in the pre and post median viral loads (92458 *vs* 25332, $p < 0.001$).

Immunological:
The average CD4 counts have gone up on the average by 51 (median counts from 312 to 363). This is of borderline statistical significance ($P = 0.06$)

Since all the parameters mentioned above are statistically highly significant (except for CD4 counts (borderline p=0.06)), the sample size seems to be adequate for these pre *vs* post comparisons of HIV patients.

The output of statistical analyses is also enclosed for your information.

With regards

(Dr. Guresh Kumar)
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Deptt. of Biostatistics
All India Institute of Medical Sciences
New Delhi-110029

RECEPTOL® Mono-therapy snapshot

- Study II – Sion Hospital, Mumbai on 51 AIDS Patients
  - Absolute CD4 cell count & HIV Viral Load – tested at IIH (ICMR)
  - Clinical & Physical symptoms study - at ART Center, Sion Hospital
  - Inclusion criteria – absolute CD4 cell count greater than 100 cells/mm3 and 100% symptomatic patients at basal.
  - Exclusion criteria – no pre- exposure to ART
  - Mean HIV log viral load has statistically significantly dropped ($p < 0.009$)
  - Statistically significant increase in CD4 cell count ($p < 0.042$)
  - Clinical symptoms disappeared in 3 weeks of treatment in All Patients ($p<0.001$)
  - Statistically significant weekly weight gain in All Patients ($p<0.001$).

Summary of study 2 data (Mumbai, India phase III)

Clinical Symptoms	N	At Baseline	Responders At Week-2
Diarrhea	51	51(100%)	12(23.53%)
Nausea	51	51(100%)	3(5.9%)
Vomiting	51	51(100%)	17(33.3%)
Fever	51	51(100%)	13(25.5%)
Cough	51	51(100%)	13(25.5%)
Paraesthesia	51	51(100%)	16(31.4%)
Disturbed Sleep	51	51(100%)	0(0%)
Skin Rash	51	51(100%)	7(13.7%)
Fatigue/Malaise	51	51(100%)	51(100%)
Herpes Zoster	51	51(100%)	18(35.3%)
Hair Changes	51	51(100%)	16(31.4%)
Leukoplakia	51	51(100%)	5(9.8%)
Oral Thrush	51	51(100%)	51(100%)

Parameter	Baseline Mean ± SD	Week 12 Mean ± SD	Difference (Week 12- Baseline) Mean ± SD	P-value
CD4 Counts (cells/ cmm)	317.16 ± 128.67	344.24 ± 165.79	+ 27.08 ± 92.47	0.042
CD8 Counts (cells / cmm)	1037.06 ± 285.02	1139.75 ± 386.76	+102.69 ± 267.44	0.008

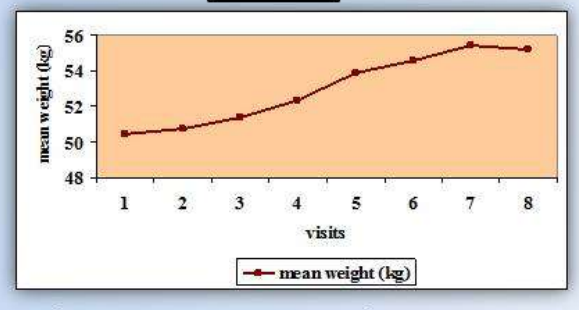
Indian Study : STAND ALONE MONOTHERAPY

SION HOSPITAL MUMBAI

Weight gain after treatment

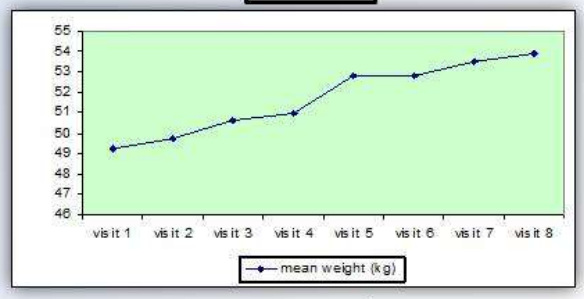
Statistically significant gain in weight p<0.05 in both the Study I and Study II

Study 1



Study I : average weight gain of **4.73 kg** after 12 weeks of Radha 108 therapy. statistically significant ($p < 0.05$)
Mean weight was **50.48 kg** at start of study.

Study 2

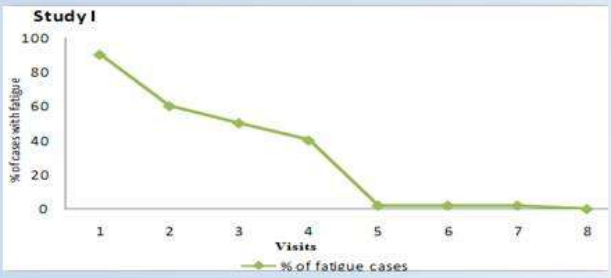


Study II : average weight gain of **4.68 ± 1.9** kg after 12 weeks of Radha108 therapy. statistically significant ($p < 0.05$)
Mean weight was **49.21kg** at start of study and **53.89 kg** after 12 wks.

Data on chronic fatigue syndrome after therapy

Statistically significant reduction in Fatigue / Malaise in both the Study I and Study II

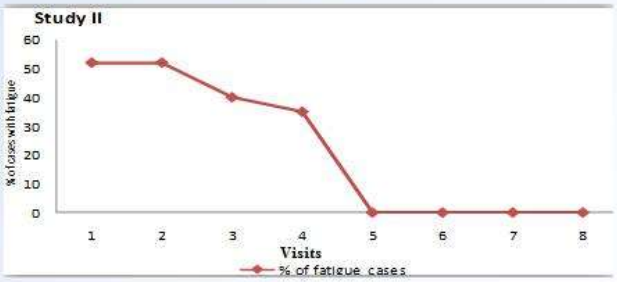
Study 1



Study I:

- 88 % of the total study cases had fatigue at basal.
- After 6th week onwards only one or two patients had fatigue, statistically significant

Study 2



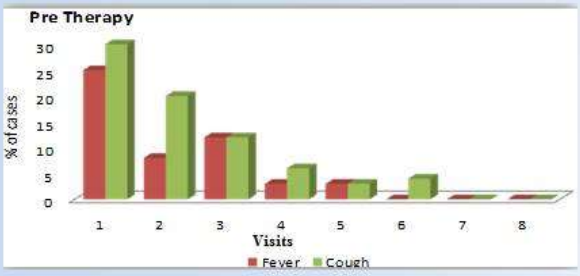
Study II:

- 100 % of the total study cases had a symptom of fatigue at basal. At the end of 2nd week proportion of symptoms of fatigue had a statistically significant fall from basal.

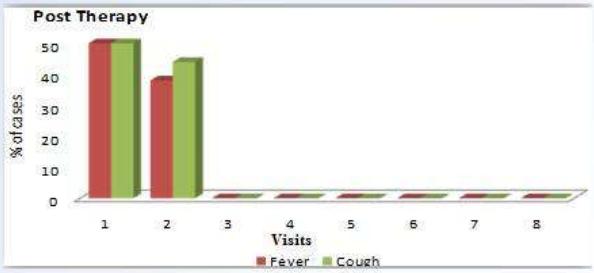
Data on fever & cough after Therapy

Statistically significant reduction in Fever and Cough in both the Study I and Study II

Study 1



Study 2



- Study I: Fever and cough was reported by 24 % and 28% of total study cases at basal respectively. After treatment at the end of 4th week proportion of patients with symptom of fever and cough had a statistically significant fall

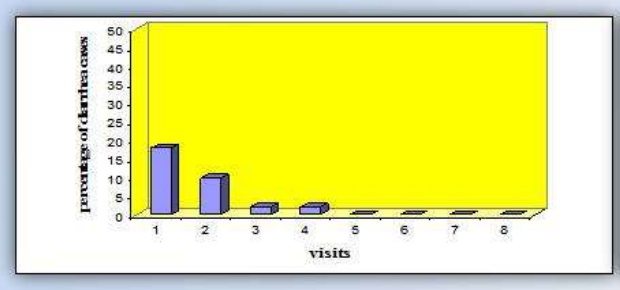
Study II: 100 % of the total study cases had fever and cough.

after treatment from 3rd week onwards all the patients had relief from fever and cough, statistically significant

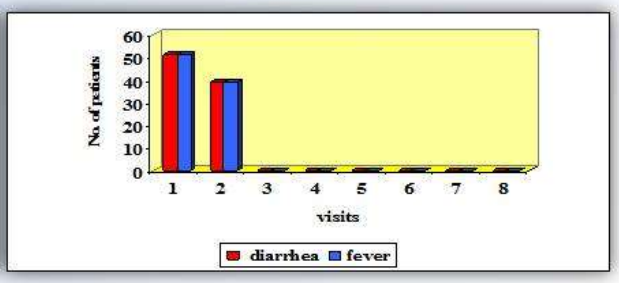
Data on Diarrhea after Therapy

Statistically significant reduction in Diarrhea in both the Study I and Study II

Study 1



Study 2



Study I: 18 % of the total study cases had diarrhea at basal and after treatment from 5th week onwards all the patients had relief from diarrhea, statistically significant

Study II: 100 % of the total study cases had diarrhea at basal and after treatment from 3rd week onwards all the patients had relief from diarrhea, statistically significant

Data on HIV viral load after Therapy

Statistically significant reduction in HIV Viral Load

Study 1

	Viral Load baseline	Viral Load 3 months
Mean	335278.23	141053.42
Median	92457.50	25332.50

Study I: The mean HIV log viral load has statistically significantly dropped from 4.63 to 4.18 after 12 weeks of treatment.
(p = 0.03)

Metropolis Health Services (I) PVT. LTD. Laboratory, Mumbai (NABL & CAP accredited)

Study 2

	Viral Load baseline	Viral Load 3 months
Mean	119243.49	38814.33
Median	38108.00	14073.00

Study II: The mean HIV log viral load has statistically significantly dropped from 4.41 to 4.02 after 12 weeks of treatment.
(p = 0.009)

Institute of Immuno Hematology (IIH), an ICMR Institute, KEM Hospital, Mumbai

Data on CD4 Cell Count after therapy

Statistically significant increase in CD4 Cell Count

Study 1

	CD4 baseline	CD4 3 months
Mean	370.63	390.65
Median	312.50	363.50

Study I: There was increase in CD4 count on the average by 51 (median CD4 cell counts from 312 to 363). this is of statistical significance
(p = 0.06)

Study 2

	CD4 baseline	CD4 3 months
Mean	317.16	344.24
Median	276.00	305.00

Study II: There was increase in CD4 count on the average by 27 (median CD4 cell counts from 276 to 305). This is of statistical significance
(p = 0.042)

Indian Phase III - Study I
Indicating resolution of TB symptoms in HIV+ subjects

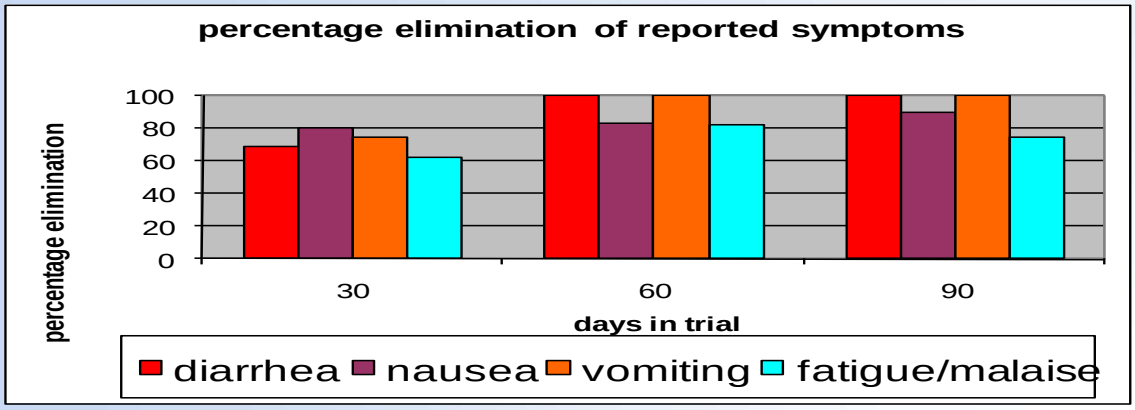
Duration (weeks)	Nausea	Vomiting	Disturbed sleep	Tuberculosis	Skin Rash	Herpes Zoster
1	8	7	13	6	7	6
2	3	2	8	0	2	2
3	2	2	3	0	1	1
4	1	1	1	0	0	0
6	0	1	0	0	0	0
8	0	0	1	0	0	0
10	0	0	0	0	0	0
12	0	0	0	0	0	0

Global Trial Results
Phase I – Ohio State University, USA

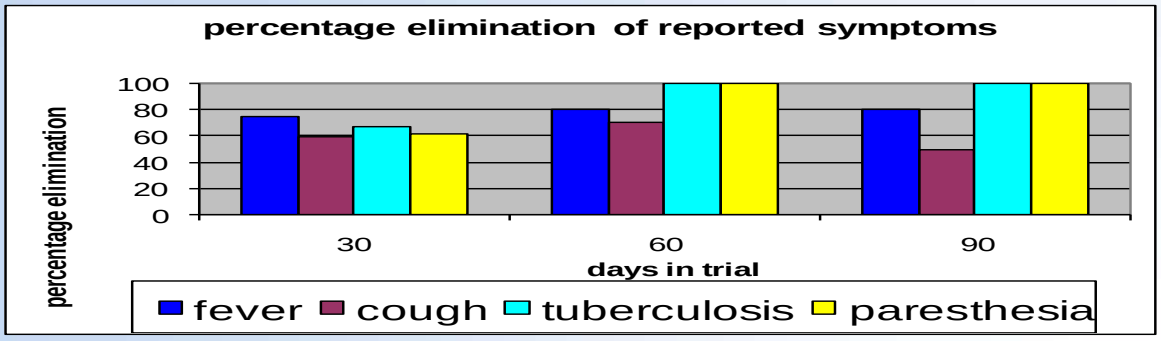
- 12 cohort, 30 days, moderate dose
- Patients may have previous exposure to AZT
- Balanced diet with vitamin-minerals provided
- 10 patients had weight gain and 7 patients had gained an average 6 lbs
- Highest weight gain was 12 lbs for a patient who was HIV positive for 10 years
- All 12 pt had improved symptom assessment score and average reduction approached 63 %

Free of side effects

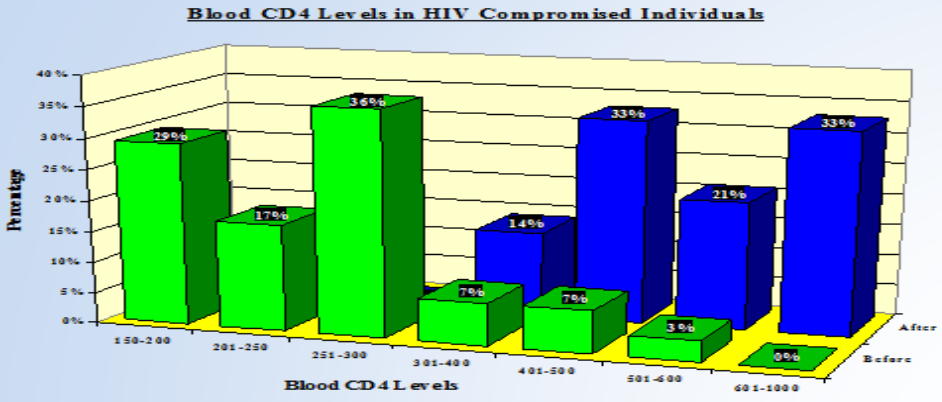
Phase I and II trial results



Phase I and II trial results



Summary of phase II – Nigeria



Phase III – Rawanda, Africa

- Safety and efficacy trial
- 60 AIDS patients – 365 days
- Patients were unaware of positive potential of drug
- Weight gain consistently observed
- After day 1 moderate level of relief of diarrhea and fever
- After 14 days, relief from skin lesion, mouth thrush, fever, diarrhea, tuberculosis symptoms
- After 90 days relief of all symptoms with increase in Absolute CD4 Counts & Reduction in Viral Load

No adverse effects observed over 12 months follow up with improved Quality of Life even after 5 years of therapy.

Highly Efficacious & Free of side effects

Comparative Study	Anti Retroviral Therapy (ART)	RECEPTOL (Complements ART)
Action	Attacks host's infected cells	Stimulate body's own defense mechanism against virus and infected cells
Weight	Weight loss is seen because of HIV itself and Nausea, vomiting due to ART, After a median follow-up of 18 months,17% patients developed lip dystrophy PI based regime. The Lancet, 357:9256, 592 - 598, 24 February 2001	Weight gain significant even within a week of starting therapy. Study one gain on average by 4.73 kg per patient after 3 month therapy :($p<0.001$) Study two: gain on the average by 4.68 ± 1.9 kg ($p<0.001$)
CD4 count	The emergence of drug resistance is a leading cause (as well as consequence) of antiretroviral therapy failure showing CD4 reduction Scand J Infect Dis Suppl. 2003 Dec;35 Suppl 106:61-6.	Increases over 12 weeks therapy, Study one - average by 51, median CD4 cell count from 312 to 363 ($p = 0.06$) Study two - on an average by 27 ($p = 0.042$)
Viral load	up to 25% of patients discontinue their initial HAART regimen because of treatment failure, toxic effects or noncompliance within the first 8 months of therapy – V Montessori and others. Adverse effects of antiretroviral therapy for HIV infection. Canadian Medical Association Journal 170 (2): 229-238. January 20, 2004.	Significant decrease in 3 months therapy documented in global and phase III trial in India. Viral load becomes undetectable after a period of 3 month in 20% patients and in all subjects in one year period for followed up patients over 5 years, in some cases up to 8years. .
Side effect	bloating, nausea and diarrhea, fatigue, headache uncommon but more serious: AZT-associated anemia, d4T-associated peripheral neuropathy, PI-associated retinoid toxicity and NNRTI-associated hypersensitivity reactions Serious: lactic acidosis, hepatic statuses, hyperlactatemia, hepatotoxicity, hyperglycemia, fat maldistribution, hyperlipidemia, bleeding disorders, osteoporosis and skin rash	All symptoms due to HIV & TB including diarrhea, nausea, vomiting, skin rashes resolved with in 3-5 weeks Natural product, safe and well tolerated)
Quality of life	compromised due to side effects, pill burden	Marked improvement in QoA with week after week consistent weight gain & drastic Improvement with relief of all symptoms in 3-4 wks for all patients

Comparative study between Receptol® and ART in India

This presentation describes the Comparative data from studies conducted on HIV positive patients using ART therapy vs Standalone Receptol® therapy.

GoI, Ministry of Health conducted studies with Receptol® on HIV patients at LTMMC & LTMG Hospital, Sion, Mumbai from 2005-2007 with follow up till 2014.

Receptol® Study I Standalone Monotherapy (2006-07) :
By GoI on 50 Patients at LTMMC & LTMG Hospital, Sion, Mumbai
(Clinical trial registry No. : CTRI-2012-08-002931)

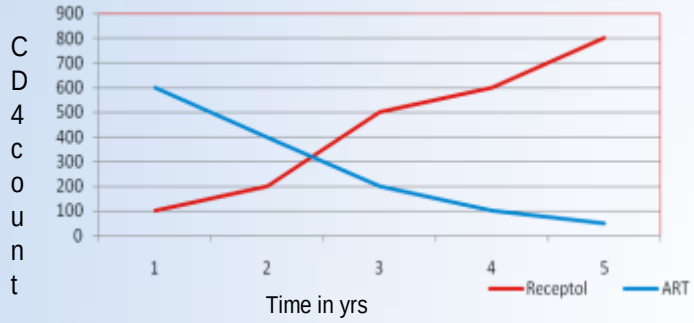
Receptol® Study II Standalone Monotherapy (2007-08) :
By GoI on 51 Patients at LTMMC & LTMG Hospital, Sion, Mumbai
(Clinical Trial registry No. : CTRI-2012-09-002959)

Comparative study data analysis on HIV patients with ART treatment between 2006-08 at ART centre at LTMMC & LTMG Hospital, Sion, Mumbai follows.

Comparative study between Receptol® and ART in India

Conclusion:

The data from Global and Indian studies indicates that there is a statistically significant increase in CD4 cell count (p = 0.06) in 3 months with Standalone Receptol® therapy as against ART therapy where there is a decrease in CD4 cell counts even after 5-9 years.



Data from National Aids Control Organization (NACO) ART Centre at LTMMC, Sion Hospital, Mumbai

9.1.3. RECEPTOL® and Japanese encephalitis

Definition

Japanese encephalitis is an infection of the brain caused by a virus. The virus is transmitted to humans by mosquitoes. The virus that causes Japanese encephalitis is called an arbovirus, which is an arthropod-borne virus. Mosquitoes are a type of arthropod. Mosquitoes in a number of regions carry this virus and are responsible for passing it along to humans. Many of these areas are in Asia, including Japan, Korea, China, India, Thailand, Indonesia, Malaysia, Vietnam, Taiwan, and the Philippines. Areas where the disease-causing arbovirus is always present are referred to as being endemic for the disease. In such areas, blood tests will reveal that more than 70% of all adults have been infected at some point with the arbovirus.

Because the virus that causes Japanese encephalitis is carried by mosquitoes, the number of people infected increases during those seasons when mosquitoes are abundant. This tends to be in the warmest, rainiest months. In addition to humans, other animals like wild birds, pigs, and horses are susceptible to infection with this arbovirus. Because the specific type of mosquito carrying the Japanese encephalitis arbovirus frequently breeds in rice paddies, the disease is considered to be primarily a rural problem.

Causes and symptoms

The virus is transferred to a human when an infected mosquito sucks that person's blood. Once in the body, the virus travels to various glands where it multiplies. The virus can then enter the bloodstream. Ultimately, the virus settles in the brain, where it causes serious problems.
Japanese encephalitis begins with fever, severe headache, nausea, and vomiting. As the tissue covering the brain and spinal cord (the meninges) becomes infected and swollen, the patient will develop a stiff and painful neck. By day two or three, the patient begins to suffer the effects of swelling in the brain. These effects include:

- Problems with balance and coordination
- Paralysis of some muscle groups
- Tremors
- Seizures
- Lapses in consciousness
- A stiff, mask-like appearance of the face.

The patient becomes dehydrated and loses weight. If the patient survives the illness, the fever will decrease by about day seven and the symptoms will begin to improve by about day 14. Other patients will continue to have extremely high fevers and their symptoms will get worse. In these cases, coma and then death occur in 7-14 days. Many patients who recover have permanent disabilities due to brain damage.

Diagnosis

Most diagnostic techniques for Japanese encephalitis do not yield results very quickly. The diagnosis is made primarily on the basis of the patient's symptoms and the knowledge of the kinds of illnesses endemic to a particular geographic region.

Immunofluorescence tests, where special viral markers react with human antibodies that have been tagged with a fluorescent chemical, are used to verify the disease. However, these results tend to be unavailable until week two of the infection. Other tests involve comparing the presence and quantity of particular antibodies in the blood or spinal fluid during week one with those present during week two of the illness.

Treatment

There are no treatments available to stop or slow the progression of Japanese encephalitis. Only the symptoms of each patient can be treated. Fluids are given to decrease dehydration and medications are given to decrease fever and pain. Medications are available to attempt to decrease brain swelling. Patients in a coma may require mechanical assistance with breathing.

Prognosis

While the majority of people infected with arbovirus never become sick, those who develop Japanese encephalitis become very ill. Some outbreaks have a 50% death rate. A variety of long-term problems may haunt those who recover from the illness. These problems include:

- Movement difficulties where the arms, legs, or body jerks or writhes involuntarily
- Shaking
- Paralysis
- Inability to control emotions
- Loss of mental abilities
- Mental disturbances, including schizophrenia (which may affect as many as 75% of Japanese encephalitis survivors).

Young children are most likely to have serious, long-term problems after an infection.

Prevention

RECEPTOL®, having informational nano peptides and Proline Rich Polypeptides (PRP), is an effective and safe prevention for this disease as it is know to increase weight, general well being of patients, decrease in viral load and increase in CD4 cell count in viral infections.

Additionally, a three-dose vaccine is available for Japanese encephalitis and is commonly given to young children in areas where the disease is endemic. Travelers to these regions can also receive the vaccine.
Controlling the mosquito population with insecticides is another preventive measure. Visitors to regions with high rates of Japanese encephalitis should take precautions (like using mosquito repellents and sleeping under a bed net) to avoid contact with mosquitoes.

References

1. Th1 immune response takeover among patients with severe Japanese encephalitis infection.Pujhari SK, Prabhakar S, Ratho R, Mishra B, Modi M, Sharma S, Singh P.J Neuroimmunol. 2013 Oct 15;263(1-2):133-8. doi: 10.1016/j.jneuroim.2013.08.003. Epub 2013 Aug 14.

2. Characterization of immune responses induced by inactivated, live attenuated and DNA vaccines against Japanese encephalitis virus in mice.Li J, Chen H, Wu N, Fan D, Liang G, Gao N, An J.Vaccine. 2013 Aug 28;31(38):4136-42. doi: 10.1016/j.vaccine.2013.06.099. Epub 2013 Jul 8.

3. Cytolytic effector pathways and IFN-γ help protect against Japanese encephalitis.Larena M, Regner M, Lobigs M.Eur J Immunol. 2013 Jul;43(7):1789-98. doi: 10.1002/eji.201243152. Epub 2013 Jun 18.

4. Japanese encephalitis virus activates autophagy as a viral immune evasion strategy.Jin R, Zhu W, Cao S, Chen R, Jin H, Liu Y, Wang S, Wang W, Xiao G.PLoS One. 2013;8(1):e52909. doi: 10.1371/journal.pone.0052909. Epub 2013 Jan 8. Erratum in: PLoS One. 2013;8(5). doi:10.1371/annotation/f7dcec2f-ed82-4a31-96c6-2953b421fd92.

5. Etanercept Reduces Neuroinflammation and Lethality in Mouse Model of Japanese Encephalitis.Ye J, Jiang R, Cui M, Zhu B, Sun L, Wang Y, Zohaib A, Dong Q, Ruan X, Song Y, He W, Chen H, Cao S.J Infect Dis. 2014 Apr 24.

6. MicroRNA 155 regulates Japanese encephalitis virus-induced inflammatory response by targeting Src homology 2-containing inositol phosphatase 1.Thounaojam MC, Kundu K, Kaushik DK, Swaroop S, Mahadevan A, Shankar SK, Basu A.J Virol. 2014 May;88(9):4798-810. doi: 10.1128/JVI.02979-13. Epub 2014 Feb 12.

7. Internal ribosome entry site-based attenuation of a flavivirus candidate vaccine and evaluation of the effect of beta interferon coexpression on vaccine properties.Frese M, Lee E, Larena M, Lim PS, Rao S, Matthaei KI, Khromykh A, Ramshaw I, Lobigs M.J Virol. 2014 Feb;88(4):2056-70. doi: 10.1128/JVI.03051-13. Epub 2013 Dec 4

8. Japanese encephalitis virus infection modulates the expression of suppressors of cytokine signaling (SOCS) in macrophages: implications for the hosts' innate immune response.Kundu K, Dutta K, Nazmi A, Basu A.Cell Immunol. 2013 Sep-Oct;285(1-2):100-10. doi: 10.1016/j.cellimm.2013.09.005. Epub 2013 Oct 3.

9. TNF-α acts as an immunoregulator in the mouse brain by reducing the incidence of severe disease following Japanese encephalitis virus infection.Hayasaka D, Shirai K, Aoki K, Nagata N, Simantini DS, Kitaura K, Takamatsu Y, Gould E, Suzuki R, Morita K.PLoS One. 2013 Aug 5;8(8):e71643. doi: 10.1371/journal.pone.0071643. Print 2013.

10. Japanese encephalitis virus non-coding RNA inhibits activation of interferon by blocking nuclear translocation of interferon regulatory factor 3.Chang RY, Hsu TW, Chen YL, Liu SF, Tsai YJ, Lin YT, Chen YS, Fan YH.Vet Microbiol. 2013 Sep 27;166(1-2):11-21. doi: 10.1016/j.vetmic.2013.04.026. Epub 2013 May 9.

11. Histone deacetylase inhibition by Japanese encephalitis virus in monocyte/macrophages: a novel viral immune evasion strategy.Adhya D, Dutta K, Kundu K, Basu A.Immunobiology. 2013 Oct;218(10):1235-47. doi: 10.1016/j.imbio.2013.04.018. Epub 2013 May 3.

12. Usutu virus growth in human cell lines: induction of and sensitivity to type I and III interferons.Scagnolari C, Caputo B, Trombetti S, Cacciotti G, Soldà A, Spano L, Villari P, della Torre A, Nowotny N, Antonelli G.J Gen Virol. 2013 Apr;94(Pt 4):789-95. doi: 10.1099/vir.0.046433-0. Epub 2012 Dec 19.

13. The role of chemokines in the pathogenesis of neurotropic flaviviruses. Bardina SV, Lim JK.Immunol Res. 2012 Dec;54(1-3):121-32. doi: 10.1007/s12026-012-8333-3.

14. Cytokine and chemokine responses to Japanese encephalitis live attenuated vaccine in a human population.Zhang JS, Zhao QM, Zuo SQ, Jia N, Guo XF. Int J Infect Dis. 2012 Apr;16(4):e285-8. doi: 10.1016/j.ijid.2011.12.010. Epub 2012 Feb 9

15. TNF-α promoter polymorphism: a factor contributing to the different immunological and clinical phenotypes in Japanese encephalitis.Pujhari SK, Ratho RK, Prabhakar S, Mishra B, Modi M.BMC Infect Dis. 2012 Jan 26;12:23. doi: 10.1186/1471-2334-12-23.

16. Status of proinflammatory and anti-inflammatory cytokines in different brain regions of a rat model of Japanese encephalitis.Srivastava R, Kalita J, Khan MY, Misra UK.Inflamm Res. 2012 Apr;61(4):381-9. doi: 10.1007/s00011-011-0423-5. Epub 2011 Dec 30.

17. Japanese encephalitis virus structural and nonstructural proteins expressed in Escherichia coli induce protective immunity in mice.Tafuku S, Miyata T, Tadano M, Mitsumata R, Kawakami H, Harakuni T, Sewaki T, Arakawa T.

18. Microbes Infect. 2012 Feb;14(2):169-76. doi: 10.1016/j.micinf.2011.09.004. Epub 2011 Oct 4 .RIG-I mediates innate immune response in mouse neurons following Japanese encephalitis virus infection.Nazmi A, Dutta K, Basu A.PLoS One. 2011;6(6):e21761. doi: 10.1371/journal.pone.0021761. Epub 2011 Jun 30.

9.1.4. RECEPTOL® and Hepatitis A & C

What is Hepatitis?

Hepatitis refers to viral infections that cause inflammation of the liver. Hepatitis A and C are the most common types. Each has different causes and symptoms.

- Hepatitis A
- Hepatitis C

What is Hepatitis A?

Hepatitis A is the most common of the seven known types of viral hepatitis. Infection with the hepatitis A virus leads to inflammation of the liver, but complications are rarely serious.

How Hepatitis A is spread?

The hepatitis A virus (HAV) is found in the faeces of someone infected with the virus. It only takes a tiny amount of faeces getting inside another person's mouth to cause hepatitis A infection. Personal hygiene, such as careful hand washing, can minimise the risk of the virus being passed on.

HAV is a common infection in many parts of the world where sanitation and sewage infrastructure is poor. Often people become infected with HAV by eating or drinking contaminated food or water.

Hepatitis A is also classed as a sexually transmitted disease (STD) because it can be passed on sexually, particularly during activities such as anilingus (rimming). The washing of genital and anal areas before sex, and the use of condoms or dental dams can help to prevent this risk.

Hepatitis A can affect all age groups. Once a person is exposed to the virus it takes between 2 and 6 weeks to produce symptoms.

Sign and symtoms of Hepatitis A

It is possible to experience mild or no symptoms whatsoever, but even if this is the case the person's faeces will still be infectious to others. Many people who become infected with HAV will have symptoms that include:

- A short, mild, flu-like illness
- Nausea, vomiting and diarrhoea
- Loss of appetite;weight loss
- Jaundice (yellow skin and whites of eyes, darker yellow urine and pale faeces)
- Itchy skin; Abdominal pain

The infection usually clears in up to 2 months, but may occasionally recur or persist longer in some people. Once a person has been infected and their body has fought off the virus they are permanently immune. Occasionally symptoms may be severe and require monitoring in hospital.

There are rarely any complications with hepatitis A infection. Permanent damage to the liver is very unlikely, but in extremely rare cases the infection can be fatal, particularly in older people.

What is Hepatitis C?

Hepatitis C, like other forms of hepatitis, causes inflammation of the liver. The hepatitis C virus is transferred primarily through blood, and is more persistent than hepatitis A or B.

How Hepatitis C is spread?

The hepatitis C virus (HCV) can be spread in the following ways:

- By sharing drug-injecting equipment (needles, heating spoons, etc). This is the primary transmission route for HCV outside sub-Saharan Africa.
- By using non-sterilised equipment for tattooing, acupuncture or body piercing. This can be a problem in countries where tattooing or scarification is a traditional ritual practice.
- Through exposure to blood during unprotected sex with an infected person. Blood may be present because of genital sores, cuts or menstruation. Sexual transmission is an uncommon way of becoming infected with hepatitis C.
- Rarely, from an infected mother to her baby during childbirth. The risk may be greater if the mother is also infected with HIV.
- Through blood transfusion. In many developing countries blood is not screened (tested) for the hepatitis C virus.
- By sharing equipment used to snort cocaine. Usually this is a rolled banknote, which can become contaminated with blood from a person's nose.

Hepatitis C cannot be passed on by hugging, sneezing, coughing, sharing food or water, sharing cutlery, or casual contact.

Signs and Symtoms of Hepatitis C

Many people do not have symptoms when they become infected with hepatitis C. Symptoms may emerge later, taking anywhere between 15 and 150 days to develop. Occasionally a person will not develop any symptoms and their immune system will successfully clear the virus without their knowledge. An infected person without symptoms can still act as a carrier and pass the virus on to others.

Symptoms may include:

- A short, mild, flu-like illness
- Nausea and vomiting
- Diarrhoea
- Loss of appetite
- Weight loss
- Jaundice (yellow skin and whites of eyes, darker yellow urine and pale faeces)
- Itchy skin

About 20% of individuals who become infected with HCV will clear the virus from their body within 6 months, though this does not mean they are immune from future infection with HCV.

The other 80% of people will develop chronic hepatitis C infection, during which the virus may cause mild symptoms or no symptoms at all. These people will however carry the hepatitis C virus for the rest of their lives and will remain infectious to others.

If a person lives with hepatitis C infection for a number of years then they may develop the following complications:

- chronic hepatitis
- liver cirrhosis
- liver cancer

If symptoms become severe then a person with hepatitis C may be admitted to hospital for monitoring and treatment.

References:

1. Stability of orally administered immunoglobulin in the gastrointestinal tract.Lee J[1], Kang HE, Woo HJ. J Immunol Methods. 2012 Oct 31;384(1-2):143-7.
2. Promoter-specific transactivation of hepatitis B virus transcription by a glutamine- and proline-richdomain of hepatocyte nuclear factor 1.Raney AK, Easton AJ, Milich DR, McLachlan A.**J Virol**. 1991 Nov;65(11):5774-81
3. Milk-derived proteins and peptides in clinical trials.Artym J, Zimecki M. **Postepy Hig Med Dosw**. 2013 Aug 6;67:800-16.
4. Therapeutic properties of proteins and peptides from colostrum and milk.Zimecki M, Artym J.Postepy Hig Med Dosw (Online). 2005;59:309-23
5. Immune responses to HCV and other hepatitis viruses.Park SH, Rehermann B.Immunity.2014 Jan 16;40(1):13-24. doi: 10.1016/j.immuni.2013.12.010
6. Association of cytokines in hepatitis E with pregnancy outcome.Kumar A, Devi SG, Kar P,Agarwal S, Husain SA, Gupta RK, Sharma S. Cytokine. 2014 Jan;65(1):95-104.
7. Interleukin-29 suppresses hepatitis A and C viral internal ribosomal entry site- mediated translation.Kanda T, Wu S, Kiyohara T, Nakamoto S, Jiang X, Miyamura T, Imazeki F, Ishii K, Wakita T, Yokosuka O.Viral Immunol. 2012 Oct;25(5):379-86.
8. Dominance of the CD4(+) T helper cell response during acute resolving hepatitis A virus infection.Zhou Y, Callendret B, Xu D, Brasky KM, Feng Z, Hensley LL, Guedj J, Perelson AS, Lemon SM, Lanford RE, Walker CM. J Exp Med. 2012 Jul 30;209(8):1481-92.
9. Cytokine expression profiles associated with distinct clinical courses in hepatitis A virus-infected children.Fierro NA, Escobedo-Melendez G, De Paz L, Realpe M, Roman S, Panduro A.Pediatr Infect Dis J. 2012 Aug;31(8):870-1

10. Acute hepatitis A virus infection is associated with a limited type I interferon response and persistence of intrahepatic viral RNA.Lanford RE, Feng Z, Chavez D, Guerra B, Brasky KM, Zhou Y, Yamane D, Perelson AS, Walker CM, Lemon SM.Proc Natl Acad Sci U S A. 2011 Jul 5;108(27):11223-8

11. Expression of a recombinant chimeric protein of hepatitis A virus VP1-Fc using a replicating vector based on Beet curly top virus in tobacco leaves and its immunogenicity in mice.Chung HY, Lee HH, Kim KI, Chung HY, Hwang-Bo J, Park JH, Sunter G, Kim JB, Shon DH, Kim W, Chung IS.Plant Cell Rep. 2011 Aug;30(8):1513-21

12. Virologic and immunologic correlates with the magnitude of antibody responses to the hepatitis Avaccine in HIV-infected children on highly active antiretroviral treatment.Weinberg A, Huang S, Fenton T, Patterson-Bartlett J, Gona P, Read JS, Dankner WM, Nachman S; IMPAACT P1008 Team.J Acquir Immune Defic Syndr. 2009 Sep 1;52(1):17-24

13. Cytokine profiles in peripheral blood mononuclear cells and sera from patients with acute self-limitedhepatitis A.Tripathy A, Chadha MS, Arankalle VA.Acta Virol. 2005;49(4):283-4.

14. Dynamics of proinflammatory cytokines serum levels during viral hepatitis type A.Fota-Markowska H, Modrzewska R, Rolla-Szczepańska R, Bielec D, Krzowska-Firych J.Ann Univ Mariae Curie Sklodowska Med. 2004;59(1):209-13.

15. Effects of cytokines on the immunogenic properties of hepatitis A vaccine.Avdeeva ZhI, Akol'zina SE, Alpatova NA, Medunitsyn NV.
Vopr Virusol. 2005 Mar-Apr;50(2):23-7.

16. Production of interferon-gamma and interleukin-10 after inactivated hepatitis A immunization.Hayney MS, Buck JM, Muller D.Pharmacotherapy. 2003 Apr;23(4):431-5.

17. Suppression of hepatitis B virus replication mediated by hepatitis A-induced cytokine production.van Nunen AB, Pontesilli O, Uytdehaag F, Osterhaus AD, de Man RA.Liver. 2001 Feb;21(1):45-9.

18. Histologic distribution of hepatitis A, B, C, D, E, and G with concomitant cytokine response in liver tissue.Nuovo GJ.Diagn Mol Pathol. 1998 Oct;7(5):267-75.

19. Immunohistochemical detection of cytokines in tissues of Aotus monkeys infected with hepatitis Avirus.Polotsky YE, Vassell RA, Binn LN, Asher LV.Ann N Y Acad Sci. 1994 Aug 15;730:318-21.

20. Cytolytic activity of natural killer cells and lymphokine activated killer cells against hepatitis A virus infected fibroblasts.Baba M, Hasegawa H, Nakayabu M, Fukai K, Suzuki S.J Clin Lab Immunol. 1993;40(2):47-60.

21. Interleukin-6 production by peripheral blood monocytes in patients with chronic liver disease and acute viral hepatitis.Müller C, Zielinski CC.J Hepatol. 1992 Jul;15(3):372-7.

22. Interferon as treatment for viral hepatitis: a progress report.Lee WM. J S C Med Assoc. 1990 Aug;86(8):440-4.

23. Serology and interferon production during the early phase of acute hepatitis A.Zachoval R, Kroener M, Brommer M, Deinhardt F.J Infect Dis. 1990 Feb;161(2):353-4

24. Interleukin-1 production in acute viral hepatitis.Müller C, Gödl I, Ahmad R, Wolf HM, Mannhalter JW, Eibl MM.Arch Dis Child. 1989 Feb;64(2):205-10.

25.Immunotherapy in virus diseases.Schulte-Wissermann H, Schofer O. onatsschr Kinderheilkd. 1986 Apr;134(4):172-81.

26. Interferon production in acute virus hepatitis..Pirovino M, Aguet M, Huber M, Altorfer J, Schmid M.Leber Magen Darm. 1984 Nov;14(6):258-60.

27. Production of interferon and alpha 2-macroglobulin involvement in immune response during human viral hepatitis A (author's transl).Bador H, Colobert L, Giroud M, Lesbre F.Clin Chim Acta. 1977 Jul 15;78(2):217-26

28. Interferon In Human Serum During Clinical Viral Infections. Wheelock EF, Sibley Wa, Lancet, 1964, Aug 22:2 (7356):382-5.

29. Immunoglobulins and interferon responses in infectious and transfusion associated hepatitis.LoGrippo GA, Hayashi H, Sharpless N. Henry Ford Hosp Med J. 1967 Mar;15(1):57-63

30. Research on interferon in childhood viral hepatitis.Nigro N, Bonenti G, Benso L.Riv Ist Sieroter Ital. 1966 Mar-Apr;41(2):157-62

9.1.5 RECEPTOL® and Rabies disease

What is rabies?

Rabies is a disease caused by a virus that enters the body through the bite of infected animals and causes brain swelling and, if not quickly treated, results in convulsions,respiratory failure, and death in almost every person infected. Very rarely, rabies has been transmitted only by saliva droplets from an infected animal that contacts a skin break (abrasion or cut, not a bite) or in rabies research laboratory accidents. Aerosols of saliva droplets or bat guano may also rarely cause rabies.

Rabies is worldwide (except for Australia and New Zealand currently); developing countries have dogs as the most common source of bites that lead to rabies. However, many wild animals (especially foxes, skunks, raccoons, and bats) in both developed and developing countries can be infected with rabies virus so their bites (and saliva) can transmit the disease to other animals and humans. Most developed countries have animal vaccination programs that effectively reduce or eliminate the source of rabies in domestic animals (especially dogs and cats); some even have programs to reduce or eliminate the virus in wild animals.

For example, vaccine materials are set out in the wild for coyotes to ingest to reduce or eliminate rabies in their population in Texas. Until recently, when rabies-infected bats were found in Scotland, all of England was rabies-free due to its vaccine program. Rabies is termed azoonosis, which means a disease that is usually transmitted from animals to other animals and but can also be transmitted to humans. The terms rabiesand rabies virus (Lyssavirus rabies) are currently interchanged in most of the medical literature although technically rabies is the disease process and rabies virus is the species of lyssavirus that causes the disease. However, the dual meaning is so pervasive in the medical and lay literature that rabies will be used in this article to mean both the disease and the viral cause of the disease. About 55,000 deaths per year worldwide are due to rabies (World Health Organization statistics), and the majority of these deaths occur in children.

What are the symptoms of the disease?

Normally between one to three months can pass between infection and the onset of symptoms (incubation period). But in individual instances, it may be more than a year. In spite of being bitten by an animal with rabies, it's not certain that you have been infected. Only one out of six people who have been bitten develop symptoms – even if they have not been treated. If you get rabies and do not manage to be treated in time, the disease evolves in two phases.

The prodomal phase (prelude)

In this phase, the patient may have a fever, vomiting and loss of appetite, headache and pain at the site of the original bite.
The autonomic nervous system is affected. This manifests itself as copious salivation and weeping.

The neurological phase

Paralysis may occur in this phase. In particular, there are spasms in the throat, making swallowing difficult.
The person affected becomes terrified of water (which is why it's also called 'hydrophobia') and becomes anxious and hyperactive.

It is in this phase that animals become mad and bite. Symptoms such as those seen in encephalitis are also present, along with increasingly uncontrolled movement, confusion and delirium.

What causes rabies?

The virus that causes rabies is a lyssa virus. It's one of the few, in that particular group, that can cause illness in man.

The rabies virus is good at 'hiding' from the immune system. As a result, no immune response really develops, so the body finds it hard to combat.

After a bite, when the virus has travelled from the nerve pathways of the muscles into the central nervous system (CNS), it replicates quickly and spreads into many parts of the brain. The brain becomes inflamed and many functions of the CNS are affected.

The virus spreads via the nervous system to many of the tissues of the body, including the skin, mucous membranes and salivary glands.

References:

1. Vaccine immune response and interference of colostral antibodies in calves vaccinated against rabies at 2, 4 and 6 months of age born from antirabies revaccinated females. Filho OA, Megid J, Geronutti L, Ratti J Jr, Almeida MF, Kataoka AP, Martorelli LF. Res Vet Sci. 2012 Jun;92(3):396-400. doi: 10.1016/j.rvsc.2011.03.025. Epub 2011 May 4.

2. Kinetics of humoral immune response after rabies VR-G oral vaccination of captive fox cubs (Vulpes vulpes) with or without maternally derived antibodies against the vaccine.Blasco E, Lambot M, Barrat J, Cliquet F, Brochier B, Renders C, Krafft N, Bailly J, Munier M, Pastoret PP, Aubert MF.Vaccine. 2001 Sep 14;19(32):4805-15.

3. Immunology of experimental rabies in rats; influence of the age factor.Oyrzanowska-Poplewska J.Acta Microbiol Pol A. 1969;1(1):55-9.

4. Colostral antibody to rabies in cattle vaccinated with HEP Flury strain of the virus.WILLIAMS HE. Am J Vet Res. 1961 Sep;22:902-5.

5. Some immunity parameters in different physiological conditions and following infection of sheep with rabies virus. I. Effect of pregnancy and seasons.Sommer E. Pol Arch Weter. 1973;16(1):95-104.

6. Vaccine immune response and interference of colostral antibodies in calves vaccinated against rabies at 2, 4 and 6 months of age born from antirabies revaccinated females. Filho OA, Megid J, Geronutti L, Ratti J Jr, Almeida MF, Kataoka AP, Martorelli LF. Res Vet Sci. 2012 Jun;92(3):396-400. doi: 10.1016/j.rvsc.2011.03.025. Epub 2011 May 4.

9.1.6 RECEPTOL® & Acute Viral Infections

What is Acute viral infections?

An acute viral infection is characterized by rapid onset of disease, a relatively brief period of symptoms, and resolution within days. It is usually accompanied by early production of infectious virions and elimination of infection by the host immune system. Acute viral infections are typically observed with pathogens such as influenza virus and rhinovirus. Ebola hemorrhagic fever is an acute viral infection, although the course of disease is unusually severe.

Often an acute infection may cause little or no clinical symptoms – the so-called inapparent infection. A well-known example is poliovirus infection: over 90% are without symptoms. During an inapparent infection, sufficient virus replication occurs in the host to induce antiviral antibodies, but not enough to cause disease. Such infections are important for the spread of infection, because they are not easily detected. During the height of the polio epidemic in the US, the quarantine of paralyzed patients had no effect on the spread of the disease, because 99% of the infected individuals had no symptoms and were leading normal lives and spreading infection. Inapparent infections probably are important features of pathogens that are well-adapted to their hosts. They replicate sufficiently to ensure spread to new hosts, but not enough to damage the host and prevent transmission.

Acute infections begin with an incubation period, during which the genomes replicate and the host innate responses are initiated. The cytokines produced early in infection lead to classical symptoms of an acute infection: aches, pains, fever, malaise, and nausea. Some incubation periods are as short as 1 day (influenza, rhinovirus), indicating that the symptoms are produced by local viral multiplication near the site of entry. For some infections, incubation periods can last many days (papilloma, 50-150 days) or even years (AIDS, 1-10 years). In these infections, the symptoms are likely produced by virus- or immune-induced tissue damage far from the site of entry.

An example of a classic acute infection is uncomplicated influenza. Virus particles are inhaled in droplets produced by sneezing or coughing, and begin replicating in ciliated columnar epithelial cells of the respiratory tract. As new infectious virions are produced, they spread to neighboring cells. Virus can be isolated from throat swabs or nasal secretions from day 1 to day 7 after infection. Within 48 hr after infection symptoms appear; these last 3 days and then subside. The infection is usually cleared by the innate and adaptive responses in 7 days. However, the patient usually feels unwell for several weeks, a consequence of the damage to the respiratory epithelium, and the cytokines produced during infection.

Acute viral infections are responsible for epidemics of disease involving millions of individuals each year, such as influenza and measles. When vaccines are not available, acute infections are difficult to control – most are complete by the time the patient feels ill, and the virus has already spread to another host. This characteristic makes it exceedingly difficult to control acute infections in large populations and crowded areas (such as colleges, nursing homes, military camps). The outbreaks of norovirus gastroenteritis this winter – a classic acute infection – highlights the problem. Antiviral therapy cannot be used, because it must be given early in infection to be effective. There is little hope of treating most acute viral infections with antiviral drugs until rapid diagnostic tests are become available. But the point is moot – there are no antivirals for most common acute viral diseases.

The rapid clearance of acute viral infections is a consequence of robust host defenses. The same virus may cause a long-term, or persistent infection, in immunocompromised hosts. An example is norovirus infection, which is self-limiting in immunocompetent hosts, but causes a chronic infection in immunosuppressed kidney transplant recipients.

References

1. Quantification and determination of spread mechanisms of bovine viral diarrhoea virus in blood and tissues from colostrum-deprived calves during an experimental acute infection induced by a non-cytopathic genotype 1 strain.Pedrera M, Gómez-Villamandos JC, Molina V, Risalde MA, Rodríguez-Sánchez B, Sánchez-Cordón PJ.Transbound Emerg Dis. 2012 Oct;59(5):377-84.

2. Evaluation of a bovine rotavirus VP6 vaccine efficacy in the calf model of infection and disease.Gonzalez DD, Mozgovoj MV, Bellido D, Rodriguez DV, Fernandez FM, Wigdorovitz A, Parreño VG, Dus Santos MJ.Vet Immunol Immunopathol. 2010 Sep 15;137(1-2):155-60.

3. Comparative analysis of innate immune responses following infection of newborn calves with bovinerotavirus and bovine coronavirus.Aich P, Wilson HL, Kaushik RS, Potter AA, Babiuk LA, Griebel P.J Gen Virol. 2007 Oct;88(Pt 10):2749-61.

4. Bovine colostrums: a review of clinical uses.Kelly GS.Altern Med Rev. 2003 Nov;8(4):378-94. Review. Erratum in: Altern Med Rev. 2004 Mar;9(1):69.

5. Successful treatment of rotavirus diarrhea in children with immunoglobulin from immunized bovinecolostrum.Sarker SA, Casswall TH, Mahalanabis D, Alam NH, Albert MJ, Brüssow H, Fuchs GJ, Hammerström L.Pediatr Infect Dis J. 1998 Dec;17(12):1149-54.

6. Protection of newborn calves against fatal multisystemic infectious bovine rhinotracheitis by feedingcolostrum from vaccinated cows.
   Mechor GD, Rousseaux CG, Radostits OM, Babiuk LA, Petrie L. Can J Vet Res. 1987 Oct;51(4):452-9.

7. Passive protection of newborn calves against rotavirus by vaccination of their dams.Dauvergne M, Brun A, Soulebot JP.Dev Biol Stand. 1983;53:245-55.

8. Molecular identification and expression analysis of two distinct BPI/LBPs (bactericidal permeability-increasing protein/LPS-binding protein) from rock bream, Oplegnathus fasciatus.Kim JW, Gerwick L, Park CI.Fish Shellfish Immunol. 2012 Jul;33(1):75-84

9. Molecular cloning, characterization and expression analysis of interferon-β promoter stimulator 1 (IPS-1) gene from grass carp Ctenopharyngodon idella. Su J, Huang T, Yang C, Zhang R.Fish Shellfish Immunol. 2011 Jan;30(1):317-23.

10. Distribution of cytopathic and noncytopathic bovine viral diarrhea virus antigens in tissues of calves followingacute experimental infection. Spagnuolo-Weaver M[1], Allan GM, Kennedy S, Foster JC, Adair BM. J Vet Diagn Invest. 1997 Jul;9(3):287-97.

11. Interferon-α/β receptor signaling amplifies early pro-inflammatory cytokine production in the lung during Respiratory Syncytial Virus infection. Goritzka M, Durant LR, Pereira C, Salek-Ardakani S, Openshaw PJ, Johansson C.J Virol. 2014 Mar 19.

12. Severe acute respiratory syndrome-coronavirus infection in aged nonhuman primates is associated with modulated pulmonary and systemic immune responses.Clay CC, Donart N, Fomukong N, Knight JB, Overheim K, Tipper J, Van Westrienen J, Hahn F, Harrod KS.Immun Ageing. 2014 Mar 19;11(1):4.

13. Respiratory syncytial virus infection, TLR3 ligands, and proinflammatory cytokines induce CD161 ligand LLT1 expression on the respiratory epithelium.Satkunanathan S, Kumar N, Bajorek M, Purbhoo MA, Culley FJ.J Virol. 2014 Mar;88(5):2366-73. doi: 10.1128/JVI.02789-13.

14. Direct, interferon-independent activation of the CXCL10 promoter by NF-κB and interferon regulatory factor 3 during hepatitis C virus infection. Brownell J, Bruckner J, Wagoner J, Thomas E, Loo YM, Gale M Jr, Liang TJ, Polyak SJ.JVirol. 2014 Feb;88(3):1582-90.

15. Host-Viral Interactions: Role of Pattern Recognition Receptors (PRRs) in Human PneumovirusInfections.Kolli D, Velayutham TS, Casola A.Pathogens. 2013 Jun 1;2(2)

16. Long-lasting T cell-independent IgG responses require MyD88-mediated pathways and are maintained by high levels of virus persistence. Raval FM, Mishra R, Garcea RL, Welsh RM, Szomolanyi-Tsuda E.MBio. 2013 Nov 5;4(6):e00812-13.

9.1.7. RECEPTOL® & Dengue fever

What is Dengue?

Dengue fever, also known as **break bone fever**, is a mosquito-borne infection that causes a severe flu-like illness. There are four different viruses that can cause dengue fever, all of which spread by a certain type of mosquito. Dengue can vary from mild to severe; the more severe forms include dengue shock syndrome and dengue hemorrhagic fever (DHF). Patients who develop the more serious forms of dengue fever usually need to be hospitalized.

There are currently no vaccines for Dengue fever. The best way to prevent the disease is to avoid being bitten by mosquitos' altogether. Although there is no certain treatment for Dengue, it can be treated as long as it is caught before developing into dengue shock syndrome or dengue hemorrhagic fever.

Dengue (pronounced DEN gee) fever is a painful, debilitating mosquito-borne disease caused by any one of four closely related dengue viruses. These viruses are related to the viruses that cause West Nile infection and yellow fever

Symptoms of Dengue

- Sudden, high fever
- Severe headaches
- Pain behind the eyes
- Severe joint and muscle pain
- Nausea
- Vomiting
- Skin rash, which appears three to four days after the onset of fever
- Mild bleeding (such a nose bleed, bleeding gums, or easy bruising)

Sometimes symptoms are mild and can be mistaken for those of the flu or another viral. Younger children and people who have never had the infection before tend to have milder cases than older children and adults. However, serious problems can develop. These include dengue hemorrhagic fever, a rare complication characterized by high fever, damage to lymph and blood vessels, bleeding from the nose and gums, enlargement of the liver, and failure of the circulatory system. The symptoms may progress to massive bleeding, shock, and death. This is called dengue shock syndrome (DSS).

How RECEPTOL® Oral Spray can help people with Dengue

RECEPTOL® contains important components called Proline-Rich-Polypeptides (PRPs); which helps in naturally building the autoimmune system of body and prepare body to fight the virus.

"The Label claims are based on global studies on API: PRPs (Radha108 as class of PRPs being part of it) for which we have sent and up loaded claims on various indications based on published data in first rate Medical Journals. BMJ has accepted our two articles and two more are likely to be in leading Science Journal like NATURE by end of 2014 since our Global Medical Advisory Board has recommended to wait for follow up of patients who tried the product over 6 to 7 years a go and still have not shown any sign of disease reappearance, indicating that all Hibernation Viruses (crossing a window period of 8 years), including HIV have been stopped its reproduction leading to a possible

claim for treatment & cure of AIDS & other major immune disorders, for which we have just received an approval for new US Product Patent as well".

References

1. World Health Organization 2008. Dengue and dengue haemorrhagic fever. Factsheet no. 117, revised May 2008 [cited 2008 Jun 5]. Available from http://www.who.int/mediacentre/factsheets/fs117/en

2. Vaughn DW, Green S, Kalayanarooj S, Innis BL, Nimmannitya S, Suntayakorn S, et al. Dengue in the early febrile phase: viremia and antibody responses. J Infect Dis. 1997; 176:322–30.

3. Innis BL, Nisalak A, Nimmannitya S, Kusalerdchariya S, Chongswasdi V, Suntayakorn S, et al. An enzyme-linked immunosorbent assay to characterize dengue infections where dengue and Japanese encephalitis co-circulate. Am J Trop Med Hyg. 1989; 40:418–27.

9.1.8 RECEPTOL® and Human Pappilloma Virus

What is Human Pappilloma Virus?

- "HPV" redirects here. For other uses, see HPV (disambiguation).
- The Papillomavirus article covers the general biological features of human and animal papillomaviruses.

Human papillomavirus (**HPV**) is a DNA virus from the papillomavirus family that is capable of infecting humans. Like all papillomaviruses, HPVs establish productive infections only in keratinocytes of the skin or mucous membranes. Most HPV infections are subclinical and will cause no physical symptoms; however, in some people subclinical infections will become clinical and may cause benign papillomas (such as warts [verrucae] or squamous cell papilloma), or cancers of the cervix, vulva, vagina, penis,oropharynx and anus. HPV has been linked with an increased risk of cardiovascular disease. In addition, HPV 16 and 18 infections are a cause of a unique type of oropharyngeal (throat) cancer.

More than 30 to 40 types of HPV are typically transmitted through sexual contact and infect the anogenital region. Some sexually transmitted HPV types may cause genital warts. Persistent infection with "high-risk" HPV types—different from the ones that cause skin warts—may progress to precancerous lesions and invasive cancer. HPV infection is a cause of nearly all cases of cervical cancer. However, most infections do not cause disease.

Seventy percent of clinical HPV infections, in young men and women, may regress to subclinical in one year and ninety percent in two years. However, when the subclinical infection persists—in 5% to 10% of infected women—there is high risk of developing precancerous lesions of the vulva and cervix, which can progress to invasive cancer. Progression from subclinical to clinical infection may take years; providing opportunities for detection and treatment of pre-cancerous lesions. Progression to invasive cancer can be prevented when subclinical HPV infection is detected early and regular examinations are performed.

In more developed countries, cervical screening using a Papanicolaou (Pap) test or liquid-based cytology is used to detect abnormal cells that may develop into cancer. If abnormal cells are found, women are invited to have a colposcopy. During a colposcopic inspection, biopsies can be taken and abnormal areas can be removed with a simple procedure, typically with a cauterizing loop or, more commonly in the developing world—by freezing (cryotherapy). Treating abnormal cells in this way can prevent them from developing into cervical cancer.

Pap smears have reduced the incidence and fatalities of cervical cancer in the developed world, but even so there were 11,000 cases and 3,900 deaths in the U.S. in 2008. Cervical cancer has substantial mortality in resource-poor areas; worldwide, there are an estimated 490,000 cases and 270,000 deaths each year.

HPV vaccines (Cervarix and Gardasil), which prevent infection with the HPV types (16 and 18) that cause 70% of cervical cancer, may lead to further decreases.

What are the symptoms of human papillomavirus infection?

Symptoms of human papillomavirus (HPV) infection include the appearance of warts that may vary in size from small to large and may be raised, flat, or cauliflower shaped. Warts can appear on the skin (cutaneous warts), in the throat (recurrent respiratory papillomatosis), or in the genital areas. Left untreated, warts may persist, disappear, or increase in size and number. Many cases of HPV do not cause symptoms and resolve by themselves without treatment.

Other types of HPV can cause cancers, including cervical, anal, penile, vaginal and vulvar cancers. They also cause precancerous, or dysplastic, changes at these sites. Among the types of HPV that can infect the genital area, the so-called low-risk HPV types are most likely to result in genital warts, while the high-risk HPV types are more likely to cause cancers and precancerous changes.

Common symptoms of human papilloma virus infection

The visible signs of HPV vary, and some people do not experience symptoms at all. Symptoms that may appear include:

- Warts of varying size and shape (including large, small, flat, raised, and cauliflower shaped) on the skin, including on the genitals
- Warts in the throat that cause problems with speaking or breathing
- Warts that appear weeks or months after sexual contact

Symptoms that might indicate a serious condition

In some cases, HPV infection can lead to cancers, such as cancer of the cervix in women. **Seek prompt medical care** if you have symptoms of cervical cancer including:

- Pain or bleeding during sexual intercourse
- Pelvic pain
- Unexplained vaginal bleeding

What causes human papilloma virus infection?

About one-third of the HPV types can be spread through sexual contact.

Some types of Human papilloma virus (HPV) cause common skin warts. Several types can lead to genital warts, the most recognizable sign of HPV infection. In genital warts, simultaneous infection with numerous wart subtypes is common.

Other types of HPV are associated with the development of cervical cancer.

Laboratory evidence exists that shows that there is a malignant transformation induced by HPV, especially by high-risk viral types.

Despite the strong links between HPV and cervical cancer, most HPV infections resolve spontaneously and do not cause progressive lesions. Although HPV infection is common, cancer eventually develops in only a small percentage of infected patients. Other factors almost certainly act with HPV to produce cervical cancer, including:

- Cigarette smoking,,Long-term use of oral contraceptives (more than 5 years)
- Young age at first intercourse, Having multiple sexual partners
- Having non-HPV sexually transmitted diseases

References:

1. Human dendritic cells transfected with a human papilloma virus-18 construct display decreased mobility and upregulated cytokine production. Khaiboullina SF, Morzunov SP, Hall MR, De Meirleir KL, Rizvanov AA, Lombardi VC. Int J Oncol. 2013 Nov;43(5):1701-9. doi: 10.3892/ijo.2013.2074. Epub 2013 Aug 21.

2. HPV16 synthetic long peptide (HPV16-SLP) vaccination therapy of patients with advanced or recurrent HPV16-induced gynecological carcinoma, a phase II trial.Van Poelgeest MI, Welters MJ, van Esch EM, Stynenbosch LF, Kerpershoek G, van Persijn van Meerten EL, van den Hende M, Löwik MJ, Berends-van der Meer DM, Fathers LM, Valentijn AR, Oostendorp J, Fleuren GJ, Melief CJ, Kenter GG, van der Burg SH. J Transl Med. 2013 Apr 4;11:88. doi: 10.1186/1479-5876-11-88.

3. Interferon-β induces cellular senescence in cutaneous human papilloma virus-transformed human keratinocytes by affecting p53 transactivating activity.Chiantore MV, Vannucchi S, Accardi R, Tommasino M, Percario ZA, Vaccari G, Affabris E, Fiorucci G, Romeo G.PLoS One. 2012;7(5):e36909. doi: 10.1371/journal.pone.0036909. Epub 2012 May 16.

4. Concentration levels of IL-10 and TNFα cytokines in patients with human papilloma virus (HPV) DNA^{+} and DNA^{-} cervical lesions. Ali KS, Ali HY, Jubrael JM. J Immunotoxicol. 2012 Apr-Jun;9(2):168-72. doi: 10.3109/1547691X.2011.642419. Epub 2012 Apr 4.

5. Immune suppression in premalignant respiratory papillomas: enriched functional CD4+Foxp3+ regulatory T cells and PD-1/PD-L1/L2 expression. Hatam LJ, Devoti JA, Rosenthal DW, Lam F, Abramson AL, Steinberg BM, Bonagura VR. Clin Cancer Res. 2012 Apr 1;18(7):1925-35. doi: 10.1158/1078-0432.CCR-11-2941. Epub 2012 Feb 9.

9.1.9 RECEPTOL® and Parvo disease

What is Parvo disease?

Parvovirus, sometimes truncated to "**parvo**", is both the common name in English casually applied to all the viruses in the Parvoviridaetaxonomic family and also the taxonomic name of the Parvovirus genus within the Parvoviridae family. This creates a confusion of terms because the parvoviruses which cause human and animal diseases are not in the genus Parvovirus, though they are casually called parvoviruses. Parvoviruses are typically linear, non-segmented single-stranded DNA viruses, with an average genome size of 5000 nucleotides. Parvoviruses are some of the smallest viruses (hence the name, from Latin parvus meaning small) and are 18–26 nm in diameter.

Many types of mammalian species have a strain of parvovirus associated with them. Parvoviruses tend to be specific about the taxon of animal they will infect, but this is a somewhat flexible characteristic. Thus, all strains of canine parvovirus will affect dogs, wolves, and foxes, but only some of them will infect cats.

No members of the genus Parvovirus are currently known to infect humans, but humans can be infected by viruses within three other genera from the family Parvoviridae, including the one popularly known by the common name Parvovirus B19. These are the Dependoviruses (e.g.Adeno-Associated Virus), the Erythroviruses (e.g. Parvovirus B19) and the Bocaviruses.

Structure

The viral capsid of a parvovirus is made up of two or three proteins, known as VP1-3 that form an icosahedral structure that is resistant to acids,bases, solvents and temperature up to 50°C (122 degrees Fahrenheit).
Inside the capsid is a single-stranded DNA genome. At the 5’ and 3’ ends of this genome are palindromic sequences of approximately 120 to 250nucleotides, that form hairpins and are essential for viral genome replication.

Replication as disease vector

To enter host cells, parvoviruses bind to a sialic acid-bearing cell surface receptor. Penetration into the cytoplasm is mediated by a phospholipase A2 activity carried on the amino-terminal peptide of the capsid VP1 polypeptide. Once in the cytoplasm, the intact virus is translocated to the nucleus prior to uncoating. Transcription only initiates when the host cell enters S-phase under its own cell cycle control, at which time the cell's replication machinery converts the incoming single strand into a duplex transcription template, allowing synthesis of mRNAs encoding the non-structural proteins, NS1 and NS2.

The mRNAs are transported out of the nucleus into the cytoplasm where the host ribosomestranslate them into viral proteins. Viral DNA replication proceeds through a series of monomeric and concatemeric duplex intermediates by a unidirectional strand-displacement mechanism that is mediated by components of the host replication fork, aided and orchestrated by the viral NS1 polypeptide.
NS1 also transactivates an internal transcriptional promoter that directs synthesis of the structural VP polypeptides. Once assembled capsids are available, replication shifts from synthesizing duplex DNA to displacement of progeny single strands, which are typically negative-sense and are packaged in a 3'-

to-5' direction into preformed particles within the nucleus. Mature virions may be released from infected cells prior to cell lysis, which promotes rapid transmission of the virus, but if this fails then the virus is released at cell lysis.

Unlike most other DNA viruses, parvoviruses are unable to activate DNA synthesis in host cells. Thus, in order for viral replication to take place the infected cells must be non-quiescent (i.e. must be actively mitotic). Their inability to force host cells into S-phase means that parvoviruses are non-tumorigenic. Indeed they are commonly oncolytic, showing a strong tendency to replicate preferentially in cells with transformed phenotypes.

References:

1. 'Gamma' band oscillatory response to chromatic stimuli in volunteers and patients with idiopathic Parkinson's disease.Sannita WG, Carozzo S, Orsini P, Domenici L, Porciatti V, Fioretto M, Garbarino S, Sartucci F. Vision Res. 2009 Mar;49(7):726-34. doi: 10.1016/j.visres.2009.01.018. Epub 2009 Feb 14.

2. Deletion of a gene encoding an amino acid transporter in the midgut membrane causes resistance to a Bombyx parvo-like virus. Ito K, Kidokoro K, Sezutsu H, Nohata J, Yamamoto K, Kobayashi I, Uchino K, Kalyebi A, Eguchi R, Hara W, Tamura T, Katsuma S, Shimada T, Mita K, Kadono-Okuda K. Proc Natl Acad Sci U S A. 2008 May 27;105(21):7523-7. doi: 10.1073/pnas.0711841105. Epub 2008 May 21.

3. Independent patterns of damage within magno-, parvo- and koniocellular pathways in Parkinson's disease (Silva MF et al. Brain 2005; 128: 2260-2271). Gaynes BI. Brain. 2006 Dec;129(Pt 12):e61; author reply e62. No abstract available.

4. A patient with adult Still's disease with an increased Chlamydia pneumoniae antibody titer. Takeda H, Ling M, Ochi M, Watanabe K. J Infect Chemother. 2002 Sep;8(3):262-5.

9.1.10 RECEPTOL® and Pharyngitis

What is pharyngitis?

The word **pharyngitis** /comes from the Greek word pharynx meaning throat and the suffix -itis meaning inflammation. It is an inflammation of the throat. In most cases it is quite painful, and is the most common cause of a sore throat.

Like many types of inflammation, pharyngitis can be acute – characterized by a rapid onset and typically a relatively short course – or chronic. Pharyngitis can result in very large tonsils which cause trouble swallowing and breathing. Pharyngitis can be accompanied by a cough or fever, for example, if caused by a systemic infection.

Most acute cases are caused by viral infections (40–80%), with the remainder caused by bacterial infections, fungal infections, or irritants such as pollutants or chemical substances. Treatment of viral causes is mainly symptomatic while bacterial or fungal causes may be amenable to antibiotics and anti-fungal medicines respectively.

Causes of pharyngitis disease

The majority of cases are due to an infectious organism acquired from close contact with an infected individual.

Infectious viral

These comprise about 40–80% of all infectious cases and can be a feature of many different types of viral infections.

- Adenovirus – the most common of the viral causes. Typically the degree of neck lymph node enlargement is modest and the throat often does not appear red, although it is very painful.
- Orthomyxoviridae which cause influenza – present with rapid onset high temperature, headache and generalised ache. A sore throat may be associated.
- Infectious mononucleosis ("glandular fever") caused by the Epstein–Barr virus. This may cause significant lymph gland swelling and an exudative tonsillitis with marked redness and swelling of the throat. The heterophile test can be used if this is suspected.
- Herpes simplex virus can cause multiple mouth ulcers.
- Measles
- Common cold: rhinovirus, coronavirus, respiratory syncytial virus, parainfluenza virus can cause infection of the throat, ear, and lungs causing standard cold-like symptoms and often extreme pain.

Bacterial

A number of different bacteria can infect the human throat. The most common is Group A streptococcus, however others include Streptococcuspneumoniae, Haemophilus influenzae, Bordetella

pertussis, Bacillus anthracis, Corynebacterium diphtheriae, Neisseria gonorrhoeae, Chlamydophila pneumoniae, and Mycoplasma pneumoniae.

Streptococcal pharyngitis

Streptococcal pharyngitis or strep throat is caused by group A beta-hemolytic streptococcus (GAS). It is the most common bacterial cause of cases of pharyngitis (15–30%). Common symptoms include fever, sore throat, and large lymph nodes. It is a contagious infection, spread by close contact with an infected individual. A definitive diagnosis is made based on the results of a throat culture.Antibiotics are useful to both prevent complications and speed recovery.

Fusobacterium necrophorum

Fusobacterium necrophorum are normal inhabitants of the oropharyngeal flora. Occasionally however it can create a peritonsillar abscess. In 1 out of 400 untreated cases Lemierre's syndrome occurs.

Diphtheria

Diphtheria is a potentially life threatening upper respiratory infection caused by Corynebacterium diphtheriae which has been largely eradicated in developed nations since the introduction of childhood vaccination programs, but is still reported in the Third World and increasingly in some areas in Eastern Europe. Antibiotics are effective in the early stages, but recovery is generally slow.

Others

A few other causes are rare, but possibly fatal, and include parapharyngeal space infections: peritonsillar abscess ("quinsy"),submandibular space infection (Ludwig's angina), and epiglottitis.

Fungal

Some cases of pharyngitis are caused by fungal infection such as Candida albicans causing oral thrush.

Non-infectious

Pharyngitis may also be caused by mechanical, chemical or thermal irritation, for example cold air or acid reflux. Some medications may produce pharyngitis such as pramipexoleand antipsychotics.

What are Symptoms of pharyngitis?

The main symptom is a sore throat.

Other symptoms may include:

- Fever
- Headache
- Joint pain and muscle aches
- Skin rashes
- Swollen lymph nodes (glands) in the neck

References:

1. Markedly elevated CD64 expressions on neutrophils and monocytes are useful for diagnosis of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome during flares.Yamazaki T, Hokibara S, Shigemura T, Kobayashi N, Honda K, Umeda Y, and Agematsu K.Clin Rheumatol. 2014 Mar 13.

2. International periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis syndrome cohort: description of distinct phenotypes in 301 patients. Hofer M, Pillet P, Cochard MM, Berg S, Krol P, Kone-Paut I, Rigante D, Hentgen V, Anton J, Brik R, Neven B, Touitou I, Kaiser D, Duquesne A, Wouters C, Gattorno M.Rheumatology (Oxford). 2014 Mar 6.

9.1.11. RECEPTOL® & SARS

What is severe acute respiratory syndrome (SARS)?

SARS is an infectious respiratory illness caused by a coronavirus. The first cases of SARS occurred in late 2002 in the Guangdong Province of the People's Republic of China. Because of the contagious nature of the disease and the delayed public-health response, the epidemic spread rapidly around the globe. Final statistics from the World Health Organization showed 8,096 reported illnesses and 774 deaths.

The rapid transmission and high mortality rate (about 10%) of SARS drew international attention and concern. Fortunately, efforts to identify and quarantine infected people proved highly effective. By July 2003, sustained human-to-human transmission of SARS had been eliminated. This was a public-health triumph that is often underappreciated. Although illnesses such as anthrax, bird flu, or West Nile virus are potential threats, SARS was a very real problem. Unfortunately, future outbreaks of SARS are still possible because the virus lives in some wild bats and civets in China and also exists in laboratory cultures. In fact, there were a few human cases of SARS in 2004 as a result of laboratory accidents in the People's Republic of China. No human cases have been identified since.

The previously unknown coronavirus that causes this syndrome was first identified in Asia in early 2003, hence its name, "SARS-associated coronavirus" or SARS-CoV. As of October 2012, SARS-CoV has been added to the National Select Agent Registry, which regulates the handling and possession of bacteria, viruses, or toxins that have potential to pose a severe threat to public health and safety. The addition of SARS-CoV permits maintenance of a national database and inspection of entities that possess, use, or transfer SARS-CoV; it also ensures that all individuals who work with these agents undergo security-risk assessment performed by the Federal Bureau of Investigation/Criminal Justice Information Service.

Middle East respiratory syndrome coronavirus (MERS-CoV) is a new coronavirus in humans that has been identified in an outbreak in residents and travelers to the Arabian Peninsula this year. It is not the same coronavirus as SARS-CoV, but it is similar to bat coronaviruses, and it is likely to have originated in animals as well.

What are SARS Symptoms and Signs?

Symptoms of SARS can be similar to those of other viral infections. The first symptoms begin two to seven days after exposure and may include the following:

- Fever (temperature of more than 100.4 F)
- Headache
- Fatigue (tiredness)
- Muscle aches and pain
- Malaise (a feeling of general discomfort)
- Decreased appetite, Diarrhea

Respiratory symptoms develop three or more days after exposure. Respiratory symptoms include the following:

- Dry cough
- Shortness of breath
- Runny nose and sore throat (uncommon)

By day seven to 10 of the illness, almost all patients with laboratory evidence of SARS infection had pneumonia that could be detected in the lungs on X-ray films. Respiratory distress may occur. This symptom is a concern for the patient and the doctors because it suggests the disease is becoming more severe.

What Causes of SARS?

The SARS virus is spread by close person-to-person contact. Transmission may occur by droplets produced when an infected person sneezes or coughs. Droplet spread can occur when airborne droplets, produced by a cough or sneeze, are deposited on the mucous membranes of the mouth, nose, or eyes of a person up to 3 feet away. The virus can also be spread when a person touches a surface contaminated with the droplets. Oral-fecal transmission of SARS may also occur. Unprotected health care workers were at significant risk of acquiring the infection during the outbreak.

SARS virus replicates in both the lungs andgastrointestinal tract tissues. However, tissue samples show the most damage occurs in the lung alveoli where lung function is compromised producing a severe breathing disorder often termed acute respiratory distress syndrome (ARDS).

References:

1. Delayed induction of proinflammatory cytokines and suppression of innate antiviral response by the novel Middle East respiratory syndrome coronavirus: implications for pathogenesis and treatment.Lau SK, Lau CC, Chan KH, Li CP, Chen H, Jin DY, Chan JF, Woo PC, Yuen KY.J Gen Virol. 2013 Dec;94(Pt 12):2679-90. doi: 10.1099/vir.0.055533-0. Epub 2013 Sep 28

2. Active Replication of Middle East Respiratory Syndrome Coronavirus Replication and Aberrant Induction of Inflammatory Cytokines and Chemokines in Human Macrophages: Implications for Pathogenesis.Zhou J, Chu H, Li C, Wong BH, Cheng ZS, Poon VK, Sun T, Lau CC, Wong KK, Chan JY, Chan JF, To KK, Chan KH, Zheng BJ, Yuen KY.J Infect Dis. 2013 Oct 21.

3. The replication of a mouse adapted SARS-CoV in a mouse cell line stably expressing the murineSARS-CoV receptor mACE2 efficiently induces the expression of proinflammatory cytokines.Regla-Nava JA, Jimenez-Guardeño JM, Nieto-Torres JL, Gallagher TM, Enjuanes L, DeDiego ML.J Virol Methods. 2013 Nov;193(2):639-46. doi: 10.1016/j.jviromet.2013.07.039. Epub 2013 Aug 1.

4. SARS coronavirus pathogenesis: host innate immune responses and viral antagonism of interferon.Totura AL, Baric RS.Curr Opin Virol. 2012 Jun;2(3):264-75. doi: 10.1016/j.coviro.2012.04.004. Epub 2012 May 7

5. SARS coronavirus 3b accessory protein modulates transcriptional activity of RUNX1b.Varshney B, Agnihothram S, Tan YJ, Baric R, Lal SK.PLoS One. 2012;7(1):e29542. doi: 10.1371/journal.pone.0029542. Epub 2012 Jan 12. Erratum in: PLoS One. 2012;7(3). doi:10.1371/annotation/64ae6047-0f9b-4d17-a065-e08c153aa435. Agnihotram, Sudhakar

6. Severe acute respiratory syndrome coronavirus envelope protein regulates cell stress response and apoptosis.DeDiego ML, Nieto-Torres JL, Jiménez-Guardeño JM, Regla-Nava JA, Alvarez E, Oliveros JC, Zhao J, Fett C, Perlman S, Enjuanes L.PLoS Pathog. 2011 Oct;7(10):e1002315. doi: 10.1371/journal.ppat.1002315. Epub 2011 Oct 20.

7. CD8+ T cell response in HLA-A*0201 transgenic mice is elicited by epitopes from SARS-CoV S protein.Zhao K, Yang B, Xu Y, Wu C.Vaccine. 2010 Sep 24;28(41):6666-74. doi: 10.1016/j.vaccine.2010.08.013. Epub 2010 Aug 13.

8. Induction of interferon-gamma-inducible protein 10 by SARS-CoV infection, interferon alfacon 1 and interferon inducer in human bronchial epithelial Calu-3 cells and BALB/c mice.Kumaki Y, Day CW, Bailey KW, Wandersee MK, Wong MH, Madsen JR, Madsen JS, Nelson NM, Hoopes JD, Woolcott JD, McLean TZ, Blatt LM, Salazar AM, Smee DF, Barnard DL.Antivir Chem Chemother. 2010 Mar 9;20(4):169-77. doi: 10.3851/IMP1477

9. Identification of human cell line model of persistent SARS coronavirus infection and studies of the response to cytokines and chemokines.To KF, Chan PK.Hong Kong Med J. 2009 Oct;15 Suppl 6:39-43.

10. Association of cytokine and chemokine gene polymorphisms with severe acute respiratory syndrome.Lau YL, Peiris JS.Hong Kong Med J. 2009 Feb;15 Suppl 2:43-6.

11. Enhancing immune responses against SARS-CoV nucleocapsid DNA vaccine by co-inoculating interleukin-2 expressing vector in mice.Hu H, Tao L, Wang Y, Chen L, Yang J, Wang H.Biotechnol Lett. 2009 Nov;31(11):1685-93. doi: 10.1007/s10529-009-0061-y. Epub 2009 Jul 5

12. Early upregulation of acute respiratory distress syndrome associated cytokines promotes lethal disease in an aged-mouse model of severe acute respiratory syndrome coronavirus infection.Rockx B, Baas T, Zornetzer GA, Haagmans B, Sheahan T, Frieman M, Dyer MD, Teal TH, Proll S, van den Brand J, Baric R, Katze MG.J Virol. 2009 Jul;83(14):7062-74. doi: 10.1128/JVI.00127-09. Epub 2009 May 6. Erratum in: J Virol. 2009 Sep;83(17):9022.

13. Interferon and cytokine responses to SARS-coronavirus infection.Thiel V, Weber F.Cytokine Growth Factor Rev. 2008 Apr;19(2):121-32. doi: 10.1016/j.cytogfr.2008.01.001. Epub 2008 Mar 5.

9.2 GROUPS: II

9.2.1. RECEPTOL® & Viral Respiratory infection

Human respiratory syncytial virus (RSV) is a virus that causes respiratory tract infections. It is a major cause of lower respiratory tract infections and hospital visits during infancy and childhood. A prophylactic medication (not a vaccine) exists forpreterm (under 35 weeks gestation) infants, infants with certain congenital heart defects (CHD) or bronchopulmonary dysplasia(BPD), and infants with congenital malformations of the airway. Treatment is limited to supportive care (for example C-PAP), including oxygen therapy.

In temperate climates there is an annual epidemic during the winter months. In tropical climates, infection is most common during the rainy season.

What is an upper respiratory infection?

The upper respiratory tract includes the sinuses, nasal passages, pharynx, and larynx. These structures direct the air we breath from the outside to the trachea and eventually to the lungs for respiration to take place. An upper respiratory tract infection, or upper respiratory infection, is an infectious process of any of the components of the upper airway.

Infection of the specific areas of the upper respiratory tract can be named specifically. Examples of these may include rhinitis (inflammation of the nasal cavity), sinus infection (sinusitis or rhinosinusitis) - inflammation of the sinuses located around the nose, common cold (nasopharyngitis) - inflammation of the nares, pharynx, hypopharynx, uvula, and tonsils, pharyngitis (inflammation of the pharynx, uvula, and tonsils), epiglottitis (inflammation of the upper portion of the larynx or the epiglottis), laryngitis(inflammation of the larynx), laryngotracheitis (inflammation of the larynx and the trachea), and tracheitis (inflammation of the trachea). Upper respiratory infections are one of the most frequent causes of doctors visits with varying symptoms ranging from runny nose, sore throat, cough, to breathing difficulty, and lethargy.

In the United States, upper respiratory infections are the most common illness leading to missing school or work. Although upper respiratory infections can happen at any time, they are most common in the fall and winter months, from September until March. This may be explained because these are the usual school months when children and adolescents spend a lot of time in groups and inside closed doors. Furthermore, many viruses of upper respiratory infection thrive in the low humidity of the winter. Respiratory tract infections affect the nose, throat, and airways and may be caused by any of several different viruses.

- Common respiratory tract infections include the common cold and influenza.
- Typical symptoms include nasal congestion, a runny nose, scratchy throat, cough,
- The diagnosis is based on symptoms.
- Good hygiene is the best way to prevent these infections, and routine vaccination can prevent influenza. Treatment aims to relieve symptoms.

Children develop on average six viral respiratory tract infections each year. Viral respiratory tract infections include the common cold (see xref.discussed-in Smallpox) and influenza (see

xref.discussed-in Influenza). Doctors often refer to these as upper respiratory infections (URIs), because they cause symptoms mainly in the nose and throat. In small children, viruses also commonly cause infections of the lower respiratory tract—the windpipe, airways, and lungs. These infections include croup, bronchiolitis, and pneumonia. Children sometimes have infections involving both the upper and lower respiratory tracts.

In children, rhinoviruses, influenza viruses (during annual winter epidemics), parainfluenza viruses, respiratory syncytial virus (RSV), enteroviruses, and certain strains of adenovirus are the main causes of viral respiratory infections.

Most often, viral respiratory tract infections spread when children's hands come into contact with nasal secretions from an infected person. These secretions contain viruses. When the children touch their mouth, nose, or eyes, the viruses gain entry and produce a new infection. Less often, infections spread when children breathe air containing droplets that were coughed or sneezed out by an infected person. For various reasons, nasal or respiratory secretions from children with viral respiratory tract infections contain more viruses than those from infected adults. This increased output of viruses, along with typically lesser attention to hygiene, makes children more likely to spread their infection to others. The possibility of transmission is further enhanced when many children are gathered together, such as in child care centers and schools. Contrary to what people may think, other factors, such as becoming chilled, wet, or tired, do not cause colds or increase a child's susceptibility to infection.

Symptoms and Complications

When viruses invade cells of the respiratory tract, they trigger inflammation and production of mucus. This situation leads to nasal congestion, a runny nose, scratchy throat, and cough, which may last up to 14 days. Fever, with a temperature as high as 101 to 102° F (about 38.3 to 38.9° C), is common. The child's temperature may even rise to 104° F (40° C). Other typical symptoms in children include decreased appetite, lethargy, and a general feeling of illness (malaise). Headaches and body aches develop, particularly with influenza. Infants and young children are usually not able to communicate their specific symptoms and just appear cranky and uncomfortable.

Because newborns and young infants prefer to breathe through their nose, even moderate nasal congestion can create difficulty breathing. Nasal congestion leads to feeding problems as well, because infants cannot breathe while suckling from the breast or bottle. Because infants are unable to spit out mucus that they cough up, they often gag and choke.

The small airways of young children can be significantly narrowed by inflammation and mucus, making breathing difficult. Children breathe rapidly and may develop a high-pitched noise heard on breathing out (wheezing) or a similar noise heard on breathing in (stridor). Severe airway narrowing may cause children to gasp for breath and turn blue (cyanosis). Such airway problems are most common with infection caused by parainfluenza viruses and RSV. Affected children need to be seen urgently by a doctor.

Some children with a viral respiratory tract infection also develop an infection of the middle ear (otitis media) or the lung tissue (pneumonia). Otitis media and pneumonia may be caused by the virus itself or by a bacterial infection that develops because the inflammation caused by the virus makes tissue more susceptible to invasion by other germs. In children with asthma, respiratory tract infections often lead to an asthma attack.

Viruses – a cause of respiratory infections:

i) Viruses in general attack us when our immunity is low — due to poor nutrition, consumption of alcohol, smoking and lack of sleep.

ii) Once they enter the body, viruses multiply in favourable conditions. This leads to an acute attack.

iii) The white blood cells (WBCs), in particular circulating in the blood, fight back and then symptoms may subside.

iv) Sometimes the virus overpowers the human defences leading to a prolonged attack or chronic illness.

References

1. The effect of bovine colostrum on viral upper respiratory tract infections in children with immunoglobulin A deficiency. Patıroğlu T, Kondolot M.Clin Respir J. 2013 Jan;7(1):21-6. doi: 10.1111/j.1752-699X.2011.00268.x. Epub 2011 Sep 6.

2. Effect of bovine colostrum supplementation on respiratory tract mucosal defenses in swimmers.Crooks C, Cross ML, Wall C, Ali A.Int J Sport Nutr Exerc Metab. 2010 Jun;20(3):224-35.

3. Dual enteric and respiratory tropisms of winter dysentery bovine coronavirus in calves.Park SJ, Kim GY, Choy HE, Hong YJ, Saif LJ, Jeong JH, Park SI, Kim HH, Kim SK, Shin SS, Kang MI, Cho KO. Arch Virol. 2007;152(10):1885-900. Epub 2007 Jun 14.

4. Response of calves to challenge exposure with virulent bovine respiratory syncytial virus following intranasal administration of vaccines formulated for parenteral administration.Ellis J, Gow S, West K, Waldner C, Rhodes C, Mutwiri G, Rosenberg H.J Am Vet Med Assoc. 2007 Jan 15;230(2):233-43.

5. The effect of maternally derived immunoglobulin G on the risk of respiratory disease in heifers during the first 3 months of life. Virtala AM, Gröhn YT, Mechor GD, Erb HN.Prev Vet Med. 1999 Mar 12;39(1):25-37.

9.2.2. RECEPTOL® & Colds and flu

What Is the Common Cold?

On average, American adults will suffer from 2 to 4 colds per year and children will get between 6 and 10 colds per year. The common cold is probably the most common illness in the United States today, but it is also the most common reason for doctor's visits, even though there is no cure for the cold. The cold, like the flu, is a virus and cannot be treated with antibiotics

What Is the Flu?

The flu is similar to the common cold but the symptoms are usually much more severe. Five to 20 percent of the American population comes down with the flu each year. It can be very serious and even fatal.

The flu is a virus called influenza. It cannot be treated with antibiotics, but may be prevented with a flu shot and new antiviral medications, such as Tamiflu, may help shorten the duration of the flu.

It's important to know the difference between flu and cold symptoms. A cold is a milder respiratory illness than the flu. While cold symptoms can make you feel bad for a few days, flu symptoms can make you feel quite ill for a few days to weeks. The flu can also result in serious health problems such as pneumonia and hospitalizations.

What are common cold symptoms?

Cold symptoms usually begin with a sore throat, which usually goes away after a day or two. Nasal symptoms, runny nose, and congestion follow, along with acough by the fourth and fifth days. Fever is uncommon in adults, but a slight fever is possible. Children are more likely to have a fever with a cold.

With cold symptoms, the nose teems with watery nasal secretions for the first few days. Later, these become thicker and darker. Dark mucus is natural and does not usually mean you have developed a bacterial infection, such as a sinus infection. Several hundred different viruses may cause your cold symptoms.

How long do cold symptoms last?

Cold symptoms usually last for about a week. During the first three days that you have cold symptoms, you are contagious. This means you can pass the cold to others, so stay home and get some much-needed rest.
If cold symptoms do not seem to be improving after a week, you may have a bacterial infection, which means you may need antibiotics.
Sometimes you may mistake cold symptoms for allergic rhinitis (hay fever) or a sinus infection. If cold symptoms begin quickly and are improving after a week, then it is usually a cold, not allergy. If your cold symptoms do not seem to be getting better after a week, check with your doctor to see if you have developed an allergy or sinusitis.

What are common flu symptoms?

Flu symptoms are usually more severe than cold symptoms and come on quickly. Symptoms of flu include sore throat, fever, headache, muscle aches and soreness, congestion, and cough. Swine flu in particular is also associated with vomiting and diarrhea.

Most flu symptoms gradually improve over two to five days, but it's not uncommon to feel run down for a week or more. A common complication of the flu is pneumonia, particularly in the young, elderly, or people with lung or heart problems. If you notice shortness of breath, let your doctor know. Another common sign of pneumonia is fever that comes back after having been gone for a day or two.

Just like cold viruses, flu viruses enter your body through the mucous membranes of the nose, eyes, or mouth. Every time you touch your hand to one of these areas, you could be infecting yourself with a virus, which makes it very important to keep hands germ-free with frequent washing to prevent both flu and cold symptoms.

Is it flu or cold symptoms?

How do you know if you have flu or cold symptoms? Take your temperature, say many experts. Flu symptoms often mimic cold symptoms with nasal congestion, cough, aches, and malaise. But a common cold rarely has symptoms of fever above 101 degrees. With flu symptoms, you will probably have a fever initially with the flu virus and you will feel miserable. Body and muscle aches are also more common with the flu. This table can help determine if you have cold or flu symptoms.

Symptoms	Cold	Flu
Fever	Sometimes, usually mild	Usual; higher (100-102 F; occasionally higher, especially in young children); lasts 3 to 4 days
Headache	Occasionally	Common
General Aches, Pains	Slight	Usual; often severe
Fatigue, Weakness	Sometimes	Usual; can last 2 to 3 weeks
Extreme Exhaustion	Never	Usual; at the beginning of the illness
Stuffy Nose	Common	Sometimes
Sneezing	Usual	Sometimes

Sore Throat	Common	Sometimes
Chest Discomfort, Cough	Mild to moderate; hacking cough	Common; can become severe
Complications	Sinus congestion; middle ear infection	Sinusitis, bronchitis, ear infection, pneumonia; can be life-threatening
Prevention	Wash hands often; avoid close contact with anyone with a cold	Wash hands often; avoid close contact with anyone who has flu symptoms; get the annual flu vaccine

9.2.3 RECEPTOL® & Lymphoma

What Is Lymphoma?

Lymphoma is a type of cancer that begins in immune system cells called lymphocytes. Like other cancers, lymphoma occurs when lymphocytes are in a state of uncontrolled cell growth and multiplication.

Lymphocytes are white blood cells that move throughout the body in a fluid called lymph. They are transported by a network of vessels that make up the lymphatic system, part of the immune system. The lymphatic system - whose job it is to fight infections or anything else that threatens the body - is also comprised of lymph nodes that exist throughout the body to filter the lymph that flows through them. The lymph nodes swell and tenderize when a large number of microbial organisms collect inside of them, indicating local infection.

There are two primary types of lymphocytes: B cells and T cells. Both are designed to recognize and destroy infections and abnormal cells. B cells produce proteins that travel throughout the body, attaching themselves to infectious organisms and abnormal cells and alerting the immune system that the pathogen needs to be destroyed. T cells actually kill the pathogens directly and serve a function in regulating the immune system from over- or under-activity.

Lymphoma occurs when lymphocyte B or T cells transform and begin growing and multiplying uncontrollably. Abnormal lymphocytes collect in one or more lymph nodes or in lymph tissues such as the spleen or tonsils, and eventually they form a mass of cells called a tumor. Tumors grow and invade the space of surrounding tissues and organs, depriving them of oxygen and nutrients.

If abnormal lymphocytes travel from one lymph node to the next or to other organs, the cancer can spread or metastasize. Lymphoma development outside of lymphatic tissue is called extranodal disease.

In the United States each year, some 54,000 people are diagnosed with NHL and 7,000 are diagnosed HL. It is the most common type of blood cancer in the US. The European Union sees over 50,000 cases of NHL every year.

How is lymphoma classified?

There are two types of lymphoma: Hodgkin lymphoma (HL, also called Hodgkin's disease) and non-Hodgkin lymphoma (NHL). Both HL and NHL can occur in the same places and have similar symptoms. Their differences are visible at a microscopic level.

Hodgkin lymphoma develops from a specific abnormal lineage of B cells. There are five subtypes of HL. NHL may derive from either abnormal B or T cells, and its 30 subtypes are distinguished by unique genetic markers. The large number of lymphoma subtypes has led to a complicated classification scheme that involves microscopic appearance and well-defined genetic and molecular configurations. Although several NHL subtypes look similar, they function differently and respond

differently to therapies. HL subtypes are microscopically distinct, and classification is based upon the microscopic differences as well as the extent of disease.

What are the symptoms of Lymphoma?

Cancer symptoms are quite varied and depend on where the cancer is located, where it has spread, and how big the tumor is. Lymphoma usually first presents with swelling in the neck, underarm, or groin. Additional swelling may occur where other lymph nodes are located such as in the spleen. In general, enlarged lymph nodes can encroach on the space of blood vessels, nerves, or the stomach, leading to swollen arms and legs, to tingling and numbness, or to feelings of being full,respectively. Lymphoma symptoms also include nonspecific symptoms such as **fever**, chills, unexplained weight loss, night sweats, lethargy, and itching.

What causes Lymphoma?

Cancer is ultimately the result of cells that uncontrollably grow and do not die. Normal cells in the body follow an orderly path of growth, division, and death. Programmed cell death is called apoptosis, and when this process breaks down, cancer results. Scientists do not know exactly what causes lymphoma, but they have identified several potential risk factors.

Genetics

Lymphoma can be the result of a genetic predisposition that is inherited from family members. It is possible to be born with certain genetic mutations or a fault in a gene that makes one statistically more likely to develop cancer later in life.

Carcinogens

Carcinogens are a class of substances that are directly responsible for damaging DNA, promoting or aiding cancer. Exposure to certain pesticides, herbicides, and solvents such as benzene has been associated with lymphoma. Similarly, black hair dye has been linked to higher rates of NHL. When our bodies are exposed to carcinogens, free radicals are formed that try to steal electrons from other molecules in the body. These free radicals damage cells, affecting their ability to function normally, and the result can be cancerous growths. Other medical factors,

As we age, there is an increase in the number of possible cancer-causing mutations in our DNA. The risk of NHL increases as we age, and HL is most common between ages 16-34 and 55 years and older. Additional medical conditions that have been associated with higher lymphoma rates include infection with HIV, human T-lymphocytic virus type 1 (HTLV-1), Epstein-Barr virus, Helicobacter pylori, or hepatitis B or C; autoimmune disease (such as lupus); diseases that require therapies that suppress the immune system; and any other immunodeficiency diseases.

In May 2012, researchers from the Department of Medicine at Stanford University identified the risk factors that increased the likelihood of developing non-Hodgkin lymphoma early in life; they included high fetal growth, being male, low birth order, and older maternal age.

References:

1. Purification and characterization of UDP-N-acetylgalactosamine: polypeptideN-acetylgalactosaminyltransferase from bovine colostrum and murine lymphoma BW5147 cells.Elhammer A, Kornfeld S.J Biol Chem. 1986 Apr 25;261(12):5249-55.

2. Attempted transmission of bovine lymphosarcoma to swine. Koller LD, Olson C, Gillette KG.Am J Vet Res. 1970 Feb;31(2):285-9

3. Experiments on the transmission of bovine leukosis by colostrum and milk. Weinhold E, Straub OC.Bibl Haematol. 1968;30:146-8

4. Polypeptide N-acetylgalactosaminyltransferase activity in tracheal epithelial microsomes.Cottrell JM, Hall RL, Sturton RG, Kent PW.Biochem J. 1992 Apr 1;283 (Pt 1):299-305.

5. Multimeric and differential binding of CIN85/CD2AP with two atypical proline-rich sequences from CD2 and Cbl-b*. Ceregido MA, Garcia-Pino A, Ortega-Roldan JL, Casares S, López Mayorga O, Bravo J, van Nuland NA, Azuaga AI.FEBS J. 2013 Jul;280(14):3399-415

6. Involvement of Grb2 adaptor protein in nucleophosminanaplastic lymphoma kinase (NPM-ALK)-mediated signaling and anaplastic large cell lymphoma growth.Riera L, Lasorsa E, Ambrogio C, Surrenti N, Voena C, Chiarle R.J Biol Chem. 2010 Aug 20;285(34):26441-50.

7. Differential effect of B lymphocyte-induced maturation protein (Blimp-1) expression on cell fate during B cell development. Messika EJ, Lu PS, Sung YJ, Yao T, Chi JT, Chien YH, Davis MM. J Exp Med. 1998 Aug 3;188(3):515-25

9.2.4. RECEPTOL® & Herpes Simplex I & II disease

What is Herpes Simplex I & II?

Herpes simplex virus 1 and 2 (HSV-1 and HSV-2), also known as human herpesvirus 1 and 2 (HHV-1 and HHV-2), are two members of the herpesvirus family, Herpesviridae, that infect humans. Both HSV-1 (which produces most cold sores) and HSV-2 (which produces most genital herpes) are ubiquitous and contagious. They can be spread when an infected person is producing and shedding the virus. Herpes simplex can be spread through contact with saliva, such as sharing drinks.

Symptoms of herpes simplex virus infection include watery blisters in the skin or mucous membranes of the mouth, lips or genitals. Lesions heal with a scab characteristic of herpetic disease. Sometimes, the viruses cause very mild or atypical symptoms during outbreaks. However, as neurotropic and neuroinvasive viruses, HSV-1 and -2 persist in the body by becoming latent and hiding from the immune system in the cell bodies of neurons. After the initial or primary infection, some infected people experience sporadic episodes of viral reactivation or outbreaks. In an outbreak, the virus in a nerve cell becomes active and is transported via the neuron's axon to the skin, where virus replication and shedding occur and cause new sores.

What Are the Symptoms of Herpes Simplex?

Symptoms of herpes simplex virus typically appear as a blister or as multiple blisters on or around affected areas -- usually the mouth, genitals, or rectum.The blisters break, leaving tender sores.

What Causes Herpes Infections and Outbreaks?

Herpes simplex type 1, which is transmitted through oral secretions or sores on the skin, can be spread through kissing or sharing objects such as toothbrushes or eating utensils. In general, a person can only get herpes type 2 infections during sexual contact with someone who has a genital HSV-2 infection. It is important to know that both HSV-1 and HSV-2 can be spread even if sores are not present.

Pregnant women with genital herpes should talk to their doctor as genital herpes can be passed on to the baby during childbirth.

For many people with the herpes virus, which can go through periods of being dormant, attacks (or outbreaks) can be brought on by the following conditions:

General illness (from mild illnesses to serious conditions)

Fatigue, Physical or emotional stress

Immunosuppression due to AIDS or such medications as chemotherapy or steroids

Trauma to the affected area, including sexual activity, Menstruation

References:

1. Herpes simplex virus type 1 virion-derived US11 inhibits type 1 interferon-induced protein kinase R phosphorylation.Ishioka K, Ikuta K, Sato Y, Kaneko H, Sorimachi K, Fukushima E, Saijo M, Suzutani T.Microbiol Immunol. 2013 Jun;57(6):426-36. doi: 10.1111/1348-0421.12048.

2. The virion host shutoff protein of herpes simplex virus 1 blocks the replication-independent activation of NF-κB in dendritic cells in the absence of type I interferon signaling.Cotter CR, Kim WK, Nguyen ML, Yount JS, López CB, Blaho JA, Moran TM.J Virol. 2011 Dec;85(23):12662-72. doi: 10.1128/JVI.05557-11. Epub 2011 Sep 21.

3. Interleukin 29 enhances expression of Toll receptor 3 and mediates antiviral signals in human keratinocytes.Zhang SQ, Zhang Z, Luo X, Yang S, Chai Y, Huang HL, Yin XY, Hu DJ, Yang CJ, Liu JL, Zhang XJ.Inflamm Res. 2011 Nov;60(11):1031-7. doi: 10.1007/s00011-011-0364-z. Epub 2011 Aug 17.

4. Promyelocytic leukemia protein mediates interferon-based anti-herpes simplex virus 1 effects.Chee AV, Lopez P, Pandolfi PP, Roizman B. J Virol. 2003 Jun;77(12):7101-5

5. Analysis of cytokine mRNAs in murine herpes simplex virus type 1 retinitis.Saitoh-Ishibashi K, Ishibashi K, Azumi A, Negi A.Jpn J Ophthalmol. 2003 Mar Apr;47(2):166-72.

6. Interleukin-12- and gamma interferon-dependent innate immunity are essential and sufficient for long-term survival of passively immunized mice infected with herpes simplex virus type 1.Vollstedt S,Franchini M,Alber G,Ackermann M,Suter M.J Virol.2001 Oct;75(20):9596-600.

7. Are cytokine patterns in aqueous humour useful in distinguishing corneal graft rejection from opacification due to herpetic stromal keratitis?van Gelderen EB, Van der Lelij A, Völker-Dieben HJ, van der Gaag R, Peek R, Treffers WF.Doc Ophthalmol. 1999;99(2):171-82

9.3 GROUPS: III

9.3.1 RECEPTOL® & Allergies

What is an Allergy?

An allergy is a disorder of the immune system, which is caused by sensitivity to an environmental substance known as an allergen. Examples of allergic reactions are eczema, hives, hay fever, asthma, food allergies and reaction to the venom of stinging insects, such as wasps and bees. The mechanism of allergies is caused by an activation of certain white blood cells called mast cells, and basophiles, a type of immunoglobulin, know as IgE, which results in a strong inflammatory response.

Type of allergens

An allergen could be a food, an inhalant such as pollen, mould, dust, animal dander or hair, chemicals as well as additional types of allergies

- Food allergies - milk, wheat, nuts, Soya
- Environment - hay fever, dust allergies, pollution
- Chemicals - paint fumes, pesticides
- Animals - fur, hair

What are the symptoms?

Mild allergies, like hay fever (watery eyes, runny nose, sinus stuffiness, etc.) are highly prevalent in humans. An allergic reaction may manifest itself as asthma, hives, eczema, high blood pressure, abnormal fatigue, abnormal hunger, stomach cramps, vomiting, anxiety, depression, constipation, dizziness, hyperactivity, insomnia, stomach ulcers, headache etc.

How RECEPTOL® Oral Spray can help people with allergies

RECEPTOL® contains Proline-Rich- Polypeptide (PRP), a powerful regulator of the immune system. It improves the permeability of the skin vessels; it is proved that it can help to regulate the over-reaction of the immune system to allergens. According to APS BioGroup, PRP has the same ability to regulate activity of the immune system as do hormones produced by the thymus gland. It can stimulate an under-active immune system into dealing with disease-causing organisms and it can suppress an over-active immune system, which results from autoimmune disorders and allergic reactions.

RECEPTOL® can help people, who are frequently suffering with allergies and can help to relieve or reduce the symptoms with long-term colostrum supplementation. RECEPTOL® Spray extract is recommended over capsules.

"The Label claims are based on global studies on API: PRPs (Radha108 as class of PRPs being part of it) for which we have sent and up loaded claims on various indications based on published data in first rate Medical Journals.

References:

1. Saharan P, Singh T. Efficacy and Safety/Tolerability clinical trial of RECEPTOL® ®: New Nanobiotechnology based Immunomodulator in RHEUMATOID ARTHRITIS therapy. Unpublished Patented data (2005-2006).

2. Khan A. Non-specificity of transfer factor. Annals of Allergy 38(5):320-322 (1977).

3. Immunology, Immunopathology and Immunity. Sell S. Appleton and Lange: Stamford CT 1996.

4. Janusz M, Staroscik K,Zimecki M,Wieczorek Z,Lisowski J. A proline-rich polypeptide (PRP) with immunoregulatory properties isolated from ovine Colostrum. ArcRheumatoid Arthritisum immulologiae ettherapiae experimentalis (Warszava) 34(4):427-436 (1986)

5. Wieczorek Z, Zimecki M, Spiegel K ,Lisowski J, Janusz M. Differentiation of T-cells into helper cells from immature precursors : identification of a target cell for a proline-rich polypeptide(PRP) ArcRheumatoid Arthritisum immulologiae et therapiae experimentalis (Warszava) 37(3-4):313-322 (1989)

6. Bishop GA, Haxhinasto SA, Slunz LL, Hostager BS. Antigen-specific B-lymphocyte activation. Critical reviews in Immunology 23(3):159-197(2003).

7. Shi M,Hao S,Chan T,Xiang J. CD4+ T cells stimulate memory CD8+ T cell expansion via acquired pMHC I complexes and costimulatory molecules, and IL-2 secretion. Journal of leucocyte Biology (2006).

8. Zimecki M,Staroscik K, Janusz M, Lisowski J, Wieczorek Z. The inhibitory activity of prolinerich polypeptide on the immune response to polyvinyl pyrrolidone (PVP). ArcRheumatoid Arthritisum immulologiae et therapiae experimentalis (Warszava) 31(6):895-903 (1983)

9. Julius MH, Janusz M, Lisowski J. A colostral protein that induces the growth and differentiation of resting B lymphocytes. Journal of Immunology 140(5):1366-371 (1988)

10. Dr. Zoltan Rona, The American Journal of Natural Medicine, March 1998.

11. Jackson PG, Lessof MH, Baker RWR, Ferrett J, MacDonald DM. Intestinal Permeability in Patients with Eczema and Food Allergy. Lancet, 1(8233): 1285–1286(1981).

12. Altekruse SF, Bauer N, Chanlongbutra A, DeSagun R, Naugle A, Schlosser W, Umholtz R, White P. Salmonella enteritidis in broiler chickens, United States, 2000-2005. Emerging Infectious Diseases12(12): 1848–1852 (2006).
Wrong Diagnosis. Death Statistics for Types of Food Poisoning. http://www.wrongdiagnosis.com/f/food_poisoning/death-types.htm

13. Ho PC, Lawton JW. Human colostral cells: Phagocytosis and killing of E. coli and C. albicans. Journal of Pediatrics, 93(6):910–915 (1978).

14. Kim K, Pickering LK, DuPont HL, Sullivan N, Wilkins T. In vitro and in vivo neutralizing activity of human colostrum and milk against purified toxins A and B of Clostridium difficile. Journal of Infectious Diseases 150(1):57–62 (1984).

15. Tacker CO, Binion SB, Bostwick E, Losonsky G, Roy MJ, Edelman R. Efficacy of bovine milk immunoglobulin concentrate in preventing illness after Shigella flexneri challenge. American Journal of Tropical Medicine and Hygiene, 47(3):276–283(1992).

16. Watson C, Alp NJ. Role of Chlamydia pneumoniae in atherosclerosis. Clinical Science, 114(8):509–531(2008).

17. Tortora GJ, Funke BD, Case CL. Microbiology: An Introduction. 8th edition, pp485–488.PearsonEducation,2004.

18. Aranaz P, Hurtado C, Erquiaga I, Miguéliz I, Ormazábal C, Cristobal I, García-Delgado M, Novo FJ, Vizmanos JL. Haematologica. 2012 Aug; 97(8):1234-41. doi: 10.3324/haematol.2011.052605. Epub 2012 Feb 7.

19. Jensen JM, Scherer A, Wanke C, Bräutigam M, Bongiovanni S, Letzkus M, Staedtler F, Kehren J, Zuehlsdorf M, Schwarz T, Weichenthal M, Fölster-Holst R, Proksch E. Allergy. 2012 Mar;67(3):413-23. doi: 10.1111/j.1398-9995.2011.02747.x. Epub 2011 Dec 6.

20. Lee CM, Gala S, Stewart GJ, Williamson P. Viral Immunol. 2008 Sep;21(3):347-54. doi: 10.1089/vim.2007.0093.

21. Boldogh I, Aguilera-Aguirre L, Bacsi A, Choudhury BK, Saavedra-Molina A, Kruzel M. Int Arch Allergy Immunol. 2008; 146(4):298-306. doi: 10.1159/000121464. Epub 2008 Mar 26.

22. Zimmermann N, Doepker MP, Witte DP, Stringer KF, Fulkerson PC, Pope SM, Brandt EB, Mishra A, King NE, Nikolaidis NM, Wills-Karp M, Finkelman FD, Rothenberg ME. Am J Respir Cell Mol Biol. 2005 May;32(5):428-35. Epub 2005 Feb 24.

9.3.2 RECEPTOL® & Alzheimer

What is an Alzheimer?

Alzheimer's disease (AD) or simply Alzheimer's, is the most common cause of dementia (AD). Alzheimer's is a progressive and terminal disease, affecting 24 millions people worldwide. The onset of the disease in people occurs over the age 65, but early onset of the disease also exists. It usually begins long time before it is actually diagnosed.

Symptoms of Alzheimer

In the early stages, the clearest symptom is short-term memory loss and this leads to confusion, anger, mood swings, language breakdown, long-term memory loss, and decline of all senses.

How RECEPTOL® Oral Spray can help people with Alzheimer

RECEPTOL® Oral Spray contains special Prolin-Rich-Polypeptide (PRP), which is a powerful regulator of the more immune system and increase the permeability of vessels of the skin helping to supply cells with more nutrients.

The importance of regulating the activity of the immune system is that it has the ability to stimulate or suppress the immune response. Suppressing the immune system is necessary to prevent the immune system from attacking the body as "itself", as is in the case of autoimmune illness, Alzheimer's. RECEPTOL®'s suppressive action may help prevent this type of activity involved in autoimmune diseases.

In the study by Leszek, the results obtained showed that PRP improved the outcome of Alzheimer's patients with mild and moderate dementia.

"The trials demonstrated the therapeutic benefit of CLN (RECEPTOL® Proline-rich -polypeptide complex) in Alzheimer's disease (AD) patients by delaying progress of the disease".

Colostrinin (b): a proline-rich polypeptide (PRP) complex isolated from ovine colostrum for treatment of Alzheimer's disease. A double-blind, placebo-controlled study.

"The Label claims are based on global studies on API: PRPs (Radha108 as class of PRPs being part of it) for which we have sent and up loaded claims on various indications based on published data in first rate Medical Journals. BMJ has accepted our two articles and two more are likely to be in leading Science Journal like NATURE by end of 2014 since our Global Medical Advisory Board has recommended to wait for follow up of patients who tried the product over 6 to 7 years ago and still have not shown any sign of disease reappearance, indicating that all Hibernation Viruses (crossing a window period of 8 years), including HIV have been stopped its reproduction leading to a possible claim for treatment & cure of AIDS & other major immune disorders, for which we have just received an approval for new US Product Patent as well".

A proline-rich polypeptide (PRP) complex, subsequently called Colostrinin, was isolated from ovine colostrum. The complex showed immunomodulatory properties in mice, rats, and chickens, inducing maturation and differentiation of thymocytes. It was recently found that Colostrinin is a cytokine-like

factor that acts as an inducer of interferon gamma (IFN-gamma) and other cytokines in human peripheral blood and cord blood leukocyte cultures and has psycho-immuno-enhancing activity in volunteers. These observations prompted us to study the effect of Colostrinin on patients with Alzheimer's disease (AD).

Forty six AD patients were divided into 3 groups and randomly assigned to receive orally either Colostrinin (100 microgram per tablet, every second day), commercially available bioorganic selenium (100 microgram selenium per tablet, every second day) or placebo tablets. One cycle of the treatment lasted 3 weeks and was separated from the next cycle by a 2 week hiatus. Each patient received 10 cycles of treatment during the year of the clinical trial. Outcomes were assessed by psychiatrists blinded to the treatment assignment. Eight of the 15 AD patients treated with Colostrinin improved and in the 7 others the disease had stabilized. In contrast, none of the 31 patients from the selenium or placebo groups with similar mild or moderate AD improved.

The administration of selenium promoted stabilization in 13 of the 15 patients, whereas in the placebo group only 8 of the 16 patients were stabilized at the 12 month trials end-evaluation. Colostrinin was found to be a remarkably safe drug. Mild and transient effects were anxiety, stimulation, insomnia, and tiredness. The results suggest that the beneficial effects of PRP/Colostrinin observed in AD patients may be due to an inhibition of overproduction of NO and O which promote neurodegenerative processes. The results obtained showed that oral administration of Colostrinin (b) improves the outcome of Alzheimer's disease patients with mild to moderate dementia.

The fat and casein are removed from RECEPTOL® Oral Spray and as a result, the levels of some of the components, such as PRP, are of a higher concentration. This gives our RECEPTOL® the potential to be effective for Alzheimer's disease. Long-term use of RECEPTOL® Oral Spray colostrums extract is recommended.

References

1.Zimecki M, A proline-rich polypeptide from bovine colostrum: colostrinin with immunomodulatory activity. The trials demonstrated the therapeutic benefit of CLN in Alzheimer's disease (AD) patients by delaying progress of the disease. Institute of Immunology and Experimental Therapy, Wroclaw, Poland. Adv Exp Med Biol. 2008; 606:241-50

2.Sinforiani, E.; et al. Clinical Trials Journal, Vol. 24, No. 1, 1987. Cognitive Decline in Ageing Brain. (Therapeutic Approach with Phosphatidylserine. Brain aging effects were reduced in elderly patients after use of phosphatidylserine, a component of milk & bovine colostrum.

3.Leszek J, Inglot AD, Janusz M, Byczkiewicz F, Kiejna A, Georgiades J, Lisowski J. Colostrinin proline-rich polypeptide complex from ovine colostrum--a long-term study of its efficacy in Alzheimer's disease. Med Sci Monit. 2002 Oct;8(10):PI93-6.

4.Nunzi, Maria Grazia; et al. Phospholipids, 1990. Therapeutic Properties of Phosphatidylserine in the Aging Brain. Research results may justify the use of natural phospholipids (a component found in bovine colostrum) as a therapy for treating brain aging.

5.Bilikiewicz A, Gaus W. Colostrinin (a naturally occurring, proline-rich, polypeptide mixture) in the treatment of Alzheimer's disease. J Alzheimers Dis. 2004 Feb; 6(1):17-26.

6.Leszek J, Inglot AD, Janusz M, Lisowski J, Krukowska K, Georgiades JA. The Psychiatric Unit, University Medical School Wroclaw, Poland. Arch Immunol Ther Exp (Warsz). 1999;47(6):377-85.

7.Janusz M, Zabłocka A.Cell Mol Biol (Noisy-le-grand). 2013 Nov 3;59(1):4-11

8.Artym J, Zimecki M. Postepy Hig Med Dosw (Online). 2013 Aug 6;67:800-16.

9.Szaniszlo P, German P, Hajas G, Saenz DN, Woodberry MW, Kruzel ML, Boldogh I. Int Immunopharmacol. 2009 Feb;9(2):181-93. doi: 10.1016/j.intimp.2008.10.022. Epub 2008 Nov 17

10.Hicks DA, Makova NZ, Gough M, Parkin ET, Nalivaeva NN, Turner AJ. J Biol Chem. 2013 Sep 6;288(36):26039-51. doi: 10.1074/jbc.M113.461269. Epub 2013 Jul 29.

11.Zabłocka A, Janusz M. Arch Immunol Ther Exp (Warsz). 2012 Oct;60(5):383-90. doi: 10.1007/s00005-012-0187-9. Epub 2012 Aug 28.

12.Yenkoyan K, Safaryan K, Chavushyan V, Meliksetyan I, Navasardyan G, Sarkissian J, Galoyan A, Aghajanov M. Brain Res Bull. 2011 Oct 10;86(3-4):262-71. doi: 10.1016/j.brainresbull.2011.08.003. Epub 2011 Aug 5.

13.Zabłocka A, Ogorzałek A, Macała J, Janusz M. Nitric Oxide. 2010 Aug 1;23(1):20-5. doi: 10.1016/j.niox.2010.03.003. Epub 2010 Mar 24.

14. Zabłocka A, Siednienko J, Mitkiewicz M, Gorczyca WA, Lisowski J, Janusz M. Biomed Pharmacother. 2010 Jan;64(1):16-20. doi: 10.1016/j.biopha.2009.01.009. Epub 2009 Sep 8.

15. Galoyan AA, Sarkissian JS, Chavushyan VA, Meliksetyan IB, Avagyan ZE, Poghosyan MV, Vahradyan HG, Mkrtchian HH, Abrahamyan DO.

16. Zimecki M. Adv Exp Med Biol. 2008;606:241-50. doi: 10.1007/978-0-387-74087-4_9. Review.

17. Gladkevich A, Bosker F, Korf J, Yenkoyan K, Vahradyan H, Aghajanov M. Prog Neuropsychopharmacol Biol Psychiatry. 2007 Oct 1;31(7):1347-55. Epub 2007 Jun 21. Review.

18. Zabłocka A, Janusz M, Macała J, Lisowski J. Int Immunopharmacol. 2007 Jul;7(7):981-8. Epub 2007 Mar 19.

19. Zimecki M, Kruzel ML. J Exp Ther Oncol. 2007;6(2):89-106. Review.

20. Kubis A, Marcinkowska E, Janusz M, Lisowski J. Peptides. 2005 Nov;26(11):2188-92.

9.3.3 RECEPTOL® and Benign Prostatic Hyperplasia disease

What is Benign Prostatic Hyperplasia?

Benign prostatic hyperplasia (BPH), also called benign enlargement of the prostate (BEP), adenofibromyomatous hyperplasia and benign prostatic hypertrophy (technically incorrect usage), is an increase in size of the prostate.

BPH involves hyperplasia of prostatic stromal and epithelial cells, resulting in the formation of large, fairly discrete nodules in the periurethral region of the prostate. When sufficiently large, the nodules compress the urethral canal to cause partial, or sometimes virtually complete, urinary tract obstruction by the urethra, which interferes with the normal flow of urine. It leads to symptoms of urinary hesitancy, frequent urination, increased risk of urinary tract infections, urinary retention, or contributes to or cause insomnia. Although prostate specific antigen levels may be elevated in these patients because of increased organ volume and inflammation due to urinary tract infections, BPH does not lead to cancer or increase the risk of cancer.

BPH involves hyperplasia (an increase in the number of cells) rather than hypertrophy (a growth in the size of individual cells), but the two terms are often used interchangeably, even amongst urologists.

Adenomatous prostatic growth is believed to begin at approximately age 30 years. An estimated 50% of men have histologic evidence of BPH by age 50 years and 75% by age 80 years; in 40–50% of these men, BPH becomes clinically significant.

What are sign and symptoms of Benign Prostatic Hyperplasia disease?

Benign prostatic hyperplasia symptoms are classified as storage or voiding. Storage symptoms include urinary frequency, urgency, urgency incontinence, and voiding at night (nocturia). Voiding symptoms include urinary stream hesitancy (needing to wait for the stream to begin), intermittency (when the stream starts and stops intermittently), straining to void, and dribbling. Pain and dysuria are usually not present. These storage and voiding symptoms are evaluated using the International Prostate Symptom Score (IPSS) questionnaire, designed to assess the severity of BPH.

BPH can be a progressive disease, especially if left untreated. Incomplete voiding results in stasis of bacteria in the bladder residue and an increased risk of urinary tract infection. Urinary bladder stones are formed from the crystallization of salts in the residual urine. Urinary retention termed acute or chronic, is another form of progression. Acute urinary retention is the inability to void, while in chronic urinary retention the residual urinary volume gradually increases, and the bladder distends. This can result in bladder hypotonia. Some patients who suffer from chronic urinary retention may eventually progress to renal failure, a condition termed obstructive uropathy.

What causes Benign Prostatic Hyperplasia disease?

Most experts consider androgens (testosterone and related hormones) to play a permissive role. This means that androgens have to be present for BPH to occur, but do not necessarily directly cause the condition. This is supported by the fact that castrated boys do not develop BPH when they age. On the other hand, administering exogenous testosterone is not associated with a significant increase in the risk of BPH symptoms. Dihydrotestosterone (DHT), a metabolite of testosterone, is a critical mediator

of prostatic growth. DHT is synthesized in the prostate from circulating testosterone by the action of the enzyme 5α-reductase, type 2. This enzyme is localized principally in thestromal cells; hence, those cells are the main site for the synthesis of DHT.

DHT can act in an autocrine fashion on the stromal cells or in paracrine fashion by diffusing into nearby epithelial cells. In both of these cell types, DHT binds to nuclear androgen receptors and signals the transcription of growth factors that are mitogenic to the epithelial and stromal cells. DHT is 10 times more potent than testosterone because it dissociates from the androgen receptor more slowly. The importance of DHT in causing nodular hyperplasia is supported by clinical observations in which an inhibitor of 5α-reductase such as finasteride is given to men with this condition. Therapy with a 5α-reductase inhibitor markedly reduces the DHT content of the prostate and, in turn, reduces prostate volume and, in many cases, BPH symptoms.

Testosterone promotes prostate cell proliferation, but relatively low levels of serum testosterone are found in patients with BPH. One small study has shown that medical castration lowers the serum and prostate hormone levels unevenly, having less effect on testosterone and dihydrotestosterone levels in the prostate.

While there is some evidence that estrogen may play a role in the etiology of BPH, this effect appears to be mediated mainly through local conversion of androgens to estrogen in the prostate tissue rather than a direct effect of estrogen itself. In canine in vivo studies castration, which significantly reduced androgen levels but left estrogen levels unchanged, caused significant atrophy of the prostate. Studies looking for a correlation between prostatic hyperplasia and serum estrogen levels in humans have generally shown none.

In 2008, Yigal Gat et al. published evidence that BPH is caused by failure in the spermatic venous drainage system resulting in increased hydrostatic pressure and local testosterone levels elevated more than 100 fold above serum levels. If confirmed, this mechanism explains why serum androgen levels do not seem to correlate with BPH and why giving exogenous testosterone would not make much difference. This also has implications for treatment.

On a microscopic level, BPH can be seen in the vast majority of men as they age, in particular over the age of 70 years, around the world. However, rates of clinically significant, symptomatic BPH vary dramatically depending on lifestyle. Men who lead a western lifestyle have a much higher incidence of symptomatic BPH than men who lead a traditional or rural lifestyle. This is supported by research in China showing that men in rural areas have very low rates of clinical BPH, while men living in cities adopting a western lifestyle have a skyrocketing incidence of this condition, though it is still below rates seen in the West. It also seems that there is some connection between microcalcifications between prostate cancer and BPH, as is demonstrated in 50-75% of men over 50 years.

References:

1. Interleukin-6 polymorphism and prostate cancer risk in population of Eastern Croatia.Mandić S, Sudarević B, Marczi S, Horvat V, Cosić I, Mihaljević S, Milicević N, Simunović D, Galić J.Coll Antropol. 2013 Sep;37(3):907-11

2. Overexpression of signal transducer and activator of transcription (STAT-3 and STAT-5) transcription factors and alteration of suppressor of cytokine signaling (SOCS-1) protein in prostate cancer.Singh N, Hussain S, Bharadwaj M, Kakkar N, Singh SK, Sobti RC.J Recept Signal Transduct Res. 2012 Dec;32(6):321-7

3. Re: editorial comment on LHRH antagonist cetrorelix reduces prostate size and gene expression of proinflammatory cytokines and growth factors in a rat model of benign prostatic hyperplasia(Prostate 2011; 71: 736-747).Rick FG, Block NL, Schally AV.J Urol. 2013 Apr;189(4):1604-5

4. Re: LHRH antagonist Cetrorelix reduces prostate size and gene expression of proinflammatorycytokines and growth factors in a rat model of benign prostatic hyperplasia.Kaplan SA.J Urol. 2012 Sep;188(3):1046-7. doi:10.1016/j.juro.2012.05.046. Epub 2012 Jul 21

5. Diagnostic and prognostic significance of prostate specific antigen and serum interleukin 18 and 10 in patients with locally advanced prostate cancer: a prospective study.Dwivedi S, Goel A, Natu SM, Mandhani A, Khattri S, Pant KK.Asian Pac J Cancer Prev. 2011;12(7):1843-8

6. Role of interleukins, IGF and stem cells in BPH.McLaren ID, Jerde TJ, Bushman W.Differentiation. 2011 Nov-Dec;82(4-5):237-43. doi: 10.1016/j.diff.2011.06.001. Epub 2011 Aug 23

7. Serum cytokine profiling of prostate cancer and benign prostatic hyperplasia using recombinant antibody microarray].Zhang L, Sun SK, Shi LX, Zhang X.Zhonghua Nan Ke Xue. 2010 Jul;16(7):584-8.

9.3.4 RECEPTOL® & Cancer

About cancer

Nearly all cancers are caused by abnormalities in genetic material of transformed cells. Carcinogens, such as tobacco smoke, radiation, chemicals and infectious agents, may be the reason for abnormalities in the genetic cell's code. Other cancers could develop through errors in DNA replication or are inherited.

Cancer is abnormal cell growth, when cells do not replicate at normal rate in accordance with the body's growth and repair. Cancerous cells multiply faster and lose normal differentiation. Cancer develops due to the breakdown of the immune system which is meant to protect our body against precancerous cells. A healthy immune system can recognize these cells and eliminate them from the body.

What is Chemotherapy and radiotherapy

Chemotherapy is a treatment of disease by chemicals that kill cancerous cells. Chemotherapy is also called standardized treatment regimen, when a combination of drugs are used.

Radiotherapy also known as electrotherapy is the most frequently used form. The source of radiation is aimed at the particular area of the patient's body. Different x-rays are used for treating skin cancers and superficial structures and deep seated tumors' (bladder, bowel, prostate, lung, brain).

Both treatments have an adverse effect on the body and person's health. Chemotherapy has more severe side effects than radiotherapy.

Effects on human health

Almost all chemotherapeutic regimes can cause depression of the immune system, often caused by paralyzing the bone marrow and leading to decrease of white blood cells, red blood cells and platelets. White blood cells are our important for the body's defense. Nausea and vomiting are also caused by chemotherapy and fatigue or non-specific neurocognitive problems, such as an inability to concentrate, which is sometimes called chemo brain frog.

Patients also experience pain, diarrhea and constipation, anemia, malnutrition, hair loss, memory loss, infections and sepsis and hemorrhage (the loss of blood from the circulatory system through the broken skin), toxicity (heart muscle damage caused by chemicals], hepatotoxicity (chemical driven liver damage], nephroticity) (poisonous effect of chemicals or medicine on the kidney) and ototoxicity (damage of the ear by toxins).

Treatment with chemotherapy and radiotherapy

Usual treatments for cancer are with chemicals (chemo drugs) and radiotherapy (radiation) used for the treatment of malignant cells. Such treatments involve drugs which cause severe side effects in most patients. They can experience: pain, diarrhea, constipation, anemia, malnutrition, hair loss, memory loss, susceptibility to infections, haemorrhage, organ toxicity.

How RECEPTOL® Oral Spray can help people in cancer

It is iron-binding protein found in RECEPTOL®, has the ability to bind to excess iron ions, which are necessary for growth of microorganism and tumours.

Components in RECEPTOL® Oral Spray can lessen adverse effects of chemotherapy drugs, which are toxic to the body and it can enhance the effect of chemotherapy treatment by supporting the body's immune system, which is greatly affected by treatment. According to Kenneth D.Johnson "It is actually enhances chemotherapy so people can take greater dosages without getting so deadly sick.

"The Label claims are based on global studies on API: PRPs (Radha108 as class of PRPs being part of it) for which we have sent and up loaded claims on various indications based on published data in first rate Medical Journals. BMJ has accepted our two articles and two more are likely to be in leading Science Journal like NATURE by end of 2014 since our Global Medical Advisory Board has recommended to wait for follow up of patients who tried the product over 6 to 7 years a go and still have not shown any sign of disease reappearance, indicating that all Hibernation Viruses (crossing a window period of 8 years), including HIV have been stopped its reproduction leading to a possible claim for treatment & cure of AIDS & other major immune disorders, for which we have just received an approval for new US Product Patent as well".

RECEPTOL® and chemo-radiotherapy support

Components in RECEPTOL® Oral Spray can lessen the adverse effects of chemotherapy drugs which are toxic to the body. The immune factors and growth factors in colostrum help to boost the depressed immune system eliminate the toxins out of the body's cells and help to regenerate damaged cells. PRPS can also enhance the effect of the chemotherapy treatment by supporting the body's immune system, which is greatly affected by treatment. RECEPTOL® Oral Spray can help people to stay on the treatment regime who would have otherwise have to stop due to the severe side effects.

References

1. Lawrence HS, Borkowsky W: TRANSFER FACTOR: current status and future prospects. Biotherapy 9:1-5, 1996.

2. Masuda C, Wanibuchi H, Sekine K, Yano Y, Otani S, Kishimoto T, Tsuda H, Fukushima S. Jpn J Cancer Res. 2000 Jun;91(6):582-8.

3. Kim S, Lira SM, Dalal MA, Verity MA, Voskuhl RR: Estriol ameliorates autoimmune demyelinating disease. Neurology 4:P1230-1237, 1999.

4. Formby: Immunologic response in pregnancy. Endocrine Metabol Clinic North Am 24:187-205, 1995.

5. Bjorksten B: Environment and infant immunity. Proc Nutr Soc 58(3):729-732, August 1999.

6. Nicolini A, Ferrari P, Spinelli R, Carpi A, Sagripanti A, Amborgi F: Cell-mediated immunity in breast cancer patients. Biomed Pharmacother 50(8):337-343, 1996.

7. Bansal AS, Bruce J, Devine PL, Scells B, Zimmermann PV: Serum cytokines and tumor markers in patients with non-small cell carcinoma of the lung. Dis Markers 13(3):195-199, November 1997.

8. Aziz M, Akhtar S, Malik A: Evaluation of cell-mediated immunity and circulating immune complexes as prognostic indicators in cancer patients. Cancer Detect Prev 22(2):87-99, 1998.

9. Czarnechi D, Zaleberg J, Kulinshaya E, Kaz T: Impaired cell-mediated immunity of apparently normal patients who had multiple skin cancers. Cancer 76(2):228-231, July 15, 1995.

10. Mallmann P, Krebs D: The effect of immunotherapy with thymopentin on the parameters of cellular immunity and the clinical course of gynecologic tumor patients. (Abstract) Onkologie 12(Suppl 3):15-21, June 1989.

11. Mallmann P, Krebs D: Investigations on cell-mediated immunity in patients with breast and ovarian carcinomas receiving a combination of chemotherapy and immunotherapy with thymopentin. Methods Find Exp Clin Pharmacol 12(5):333-340, June 1990.

12. Kitahara T, Takeaka T, Yoshino M: Infection and immunosuppression in cancer patients. (Abstract) Gan To Kagaku Ryoho 16(4 Pt 2-1):1108-1114, April 1989.

13. O'Byrne KJ, Dalgleish AG, Browning MJ, Steward WP, Harris AL: The relationship between angiogenesis and the immune response in carcinogenesis and the progression of malignant disease. European Journal of Cancer 36(2000):151-169, September 21, 1999.

14. Lawrence HS: TRANSFER FACTOR in cellular immunity. The Harvey Lecture Series 68. New York: Academic Press, 1987.

15. Pizza G, De Vinci C, Cuzzocrea D, Menniti D, Aiello E, Maver P, Corrado G, Romagnoli P, Dragoni E, LoConte G, Riolo U, Palareti A, Zucchelli P, Fornarola V, Viza D: A preliminary report on the use of TRANSFER FACTOR for treating stage D3 hormone-unresponsive metastatic prostate cancer. Biotherapy 9(3-1):123-132, 1996.

16. Pilotti V, Mastrotilli M, Pizza G, De Vinci C, Busutti L, Palareti A, Gozzetti G, Cavallari A: TRANSFER FACTOR as an adjuvant to non-small cell lung cancer (NSCLC) therapy. Biotherapy 9:117-121, 1996.

17. Jirova D, Sperlingova I, Halaskova M, Bendova H, Dabrowska L: Immunotoxic effects of carbon tetrachloride: the effect on morphology and function of the immune system in mice. Cent Eur J Public Health 4(1):16-20, February 1996.

18. Heo Y, Lee WT, Lawrence DA: In vivo the environmental pollutants lead and mercury induce oligoclonal T cell responses skewed toward type-2 reactivities. Cell Immunol 179(2):185-195, August 1, 1997.

19. Khan A: TRANSFER FACTOR in viral diseases. The Lancet 1 (8059):328-329, February 11, 1978.

20. Milich DR, Chen MK, Hughes JL, Jones JE: The secreted hepatitis precove antigen can modulate the immune response to the nucleocapsid: a mechanism for persistence. J Immunol 160:2013-2021, 1998.

21. Tsai SL, Liaw TF, Chen MH, Huang LY, Kuo GC: Detection of type-2 like T helper cells in hepatitis C detection: implications for hepatitis C virus chronicity. Hepatology 25:449-458, 1997.

22. Ferrer-Argote VE, Romero-Cabello R, Hernandez-Medoza L, Arista-Viveros A, Rojo-Medina J, Balseca-Olivera F, Fierro M, Gonzalez-Constandse R: Successful treatment of severe complicated measles with non-specific TRANSFER FACTOR. In Vivo 8:555-558, 1994.

23. McCormick DP, Lim-Melia E, Sneed K, Baldwin CD, Chonmaitice T: Detection of respiratory viruses in middle ear fluids of children with otitis media infections. Ped Infectious Disease Journal 19(3):256-258, March 2000.

24. Ramilio O: Role of respiratory viruses in acute otitis media: implications for management of AOM. Ped Infectious Disease 18(12):1125-1129, December 1999.

25. Khan A, Sellars W, Grater W, Graham M, Pflanzer J, Antonetti A, Bailey J, Hill NO: The usefulness of TRANSFER FACTOR in asthma associated with frequent infections. Annals of Allergy 40(4):229-232, April 1978.

26. Viander B, Ala-Uotila S, Jalkanen M, Pakkanen R. Biotechniques. 1996 Apr;20(4):702-7.

27. Khan A: The syndrome of asthma, recurrent viral infections and T-cell immuno-deficiency: investigations and management. Annals of Allergy 43(2):69-72, August 1979.

28. Clerici M, Merola M, Ferrario E, Trabattoni D, Villa ML, Stefanon B, Venzon DJ, Shearer GM, De Palo G, Clerici E: Cytokine production patterns in cervical intraepithelial neoplasis: association with human papillomavirus infection. J Natl Cancer Inst 89(3):245-250, February 5, 1997.

29. Grohn P: TRANSFER FACTOR in chronic and recurrent respiratory tract infections in children. Acta Paediatr Scand 66:211-217, 1977.

30. De Vinci C, Pizza G, Cuzzocrea D, Menniti D, Aiello E, Maver P, Corrado G, Romagnoli P, Dragoni E, LoConte G, Riolo U, Masi M, Severini G, Fornarola V, Viza D: Use of TRANSFER FACTOR for the treatment of recurrent non-bacterial female cystitis (NBRC): a preliminary report. Biotherapy 9(1-3):133-138, 1996.

31. Masi M, De Vinci C, Baricordi OR: TRANSFER FACTOR in chronic mucocutaneous candidiasis. Biotherapy 9(1-3):97-103, 1996.

32. Matyniak JE, Reiner SL: T helper phenotype and genetic susceptibility in experimental Lyme disease. Journal Exp Med 181(3):1251-1254, March 1, 1995.

33. Sherwood Lawrence H, Borkowsky W: TRANSFER FACTOR: current status and future prospects. Biotherapy 9:1-5, 1996.

34. Hana I, Vrubel J, Pekarek J, Cech K: The influence of age on TRANSFER FACTOR treatment of cellular immunodeficiency, chronic fatigue syndrome and/or chronic viral infections. Biotherapy 9(1-3):91-95, 1996.

35. Ablashi DV, Levine PH, De Vinci C, Whitman JE Jr, Pizza G, Viza D: Use of anti HHV-6 TRANSFER FACTOR for the treatment of two patients with chronic fatigue syndrome (CFS): two case reports. Biotherapy 9(1-3):81-86, 1996.

36. Pizza G, Viza D, De Vinci C, Palareti A, Cuzzocrea D, Fornarola V, Baricordi R: Orally administered HSV: specific TRANSFER FACTOR (TF) prevents genital or labial herpes relapses. Biotherapy 9(1-3):67-72, 1996.

37. Meduri R, Campos E, Scorolli L, De Vinci C, Pizza G, Viza D: Efficacy of TRANSFER FACTOR in treating patients with recurrent ocular herpes infections. Biotherapy 9(1-3):61-66, 1996.

38. Basten A, Pollard JD, Stewart GJ, Frith JA, McLeod JG, Walsh JC, Garrick R, Van Der Brink CM: TRANSFER FACTOR in treatment of multiple sclerosis. The Lancet 931-934, November 1980.

39. Long KZ, Santos JI: Vitamins and the regulation of the immune response. Pediatr Infect Dis J 18:283-290, 1999.

40. Wu B: Effect of acupuncture on the regulation of cell-mediated immunity in the patients with malignant tumors. (Abstract) Chen Tzu Yen Chiu 20(3):67-71, 1995.

41. Lawrence HS: Immune Regulation in TRANSFER FACTOR. New York: Academic Press, 1979, p. 613.

42. Khan A, Sellars WA, Gabela P, Thometz D: TRANSFER FACTOR, thymosin and E rosettes. NEJM 292:868, 1975.

43. See D, Gurnce K, Leclair M: An in vitro screening study of 196 natural products for toxicity and efficacy. JAMA 2(1), December 1999.

44. Artym J, Zimecki M. Postepy Hig Med Dosw (Online). 2013 Aug 6;67:800-16.

45. Gutiérrez G, Alvarez I, Politzki R, Lomónaco M, Dus Santos MJ, Rondelli F, Fondevila N, Trono K. Vet Microbiol. 2011 Aug 5;151(3-4):255-63. doi: 10.1016/j.vetmic.2011.03.035. Epub 2011 Apr 12.

46. Kobayashi S, Tsutsui T, Yamamoto T, Hayama Y, Kameyama K, Konishi M, Murakami K. BMC Vet Res. 2010 Jan 7;6:1. doi: 10.1186/1746-6148-6-1.

47. Chen CH, Thai P, Yoneda K, Adler KB, Yang PC, Wu R. Oncogene. 2013 Aug 19. doi: 10.1038/onc.2013.336.

48. Byrne C, Miclet E, Broutin I, Gallo D, Pelekanou V, Kampa M, Castanas E, Leclercq G, Jacquot Y. Chirality. 2013 Oct;25(10):628-42. doi: 10.1002/chir.22188. Epub 2013 Aug 8.

49. Zhu Y, Feng F, Yu J, Song B, Hu M, Gao X, Wang Y, Zhang Q. DNA Cell Biol. 2013 Sep;32(9):531-40. doi: 10.1089/dna.2013.2097. Epub 2013 Jul 17.

50. Bengtson NW and Linzer DI Inhibition of tumor growth by the antiangiogenic placental hormone, proliferin-related protein. Molecular Endocrinology 14(12): 1934-43 (2000);

51. Linzer DI and Nathans D A new member of the prolactin-growth hormone gene family expressed in mouse placenta EMBO Journal 4(6): 1419-23 (1985);

52. Regulier E et al Adenovirus-mediated delivery of antiangiogenic genes as an antitumor approach. Cancer Gene Therapy 8(1): 45-54 (2001);

53. Yamaguchi M et al Cyclic adenosine 3',5'-monophosphate stimulation of placental proliferin and proliferin-related protein secretion. Endocrinology 136(5): 2040-6 (1995);

54. Yamaguchi M et al Selective inhibition of mouse placental lactogen II secretion by tumour necrosis factor-alpha. Journal of Endocrinology 143(1): 95-105 (1994).

55. Blach-Olszewska Z and Janusz M Stimulatory effect of ovine colostrinine (a proline-rich polypeptide) on interferons and tumor necrosis factor production by murine resident peritoneal cells. Arch. Immunol. Ther. Exp. Warsz. 45(1): 43-47 (1997);

56. Inglot AD et al Colostrinine: a proline-rich polypeptide from ovine colostrum is a modest cytokine inducer in human leukocytes. Arch. Immunol. Ther. Exp. Warsz. 44(4): 215-224 (1996).

57. Aisha AF, Ismail Z, Abu-Salah KM, Siddiqui JM, Ghafar G, Abdul Majid AM. BMC Complement Altern Med. 2013 Jul 11;13:168. doi: 10.1186/1472-6882-13-168.

58. Fukai K, Sato M, Kawara M, Hoshi Z, Ueno S, Chyou N, Akashi H. Zentralbl Veterinarmed B. 1999 Oct;46(8):511-5.

59. Cheung NV. Therapeutic antibodies and immunologic conjugates. In: Abe off MD, et al. Bailiff's Clinical Oncology. 4th ed. Philadelphia, Pa.: Churchill Livingstone; 2008:531.

60.Monoclonalantibodies.AmericanCancerSociety.http://www.cancer.org/Treatment/TreatmentsandSideEffects/TreatmentTypes/Immunotherapy/immunotherapy-monoclonal-antibodies. Accessed Nov. 17, 2010.

61. Found 2042 studies with search of: monoclonal antibody AND cancer. ClinicalTrials.gov. http://clinicaltrials.gov/ct2/results?term=monoclonal+antibody+AND+cancer. Accessed Nov. 18, 2010.

62. Czarnechi D, Zaleberg J, Kulinshaya E, Kaz T: Impaired cell-mediated immunity of apparently normal patients who had multiple skin cancers. Cancer 76(2):228-231, July 15, 1995.

63. Mallmann P, Krebs D: The effect of immunotherapy with thymopentin on the parameters of cellular immunity and the clinical course of gynecologic tumor patients. (Abstract) Onkologie 12(Suppl 3):15-21, June 1989.

64. Mallmann P, Krebs D: Investigations on cell-mediated immunity in patients with breast and ovarian carcinomas receiving a combination of chemotherapy and immunotherapy with thymopentin. Methods Find Exp Clin Pharmacol 12(5):333-340, June 1990.

65. Kitahara T, Takeaka T, Yoshino M: Infection and immunosuppression in cancer patients. (Abstract) Gan To Kagaku Ryoho 16(4 Pt 2-1):1108-1114, April 1989.

66. O'Byrne KJ, Dalgleish AG, Browning MJ, Steward WP, Harris AL: The relationship between angiogenesis and the immune response in carcinogenesis and the progression of malignant disease. European Journal of Cancer 36(2000):151-169, September 21, 1999.

67. Lawrence HS: TRANSFER FACTOR in cellular immunity. The Harvey Lecture Series 68. New York: Academic Press, 1987.

68. Pizza G, De Vinci C, Cuzzocrea D, Menniti D, Aiello E, Maver P, Corrado G, Romagnoli P, Dragoni E, LoConte G, Riolo U, Palareti A, Zucchelli P, Fornarola V, Viza D: A preliminary report on the use of TRANSFER FACTOR for treating stage D3 hormone-unresponsive metastatic prostate cancer. Biotherapy 9(3-1):123-132, 1996.

9.3.5 RECEPTOL® & Hypertension

What is hypertension?

Hypertension (**HTN**) or **high blood pressure**, sometimes called **arterial hypertension**, is a chronic medical condition in which the blood pressure in the arteries is elevated. Blood pressure is summarised by two measurements, systolic and diastolic, which depend on whether the heart muscle is contracting (systole) or relaxed between beats (diastole). This equals the maximum and minimum pressure, respectively. Normal blood pressure at rest is within the range of 100–140mmHg systolic (top reading) and 60–90mmHg diastolic (bottom reading). High blood pressure is said to be present if it is often at or above 140/90 mmHg.

Hypertension is classified as either primary (essential) hypertension or secondary hypertension; about 90–95% of cases are categorized as "primary hypertension" which means high blood pressure with no obvious underlying medical cause.[1] The remaining 5–10% of cases (secondary hypertension) are caused by other conditions that affect the kidneys, arteries, heart or endocrine system.

Hypertension puts strain on the heart, leading to hypertensive heart disease and coronary artery disease if not treated. Hypertension is also a major risk factor for stroke, aneurysms of the arteries (e.g. aortic aneurysm), peripheral arterial disease and is a cause ofchronic kidney disease. A moderately high arterial blood pressure is associated with a shortened life expectancy while mild elevation is not. Dietary and lifestyle changes can improve blood pressure control and decrease the risk of health complications, although drug treatment is still often necessary in people for whom lifestyle changes are not enough or not effective.

What are the sign and symtomes of hypertension?
Hypertension is rarely accompanied by any symptoms, and its identification is usually through screening, or when seeking healthcare for an unrelated problem. A proportion of people with high blood pressure report headaches (particularly at the back of the head and in the morning),as well as light headedness, vertigo, tinnitus (buzzing or hissing in the ears), altered vision or fainting episodes. These symptoms, however, might be related to associated anxiety rather than the high blood pressure itself.

On physical examination, hypertension may be suspected on the basis of the presence of hypertensive retinopathy detected by examination of the optic fundus found in the back of the eye using ophthalmoscopy. Classically, the severity of the hypertensive retinopathy changes is graded from grade I–IV, although the milder types may be difficult to distinguish from each other. Ophthalmoscopy findings may also give some indication as to how long a person has been hypertensive.

Secondary hypertension
Some additional signs and symptoms may suggest secondary hypertension, i.e. hypertension due to an identifiable cause such as kidney diseases or endocrine diseases. For example, truncal obesity, glucose intolerance, moon face, a "buffalo hump" and purple stretch marks suggest Cushing's syndrome. Thyroid disease and acromegaly can also cause hypertension and have characteristic symptoms and signs.

An abdominal bruit may be an indicator of renal artery stenosis (a narrowing of the arteries supplying the kidneys), while decreased blood pressure in the lower extremities and/or delayed or absent femoral arterial pulses may indicate aortic coarctation (a narrowing of the aorta shortly after it leaves the heart). Labile or paroxysmal hypertension accompanied by headache, palpitations, pallor, and perspiration should prompt suspicions of pheochromocytoma.

Hypertensive crisis

Severely elevated blood pressure (equal to or greater than a systolic 180 or diastolic of 110 sometimes termed malignant or accelerated hypertension) is referred to as a "hypertensive crisis", as blood pressure at this level confers a high risk of complications. People with blood pressures in this range may have no symptoms, but are more likely to report headaches (22% of cases) and dizziness than the general population.

Other symptoms accompanying a hypertensive crisis may include visual deterioration or breathlessness due to heart failure or a general feeling of malaise due to renal failure. Most people with a hypertensive crisis are known to have elevated blood pressure, but additional triggers may have led to a sudden rise.

A "hypertensive emergency", previously "malignant hypertension", is diagnosed when there is evidence of direct damage to one or more organs as a result of the severely elevated blood pressure. This may include hypertensive encephalopathy, caused by brain swelling and dysfunction, and characterized by headaches and an altered level of consciousness (confusion or drowsiness).

Retinal papilloedema and/or fundal haemorrhages and exudates are another sign of target organ damage. Chest pain may indicate heart muscle damage (which may progress to myocardial infarction) or sometimes aortic dissection, the tearing of the inner wall of the aorta. Breathlessness, cough, and the expectoration of blood-stained sputum are characteristic signs of pulmonary edema, the swelling of lung tissue due to left ventricular failure an inability of the left ventricle of the heart to adequately pump blood from the lungs into the arterial system.
Rapid deterioration of kidney function (acute kidney injury) and microangiopathic hemolytic anemia (destruction of blood cells) may also occur. In these situations, rapid reduction of the blood pressure is mandated to stop ongoing organ damage.

In contrast there is no evidence that blood pressure needs to be lowered rapidly in hypertensive urgencies where there is no evidence of target organ damage and over aggressive reduction of blood pressure is not without risks. Use of oral medications to lower the BP gradually over 24 to 48h is advocated in hypertensive urgencies.

Pregnancy

Hypertension occurs in approximately 8–10% of pregnancies. Two blood pressure measurements six hours apart of greater than 140/90 mm Hg is considered diagnostic of hypertension in pregnancy. Most women with hypertension in pregnancy have pre-existing primary hypertension, but high blood pressure in pregnancy may be the first sign of pre-eclampsia, a serious condition of the second half of pregnancy and puerperium.

Pre-eclampsia is characterised by increased blood pressure and the presence of protein in the urine. It occurs in about 5% of pregnancies and is responsible for approximately 16% of all maternal

deaths globally. Pre-eclampsia also doubles the risk of perinatal mortality. Usually there are no symptoms in pre-eclampsia and it is detected by routine screening.

When symptoms of pre-eclampsia occur the most common are headache, visual disturbance (often "flashing lights"), vomiting, epigastric pain, and edema. Pre-eclampsia can occasionally progress to a life-threatening condition called eclampsia, which is a hypertensive emergency and has several serious complications including vision loss, cerebral edema, seizures or convulsions, renal failure, pulmonary edema, and disseminated intravascular coagulation (a blood clotting disorder).

Children

Failure to thrive, seizures, irritability, lack of energy, and difficulty breathing can be associated with hypertension in neonates and young infants. In older infants and children, hypertension can cause headache, unexplained irritability, fatigue, failure to thrive, blurred vision, nosebleeds, and facial paralysis.

What causes hypertension?

Primary hypertension

Primary (essential) hypertension is the most common form of hypertension, accounting for 90–95% of all cases of hypertension. In almost all contemporary societies, blood pressure rises with aging and the risk of becoming hypertensive in later life is considerable. Hypertension results from a complex interaction of genes and environmental factors. Numerous common genetic variants with small effects on blood pressure have been identified as well as some rare genetic variants with large effects on blood pressure but the genetic basis of hypertension is still poorly understood. Several environmental factors influence blood pressure.

Lifestyle factors that lower blood pressure include reduced dietary salt intake, increased consumption of fruits and low fat products (Dietary Approaches to Stop Hypertension (DASH diet)), exercise, weight loss and reduced alcohol intake. Stress appears to play a minor role[1] with specific relaxation techniques not supported by the evidence.The possible role of other factors such as caffeine consumption, and vitamin D deficiency are less clear cut. Insulin resistance, which is common in obesity and is a component of syndrome X (or themetabolic syndrome), is also thought to contribute to hypertension. Recent studies have also implicated events in early life (for example low birth weight, maternal smoking and lack of breast feeding) as risk factors for adult essential hypertension, although the mechanisms linking these exposures to adult hypertension remain obscure.

Secondary hypertension

Secondary hypertension results from an identifiable cause. Renal disease is the most common secondary cause of hypertension. Hypertension can also be caused by endocrine conditions, such as Cushing's syndrome, hyperthyroidism, hypothyroidism, acromegaly, Conn's syndrome or hyperaldosteronism, hyperparathyroidism and pheochromocytoma. Other causes of secondary hypertension include obesity, sleep apnea, pregnancy, coarctation of the aorta, excessive liquorice consumption and certain prescription medicines, herbal remedies and illegal drugs.

References:

1. Identification of the hypertensive principle of colostrum as a nucleotide. Werle E, Schmal A, Zach HP.Naunyn Schmiedebergs Arch Exp Pathol Pharmakol. 1967;259(1):45-55

2. Milk-derived proteins and peptides in clinical trials. Artym J, Zimecki M.Postepy Hig Med Dosw (Online). 2013 Aug 6;67:800-16.

3. Inflammatory cytokines in pulmonary hypertension.Groth A, Vrugt B, Brock M, Speich R, Ulrich S, Huber LC.Respir Res. 2014 Apr 16;15(1):47.

4. Hypertension in Obese Type 2 Diabetes Patients is Associated with Increases in Insulin Resistance and IL-6 Cytokine Levels: Potential Targets for an Efficient Preventive Intervention.Lukic L, Lalic NM, Rajkovic N, Jotic A, Lalic K, Milicic T, Seferovic JP, Macesic M, Gajovic JS.Int J Environ Res Public Health. 2014 Mar 28;11(4):3586-98.

5. Inhibition of reactive oxygen species in hypothalamic paraventricular nucleus attenuates the renin-angiotensin system and proinflammatory cytokines in hypertension.Su Q, Qin DN, Wang FX, Ren J, Li HB, Zhang M, Yang Q, Miao YW, Yu XJ, Qi J, Zhu Z, Zhu GQ, Kang YM.Toxicol Appl Pharmacol. 2014 Apr 15;276(2):115-20.

6. Exercise training attenuates hypertension and cardiac hypertrophy by modulating neurotransmitters and cytokines in hypothalamic paraventricular nucleus.Jia LL, Kang YM, Wang FX, Li HB, Zhang Y, Yu XJ, Qi J, Suo YP, Tian ZJ, Zhu Z, Zhu GQ, Qin DN. PLoS One. 2014 Jan 17;9(1)

7. Duffy antigen / receptor for chemokines correlates with inflammatory reaction in rats with venoushypertension: implication for the pathogenesis of primary chronic venous disease.Huang W, Qin W, Lv L, Deng H, Zhang H, Zhang J, Zhang L.Vasa. 2014 Jan;43(1):47-54

8. Proline rich-oligopeptides: diverse mechanisms for antihypertensive action. Morais KL, Ianzer D, Miranda JR, Melo RL, Guerreiro JR, Santos RA, Ulrich H, Lameu C.Peptides. 2013 Oct;48:124-33. doi: 10.1016/j.peptides.2013.07.016. Epub 2013 Aug 7.

9. Proline rich-oligopeptides: diverse mechanisms for antihypertensive action. Morais KL, Ianzer D, Miranda JR, Melo RL, Guerreiro JR, Santos RA, Ulrich H, Lameu C.Peptides. 2013 Oct;48:124-33. doi: 10.1016/j.peptides.2013.07.016. Epub 2013 Aug 7.

10. IPP-rich milk protein hydrolysate lowers blood pressure in subjects with stage 1 hypertension, a randomized controlled trial.Boelsma E, Kloek J. Nutr J. 2010 Nov 8;9:52. doi: 0.1186/1475-2891-9-52.

11. Regulation of activity and localization of the WNK1 protein kinase by hyperosmotic stress.Zagórska A, Pozo-Guisado E, Boudeau J, Vitari AC, Rafiqi FH, Thastrup J, Deak M,

Campbell DG, Morrice NA, Prescott AR, Alessi DR. J Cell Biol. 2007 Jan 1;176(1):89-100. Epub 2006 Dec 26.

12. Down-regulation by antisense oligonucleotides establishes a role for the proline-rich tyrosine kinase PYK2 in angiotensin ii-induced signaling in vascular smooth muscle.Rocic P, Lucchesi PA.J Biol Chem. 2001 Jun 15;276(24):21902-6. Epub 2001 Mar 21.

9.3.6 RECEPTOL® and Lupus

What is Lupus?

It is a chronic autoimmune disease, which is caused by the immune system attacking the body's cells and tissue. It can attack any part of the body including heart, joints, skin, lungs, blood vessels, liver, kidneys and nervous system.

Symptoms

Symptoms vary widely and come and go unpredictably. Some patients have unexplained symptoms for years. Common complaints are fever, malaise, joint pains and fatigue. Other symptoms include dermatological manifestations, hematological manifestations, cardiac and pulmonary problems and hepatic involvement.

How RECEPTOL® Oral Spray can help people with Lupus

RECEPTOL® Oral Spray can have potential benefits for people with lupus. Regulatory factors such as the Proline-Rich-Polypeptide (PRP) which is a powerful immune system regulator can help to calm down the over active immune system, cell and tissue repair growth factors which promote regeneration of damaged tissues and cells.

RECEPTOL® also contains all five main immunoglobulins responsible for identifying and neutralizing pathogens. Individuals with lupus have mostly low level of immunoglobulin making them susceptible to viral and bacterial infections.

These mentioned components, as well as other factors in RECEPTOL® Oral Spray, are in a unique balance made by nature and therefore they have a significant beneficial for people suffering with lupus.

9.3.7 RECEPTOL® and Thrush

What is Thrush disease?

Candidiasis or thrush is a fungal infection (mycosis) of any species from the genus Candida (one genus of yeasts). Candida albicans is the most common agent of Candidiasis in humans. Also commonly referred to as a yeast infection, candidiasis is also technically known as candidosis, moniliasis, and oidiomycosis.

Candidiasis encompasses infections that range from superficial, such as oral thrush and vaginitis, to systemic and potentially life-threatening diseases. Candida infections of the latter category are also referred to as candidemia or invasive candidiasis, and are usually confined to severely immunocompromised persons, such as cancer, transplant, and AIDS patients, as well as nontrauma emergency surgery patients.

Superficial infections of skin and mucosal membranes by Candida causing local inflammation and discomfort are common in many human populations. While clearly attributable to the presence of the opportunistic pathogens of the genus Candida, candidiasis describes a number of different disease syndromes that often differ in their causes and outcomes.

What are sign and symptoms of Thrush disease?

Symptoms of candidiasis vary depending on the area affected. Most candidial infections result in minimal complications such as redness, itching and discomfort, though complications may be severe or even fatal if left untreated in certain populations. In immunocompetent persons, candidiasis is usually a very localized infection of the skin or mucosal membranes, including the oral cavity (thrush), the pharynx or esophagus, the gastrointestinal tract, the urinary bladder, the fingernails or toenails (onychomycosis), and the genitalia (vagina, penis).

Candidiasis is a very common cause of vaginal irritation, or vaginitis, and can also occur on the male genitals. In immunocompromised patients, Candida infections can affect the esophagus with the potential of becoming systemic, causing a much more serious condition, afungemia called candidemia.

Thrush is commonly seen in infants. It is not considered abnormal in infants unless it lasts longer than a few weeks.

Infection of the vagina or vulva may cause severe itching, burning, soreness, irritation, and a whitish or whitish-gray cottage cheese-like discharge, often with a curd-like appearance. These symptoms are also present in the more common bacterial vaginosis. In a 2002 study published in the Journal of Obstetrics and Gynecology, only 33% of women who were self-treating for a yeast infection actually had a such an infection, while most had either bacterial vaginosis or a mixed-type infection. Symptoms of infection of the male genitalia (balanitis thrush) include red skin around the head of the penis, swelling, irritation, itchiness and soreness of the head of the penis, thick, lumpy discharge under the foreskin, unpleasant odour, difficulty retracting the foreskin (phimosis), and pain when passing urine or during sex.

Perianal candidiasis can cause pruritis ani. The lesion can be erythematous, papular or ulcerative in appearance, and it is not considered to be a sexually transmissible disease. Esophageal candidiasis can cause dysphagia (difficulty swallowing), or less commonly odynophagia (painful swallowing).

What causes of thrush disease?

Candida yeasts are generally present in healthy humans, particularly on the skin, but their growth is normally limited by the human immune system, by competition of other microorganisms, such as bacteria occupying the same locations in the human body, and in the case of skin, by the relative dryness of the skin, as Candida requires moisture for growth.

C. albicans was isolated from the vaginas of 19% of apparently healthy women, i.e., those who experienced few or no symptoms of infection. External use of detergents or douches or internal disturbances (hormonal or physiological) can perturb the normal vaginal flora, consisting of lactic acid bacteria, such as lactobacilli, and result in an overgrowth of Candida cells, causing symptoms of infection, such as local inflammation. Pregnancy and the use of oral contraceptives have been reported as risk factors. Diabetes mellitus and the use of antibacterial antibiotics are also linked to an increased incidence of yeast infections. Diets high in simple carbohydrates have been found to affect rates of oral candidiases, and hormone replacement therapy and infertility treatments may also be predisposing factors. Wearing wet swimwear for long periods of time is also believed to be a risk factor.

A weakened or undeveloped immune system or metabolic illnesses such as diabetes are significant predisposing factors of candidiasis. Diseases or conditions link edtocandidiasis include HIV/AIDS, mononucleosis, cancer treatments, steroids, stress, and nutrient deficiency. Almost 15% of people with weakened immune systems develop a systemic illness caused by Candida species. In extreme cases, these superficial infections of the skin or mucous membranes may enter into the bloodstream and cause systemic Candida infections.

In penile candidiasis, the causes include sexual intercourse with an infected individual, low immunity, antibiotics, and diabetes. Male genital yeast infections are less common, and incidences of infection are only a fraction of those in women; however, yeast infection on the penis from direct contact via sexual intercourse with an infected partner is not uncommon.
Candida species are frequently part of the human body's normal oral and intestinal flora. Treatment with antibiotics can lead to eliminating the yeast's natural competitors for resources, and increase the severity of the condition. In the Western Hemisphere, about 75% of females are affected at some time in their lives.

References

1. Dr. Zoltan Rona; "PRP from colostrum can work as a regulatory substance of the thymus gland. PRP inhibits the overproduction of lymphocytes and T-cells and reduces the major symptoms of allergies and autoimmune disease: pain, swelling and inflammation."The American Journal of Natural Medicine, March 1998.

2. Beth Ley, PhD; Immune System Control: Colostrum and Lactoferrin. ""Colostrum contains a special Proline-Rich-Polypeptide (PRP) that serves as a powerful regulator of the immune system. PRP in colostrum increases the permeability of the skin vessels, which offers a regulatory activity, stimulating or suppressing the immune response." (Staroscik)" 2000.

3. By the Editors of The Doctors' Prescription for Healthy Living Magazine. The Colostrum Miracle: The Anti-Aging Super Food that can boost immunity and prevent premature aging. (2005) p74.

4. The Colostrum Miracle: The Anti-aging Super Food that can boost immunity and prevent premature aging. Authors: By the Editors of The Doctors' Prescriptions for Healthy Living Magazine) "PRP from colostrum can work as a regulatory substance of the thymus gland. It has been demonstrated to improve or eliminate symptomatology of both allergies and autoimmune diseases (MS, rheumatoid arthritis, lupus, myasthenia gravis). PRP inhibits the overproduction of lymphocytes and T-cells and reduces the major symptoms of allergies and autoimmune disease: pain, swelling and inflammation." --Dr. Zoltan Rona, The American Journal of Natural Medicine, March 1998.

5. "The ability to stimulate or suppress the immune response is highly significant. Suppressing the immune system is necessary to prevent the immune system from attacking the body itself, as in the case of autoimmune disease such as rheumatoid arthritis, lupus, MS, Alzheimer's disease and allergies. Colostrum's suppressive action may help prevent this type of activity involved in autoimmune diseases." --Beth Ley, PhD Nutrition

6. Zimecki, M, Artym, J. [Therapeutic properties of proteins and peptides from colostrum and milk] Higieny i Medycyny Doswiadczalnej 59:309-323 (2005).

7. Kruzel ML, Boldogh I, Zimecki M; Lactoferrin in health and disease. Department of Integrative Biology and Pharmacology, the University of Texas, Health Science Center at Houston, Texas 77030, USA. Postepy Hig Med Dosw (Online). 2007;61:261-7.

9.3.8 RECEPTOL® & Autism

What is Autism?

Autism is a disorder of neural development characterized by impaired social interaction and verbal and non-verbal communication, and by restricted, repetitive or stereotyped behaviour. The diagnostic criteria require that symptoms become apparent before a child is three years old. Autism affects information processing in the brain by altering how nerve cells and their synapses connect and organize; how this occurs is not well understood It is one of three recognized disorders in the autism spectrum (ASDs), the other two being Asperger syndrome, which lacks delays in cognitive development and language, and pervasive developmental disorder, not otherwise specified (commonly abbreviated as PDD-NOS), which is diagnosed when the full set of criteria for autism or Asperger syndrome are not met.

Autism has a strong genetic basis, although the genetics of autism are complex and it is unclear whether ASD is explained more by rare mutations, or by rare combinations of common genetic variants. In rare cases, autism is strongly associated with agents that cause birth defects. Controversies surround other proposed environmental causes, such as heavy metals, pesticides or childhood vaccines; the vaccine hypotheses are biologically implausible and lack convincing scientific evidence. The prevalence of autism is about 1–2 per 1,000 people worldwide, and it occurs about four times more often in boys than girls. The Centres for Disease Control and Prevention (CDC) report 1.5% of children in the United States (one in 68) are diagnosed with ASD as of 2014, a 30% increase from one in 88 in 2012. The number of people diagnosed with autism has been increasing dramatically since the 1980s, partly due to changes in diagnostic practice and government-subsidized financial incentives for named diagnoses; the question of whether actual prevalence has increased is unresolved.

Parents usually notice signs in the first two years of their child's life. The signs usually develop gradually, but some autistic children first develop more normally and then regress. Early behavioural, cognitive, or speech interventions can help autistic children gain self-care, social, and communication skills. Although there is no known cure, there have been reported cases of children who recovered. Not many children with autism live independently after reaching adulthood, though some become successful. An autistic culture has developed, with some individuals seeking a cure and others believing autism should be accepted as a difference and not treated as a disorder

What are the symptoms of Autism?

Most parents of autistic children suspect that something is wrong by the time the child is 18 months old and seek help by the time the child is age 2. Children with autism typically have difficulties in:

- Pretend play
- Social interactions
- Verbal and nonverbal communication

Some children with autism appear normal before age 1 or 2 and then suddenly "regress" and lose language or social skills they had previously gained. This is called the regressive type of autism.

People with autism may:

- Be overly sensitive in sight, hearing, touch, smell, or taste (for example, they may refuse to wear "itchy" clothes and become distressed if they are forced to wear the clothes)
- Have unusual distress when routines are changed
- Perform repeated body movements
- Show unusual attachments to objects

The symptoms may vary from moderate to severe.

Communication problems may include:

- Cannot start or maintain a social conversation
- Communicates with gestures instead of words
- Develops language slowly or not at all
- Does not adjust gaze to look at objects that others are looking at
- Does not refer to self correctly (for example, says "you want water" when the child means "I want water")
- Does not point to direct others' attention to objects (occurs in the first 14 months of life)
- Repeats words or memorized passages, such as commercials

Social interaction:

- Does not make friends
- Does not play interactive games
- Is withdrawn
- May not respond to eye contact or smiles, or may avoid eye contact
- May treat others as if they are objects
- Prefers to spend time alone, rather than with others
- Shows a lack of empathy

Response to sensory information:

- Does not startle at loud noises
- Has heightened or low senses of sight, hearing, touch, smell, or taste
- May find normal noises painful and hold hands over ears
- May withdraw from physical contact because it is overstimulating or overwhelming

- Rubs surfaces, mouths or licks objects
- Seems to have a heightened or low response to pain

Play**:**

- Doesn't imitate the actions of others
- Prefers solitary or ritualistic play
- Shows little pretend or imaginative play

Behaviors:

- "Acts up" with intense tantrums
- Gets stuck on a single topic or task (perseveration)
- Has a short attention span
- Has very narrow interests
- Is overactive or very passive
- Shows aggression to others or self
- Shows a strong need for sameness
- Uses repetitive body movements

What are sign and tests of Autism?

All children should have routine developmental exams done by their pediatrician. Further testing may be needed if the doctor or parents are concerned. This is particularly true if a child fails to meet any of the following language milestones:

- Babbling by 12 months
- Gesturing (pointing, waving bye-bye) by 12 months
- Saying single words by 16 months
- Saying two-word spontaneous phrases by 24 months (not just echoing)
- Losing any language or social skills at any age

These children might receive a hearing evaluation, blood lead test, and screening test for autism (such as the Checklist for Autism in Toddlers or the Autism Screening Questionnaire).

A health care provider experienced in diagnosing and treating autism is usually needed to make the actual diagnosis. Because there is no biological test for autism, the diagnosis will often be based on very specific criteria from a book called the Diagnostic and Statistical Manual IV.

An evaluation of autism will often include a complete physical and nervous system (neurologic) examination. It may also include a specific screening tool, such as:

- Autism Diagnostic Interview - Revised (ADI-R)
- Autism Diagnostic Observation Schedule (ADOS)
- Childhood Autism rating Scale (CARS)
- Gilliam Autism Rating Scale
- Pervasive Developmental Disorders Screening Test - Stage 3

Children with known or suspected autism will often have genetic testing (looking for chromosome abnormalities) and may have metabolic testing.

Autism includes a broad spectrum of symptoms. Therefore, a single, brief evaluation cannot predict a child's true abilities. Ideally, a team of different specialists will evaluate the child. They might evaluate:

- Communication
- Language
- Motor skills
- Speech
- Success at school
- Thinking abilities

Sometimes people are reluctant to have a child diagnosed because of concerns about labelling the child. However, without a diagnosis the child may not get the necessary treatment and services.

References:

1. Elevated serum levels of macrophage-derived chemokine and thymus and activation-regulated chemokine in autistic children.Al-Ayadhi LY, Mostafa GA.J Neuroinflammation. 2013 Jun 19;10:72. doi: 10.1186/1742-2094-10-72.

2. Altered cytokine and BDNF levels in autism spectrum disorder.Ricci S, Businaro R, Ippoliti F, Lo Vasco VR, Massoni F, Onofri E, Troili GM, Pontecorvi V, Morelli M, Rapp Ricciardi M, Archer T.Neurotox Res. 2013 Nov;24(4):491-501. doi: 10.1007/s12640-013-9393-4. Epub 2013 Apr 19.

3. Plasma cytokine profiling in sibling pairs discordant for autism spectrum disorder.Napolioni V, Ober-Reynolds B, Szelinger S, Corneveaux JJ, Pawlowski T, Ober-Reynolds S, Kirwan J, Persico AM, Melmed RD, Craig DW, Smith CJ, Huentelman MJ.J Neuroinflammation. 2013 Mar 14;10:38. doi: 10.1186/1742-2094-10-38.

4. Association of IL-12p70 and IL-6:IL-10 ratio with autism-related behaviors in 22q11.2 deletion syndrome: a preliminary report.Ross HE, Guo Y, Coleman K, Ousley O, Miller AH.Brain Behav Immun. 2013 Jul;31:76-81. doi: 10.1016/j.bbi.2012.12.021. Epub 2013 Jan 24

5. Interleukin-2 and the brain: dissecting central versus peripheral contributions using unique mouse models.Petitto JM, Meola D, Huang Z.Methods Mol Biol. 2012;934:301-11. doi: 10.1007/978-1-62703-071-7_15

6. Cytokine dysregulation in autism spectrum disorders (ASD): possible role of the environment.Goines PE, Ashwood P.Neurotoxicol Teratol. 2013 Mar-Apr;36:67-81. doi: 10.1016/j.ntt.2012.07.006. Epub 2012 Aug 17

7. Neonatal levels of cytokines and risk of autism spectrum disorders: an exploratory register-based historic birth cohort study utilizing the Danish Newborn Screening Biobank.Abdallah MW, Larsen N, Mortensen EL, Atladóttir HÓ, Nørgaard-Pedersen B, Bonefeld-Jørgensen EC, Grove J, Hougaard DM., J Neuroimmunol. 2012 Nov 15;252(1-2):75-82. doi: 10.1016/j.jneuroim.2012.07.013. Epub 2012 Aug 20

8. Maternal immune activation causes age- and region-specific changes in brain **cytokines** in offspring throughout development.Garay PA, Hsiao EY, Patterson PH, McAllister AK.Brain Behav Immun. 2013 Jul;31:54-68. doi: 10.1016/j.bbi.2012.07.008. Epub 2012 Jul 25.

9. Elevated serum levels of interleukin-17A in children with autism.Al-Ayadhi LY, Mostafa GA. J Neuroinflammation. 2012 Jul 2;9:158. doi: 10.1186/1742-2094-9-158.

10. Maternal immune activation by poly I:C induces expressionof cytokines IL-1β and IL-13, chemokine MCP-1 and colony stimulating factor VEGF in fetal mouse brain.Arrode-Brusés G, Brusés JL.J Neuroinflammation. 2012 Apr 30;9:83. doi: 10.1186/1742-2094-9-83.

11. Altered neurotrophin, neuropeptide, cytokines and nitric oxide levels in autism.Tostes MH, Teixeira HC, Gattaz WF, Brandão MA, Raposo NR. Pharmacopsychiatry. 2012 Sep;45(6):241-3. doi: 10.1055/s-0032-1301914. Epub 2012 Mar 16.

12. Elevation of proinflammatory cytokines level at early age as the risk factor of neurological and mental pathology development. Zubarev OE, Klimenko VM. Ross Fiziol Zh Im I M Sechenova. 2011 Oct;97(10):1048-59.

13. Plasma cytokine levels in children with autistic disorder and unrelated siblings.Manzardo AM, Henkhaus R, Dhillon S, Butler MG.Int J Dev Neurosci. 2012 Apr;30(2):121-7. doi: 10.1016/j.ijdevneu.2011.12.003. Epub 2011 Dec 16.

14. Amniotic fluid inflammatory cytokines: potential markers of immunologic dysfunction in autismspectrum disorders.Abdallah MW, Larsen N, Grove J, Nørgaard-Pedersen B, Thorsen P,

Mortensen EL, Hougaard DM.World J Biol Psychiatry. 2013 Sep;14(7):528-38. doi: 10.3109/15622975.2011.639803. Epub 2011 Dec 19.

15. Association of a MET genetic variant with autism-associated maternal autoantibodies to fetal brain proteins and cytokine expression.Heuer L, Braunschweig D, Ashwood P, Van de Water J, Campbell DB.Transl Psychiatry. 2011 Oct 18;1:e48. doi: 10.1038/tp.2011.48

9.3.9 RECEPTOL® & Endometriosis

What is endometriosis?

Endometriosis is the abnormal growth of cells (endometrial cells) similar to those that form the inside or lining the tissue of the uterus, but in a location outside of the uterus. Endometrial cells are cells that are shed each month during menstruation.The cells of endometriosis attach themselves to tissue outside the uterus and are called endometriosis implants. These implants are most commonly found on the ovaries, the Fallopian tubes, outer surfaces of the uterus or intestines, and on the surface lining of the pelvic cavity. They can also be found in the vagina, cervix, and bladder, although less commonly than other locations in the pelvis. Rarely, endometriosis implants can occur outside the pelvis, on the liver, in old surgery scars, and even in or around the lung or brain. Endometrial implants, while they can cause problems, are benign (not cancerous).

What are endometriosis symptoms?

Most women who have endometriosis, in fact, do not have symptoms. Of those who do experience symptoms, the common symptoms are pain (usually pelvic) and infertility. Pelvic pain usually occurs during or just before menstruation and lessens after menstruation. Some women experience painful sexual intercourse (dyspareunia) or cramping during intercourse, and or/pain during bowel movements and/or urination. Even pelvic examination by a doctor can be painful. The pain intensity can change from month to month, and vary greatly among women. Some women experience progressive worsening of symptoms, while others can have resolution of pain without treatment.

- Pelvic pain in women with endometriosis depends partly on where the implants of endometriosis are located.
- Deeper implants and implants in areas with many pain-sensing nerves may be more likely to produce pain.
- The implants may also produce substances that circulate in the bloodstream and cause pain.
- Lastly, pain can result when endometriosis implants form scars. There is no relationship between severity of pain and how widespread the endometriosis is (the "stage" of endometriosis).

Endometriosis can be one of the reasons for infertility for otherwise healthy couples. When laparoscopic examinations are performed for infertility evaluations, endometrial implants can be found in some of these patients, many of whom may not have painful symptoms of endometriosis. The reasons for a decrease in fertility are not completely understood, but might be due to both anatomic and hormonal factors. The presence of endometriosis may involve masses of tissue or scarring (adhesions) within the pelvis that may distort normal anatomical structures, such as Fallopian tubes, which transport the eggs from the ovaries. Alternatively, endometriosis may affect fertility through the production of hormones and other substances that have a negative effect on ovulation, fertilization of the egg, and/or implantation of the embryo.

How RECEPTOL® Oral Spray helps with Endometrosis?

- Radha108 (PRP) promotes differentiation of B cells, differentiation and maturation of macrophages and monocytes.
- Activates natural killer (NK) cells, cytotoxic cells of the innate immune system
- Mitigates cell fusion and docks on HIV glycoprotein like Gp120, 180, 160 and 41 mimicking receptor on the cell surface closing entry of viruses.
- Stimulates production of cytokines IL-1 to IL-11, TNF-α, INF–γ.
- Stimulates the maturation of immature thymocytes into either helper or suppressor T cells
- Radha108 also functions as a molecular signaling device which works through receptors on target cell surfaces.
- Radha108 series get absorbed in the blood through buccal mucosa and crosses BBB .
- Stimulates the maturation of immature thymocytes into either helper or suppressor T cells
- Radha108 (PRP) promotes differentiation of B cells, differentiation and maturation of macrophages and monocytes.
- Activates natural killer (NK) cells, cytotoxic cells of the innate immune system
- Stimulates production of cytokines IL-1 to IL-11, TNF-α, INF–γ.
- Mitigates cell fusion and docks on HIV glycoprotein like Gp120, 180, 160 and 41 mimicking receptor on the cell surface closing spectrum entry of viruses.
- Radha108 also functions as a molecular signaling device which works through receptors on target cell surfaces.

References:

1. Correlation Between Altered Central Pain Processing and Concentration of Peritoneal Fluid Inflammatory Cytokines in Endometriosis Patients With Chronic Pelvic Pain.Neziri AY, Bersinger NA, Andersen OK, Arendt-Nielsen L, Mueller MD, Curatolo M.Reg Anesth Pain Med. 2014 Apr 1.

2. Expression of natural cytotoxicity receptors on peritoneal fluid natural killer cell and cytokine production by peritoneal fluid natural killer cell in women with endometriosis.Funamizu A, Fukui A, Kamoi M, Fuchinoue K, Yokota M, Fukuhara R, Mizunuma H.Am J Reprod Immunol. 2014 Apr;71(4):359-67. doi: 10.1111/aji.12206. Epub 2014 Feb 5.

3. Suppression of COUP-TFII by proinflammatory cytokines contributes to the pathogenesis of endometriosis.Lin SC, Li YH, Wu MH, Chang YF, Lee DK, Tsai SY, Tsai MJ, Tsai SJ.J Clin Endocrinol Metab. 2014 Jan 1:jc20133717.

4. Chemokines in the pathogenesis of endometriosis and infertility, Borrelli GM, Carvalho KI, Kallas EG, Mechsner S, Baracat EC, Abrão MS. J Reprod Immunol. 2013 Jun;98(1-2):1-9. doi: 10.1016/j.jri.2013.03.003. Epub 2013 Apr 25.

5. Diagnostic accuracy of interleukin-6 levels in peritoneal fluid for detection of endometriosis.Wickiewicz D, Chrobak A, Gmyrek GB, Halbersztadt A, Gabryś MS, Goluda M,

Chełmońska-Soyta A.Arch Gynecol Obstet. 2013 Oct;288(4):805-14. doi: 10.1007/s00404-013-2828-6. Epub 2013 Apr 4.

6. Transcriptional changes in the expression of chemokines related to natural killer and T-regulatory cells in patients with deep infiltrative endometriosis. Bellelis P, Barbeiro DF, Rizzo LV, Baracat EC, Abrão MS, Podgaec S.Fertil Steril. 2013 Jun;99(7):1987-93

7. Peritoneal fluid concentrations of β-chemokines in endometriosis.Margari KM, Zafiropoulos A, Hatzidaki E, Giannakopoulou C, Arici A, Matalliotakis I.Eur J Obstet Gynecol Reprod Biol. 2013 Jul;169(1):103-7

8. Association between interleukin-10 promoter polymorphisms and endometriosis: a meta-analysis.Fan W, Li S, Chen Q, Huang Z, Ma Q, Xiao Z.Gene. 2013 Feb 15;515(1):49-55

9. Targeting of syndecan-1 by micro-ribonucleic acid miR-10b modulates invasiveness of endometriotic cells via dysregulation of the proteolytic milieu and interleukin-6 secretion.Schneider C, Kässens N, Greve B, Hassan H, Schüring AN, Starzinski-Powitz A, Kiesel L, Seidler DG, Götte M.Fertil Steril. 2013 Mar 1;99(3):871-881.

10. Interleukin-19 and interleukin-22 serum levels are decreased in patients with ovarian endometrioma.Santulli P, Borghese B, Chouzenoux S, Streuli I, Borderie D, de Ziegler D, Weill B, Chapron C, Batteux F.Fertil Steril. 2013 Jan;99(1):219-26 145

11. Selected cytokines and glycodelin A levels in serum and peritoneal fluid in girls withendometriosis.Drosdzol-Cop A, Skrzypulec-Plinta V.J Obstet Gynaecol Res. 2012 Oct;38(10):1245-53.

12. Analysis of cytokines in the peritoneal fluid of endometriosis patients as a function of the menstrual cycle stage using the Bio-Plex® platform. Bersinger NA, Dechaud H, McKinnon B, Mueller MD. Arch Physiol Biochem. 2012Oct;118(4):210-8

9.4 Groups: IV

9.4.1 RECEPTOL® and Spinal Muscular Atrophy

What is spinal muscular atrophy?

Spinal muscular atrophy is a genetic disorder that affects the control of muscle movement. It is caused by a loss of specialized nerve cells, called motor neurons, in the spinal cord and the part of the brain that is connected to the spinal cord (the brainstem). The loss of motor neurons leads to weakness and wasting (atrophy) of muscles used for activities such as crawling, walking, sitting up, and controlling head movement. In severe cases of spinal muscular atrophy, the muscles used for breathing and swallowing are affected. There are many types of spinal muscular atrophy distinguished by the pattern of features, severity of muscle weakness, and age when the muscle problems begin.

Type I spinal muscular atrophy (also called Werdnig-Hoffman disease) is a severe form of the disorder that is evident at birth or within the first few months of life. Affected infants are developmentally delayed; most are unable to support their head or sit unassisted. Children with this type have breathing and swallowing problems that may lead to choking or gagging.

Type II spinal muscular atrophy is characterized by muscle weakness that develops in children between ages 6 and 12 months. Children with type II can sit without support, although they may need help getting to a seated position. Individuals with this type of spinal muscular atrophy cannot stand or walk unaided.

Type III spinal muscular atrophy (also called Kugelberg-Welander disease or juvenile type) has milder features that typically develop between early childhood and adolescence. Individuals with type III spinal muscular atrophy can stand and walk unaided, but walking and climbing stairs may become increasingly difficult. Many affected individuals will require wheelchair assistance later in life.

The signs and symptoms of type IV spinal muscular atrophy often occur after age 30. Affected individuals usually experience mild to moderate muscle weakness, tremor, twitching, or mild breathing problems. Typically, only muscles close to the center of the body (proximal muscles), such as the upper arms and legs, are affected in type IV spinal muscular atrophy.

The features of X-linked spinal muscular atrophy appear in infancy and include severe muscle weakness and difficulty breathing. Children with this type often have joint deformities (contractures) that impair movement. In severe cases, affected infants are born with broken bones. Poor muscle tone before birth may contribute to the contractures and broken bones seen in these children.

Spinal muscular atrophy, lower extremity, dominant (SMA-LED) is characterized by leg muscle weakness that is most severe in the thigh muscles (quadriceps). This weakness begins in infancy or early childhood and progresses slowly. Affected individuals often have a waddling or unsteady walk and have difficulty rising from a seated position and climbing stairs.

An adult-onset form of spinal muscular atrophy that begins in early to mid-adulthood affects the proximal muscles and is characterized by muscle cramping of the limbs and abdomen, weakness in the leg muscles, involuntary muscle contractions, tremors, and a protrusion of the abdomen thought to be related to muscle weakness. Some affected individuals experience difficulty swallowing and problems with bladder and bowel function.

How common is spinal muscular atrophy?

Spinal muscular atrophy affects 1 in 6,000 to 1 in 10,000 people.

The adult-onset form of spinal muscular atrophy is caused by a mutation in the VAPB gene. The VAPB gene provides instructions for making a protein that is found in cells throughout the body. Researchers suggest that this protein may play a role in preventing the builtup of unfolded or mis folded proteins within cells. It is unclear how a VAPB gene mutation leads to the loss of motor neurons. An impaired VAPB protein might cause mis folded and unfolded proteins to accumulate and impair the normal function of motor neurons.

Other types of spinal muscular atrophy that primarily affect the lower legs and feet and the lower arms and hands are caused by the dysfunction of neurons in the spinal cord. When spinal muscular atrophy shows this pattern of signs and symptoms, it is also known as distal hereditary motor neuropathy. The various types of this condition are caused by mutations in other genes.

How RECEPTOL® Oral Spray helps with Spinal Muscular Atrophy:

This condition is a genetic disorder that affects the control of muscle movement. It is caused by a loss of specialized nerve cells, called motor neurons, in the spinal cord and the part of the brain that is connected to the spinal cord (the brainstem). The loss of motor neurons leads to weakness and wasting (atrophy) of muscles used for activities such as crawling, walking, sitting up, and controlling head movement. In severe cases of spinal muscular atrophy, the muscles used for breathing and swallowing are affected immune system also.

RECEPTOL® Oral Spray contains several components and all of them work together in the process of regeneration of all cells in the human body, including neurogens. RECEPTOL® can help to increase the level of energy; it contains immune factors, amino-acids and growth factors helping the body to fight off common infections and to enhance weakened immune and digestive systems. It helps to improve a general sense of well-being and body functions by balancing the body's hormones through the thymus gland.

A long term use of our RECEPTOL® Oral Spray could be very beneficial for people who are suffering from spinal muscular atrophy; however more research has to be done in this field.

"The Label claims are based on global studies on API: PRPs (Radha108 as class of PRPs being part of it) for which we have sent and up loaded claims on various indications based on published data in first rate Medical Journals. BMJ has accepted our two articles and two more are likely to be in leading Science Journal like NATURE by end of 2014 since our Global Medical Advisory Board has recommended to wait for follow up of patients who tried the product over 6 to 7 years a go and still have not shown any sign of disease reappearance, indicating that all Hibernation Viruses (crossing a window period of 8 years), including HIV have been stopped its reproduction leading to a possible claim for treatment & cure of AIDS & other major immune disorders, for which we have just received an approval for new US Product Patent as well".

References:

1. Multilevel Anterior Cervical Discectomy and Fusion with Plate Fixation for Juvenile Unilateral Muscular Atrophy of the Distal Upper Extremity Accompanied by Cervical Kyphosis. Guo X, Lu M, Xie N, Guo Q, Ni B. J Spinal Disord Tech. 2014 Mar 27.

2. A polyglutamine expansion disease protein sequesters PTIP to attenuate DNA repair and increase genomic instability. Xiao H, Yu Z, Wu Y, Nan J, Merry DE, Sekiguchi JM, Ferguson DO, Lieberman AP, Dressler GR. Hum Mol Genet. 2012 Oct 1;21(19):4225-36. doi: 10.1093/hmg/dds246. Epub 2012 Jun 26.

3. Fibroblast growth factor-2(23) binds directly to the survival of motoneuron protein and is associated with small nuclear RNAs. Claus P, Bruns AF, Grothe C. Biochem J. 2004 Dec 15;384(Pt 3):559-65.

4. A role for polyproline motifs in the spinal muscular atrophy protein SMN. Profilins bind to and colocalize with smn in nuclear gems. Giesemann T, Rathke-Hartlieb S, Rothkegel M, Bartsch JW, Buchmeier S, Jockusch BM, Jockusch H. J Biol Chem. 1999 Dec 31;274(53):37908-14.

5. Multilevel Anterior Cervical Discectomy and Fusion with Plate Fixation for Juvenile Unilateral Muscular Atrophy of the Distal Upper Extremity Accompanied by Cervical Kyphosis. Guo X, Lu M, Xie N, Guo Q, Ni B. J Spinal Disord Tech. 2014 Mar 27.

6. Polyethylene glycol-coupled IGF1 delays motor function defects in a mouse model of spinal muscular atrophy with respiratory distress type 1. Krieger F, Elflein N, Saenger S, Wirthgen E, Rak K, Frantz S, Hoeflich A, Toyka KV, Metzger F, Jablonka S. Brain. 2014 Mar 27.

7. Health-Related Quality of Life in Children and Adolescents With Spinal Muscular Atrophy in the Czech Republic.Kocova H, Dvorackova O, Vondracek P, Haberlova J. Pediatr Neurol. 2014 Jan 23. pii: S0887-8994(14)00064-2. doi: 10.1016/j.pediatrneurol.2014.01.037.

8. Skeletal Muscle DNA Damage Precedes Spinal Motor Neuron DNA Damage in a Mouse Model of Spinal Muscular Atrophy (SMA). Fayzullina S, Martin LJ. PLoS One. 2014 Mar 25;9(3):e93329. doi: 10.1371/journal.pone.0093329. eCollection 2014.

9.4.2 RECEPTOL® and Thrombocytopenia

What Is Thrombocytopenia?

Thrombocytopenia (THROM-bo-si-to-PE-ne-ah) is a condition in which your blood has a lower than normal number of blood cell fragments called platelets (PLATE-lets).

Platelets are made in your bone marrow along with other kinds of blood cells. They travel through your blood vessels and stick together (clot) to stop any bleeding that may happen if a blood vessel is damaged. Platelets also are called thrombocytes (THROM-bo-sites) because a clot also is called a thrombus.

How does thrombocytopenia occur?

Blood cells (including platelets) are made in the bone marrow, the spongy tissue inside of bones. Certain factors may interfere with the body's ability to make platelets. Under other circumstances production is normal, but platelets are removed prematurely from the blood. Causes of thrombocytopenia can include:

- A bone marrow disease or treatment for disease. For instance, diseases such as leukemia (cancer of the bone marrow and bloodstream) and lymphoma (cancer of the lymph system) can cause dysfunction of the bone marrow.
- Aplastic anemia, a disease that prevents the bone marrow from making blood cells of all types.
- Radiation and chemotherapy treatment for cancer can damage the blood stem cells that eventually become blood cells.
- Exposure to certain viruses, including Epstein-Barr, cytomegalovirus, hepatitis, and HIV.
- An autoimmune disease (the body's immune system attacks the body), such as immune thrombocytopenic purpura or ITP).
- An enlarged spleen (an organ that acts as a filter for the blood and helps the body fight infection). The enlarged spleen tends to trap platelets and prevent them from circulating in the bloodstream.
- Heredity (the condition is passed down from a parent)
- Exposure to toxic chemicals.
- Taking certain medications, such as certain antibiotics, cardiovascular drugs, and seizure medications.
- Drinking too much alcohol.

What are the symptoms of thrombocytopenia?

The main symptom of thrombocytopenia is bleeding, either on the surface of the skin or inside the body. (In mild cases of thrombocytopenia, there may not be any symptoms.)

Symptoms of thrombocytopenia include the following:

- Bleeding on various parts of the skin. You may have small red or purple spots called petechiae on your lower legs, or bruising that is purple, red, or brown (known as purpura).
- Bleeding that doesn't stop on its own, such as a nosebleed or bleeding from your gums when you brush your teeth.
- Heavier bleeding during menstrual periods.
- Internal bleeding, such as blood in the urine or stool or bleeding from the rectum.

How RECEPTOL® Oral Spray helps with Thrombocytopenia:

If the thrombocytopenia is caused by problems with immune system, doctor may prescribe steroids, immunoglobulin. And the RECEPTOL® is the immunity booster as it contains different types of immunoglobulin so it can helps to reduce the condition of thrombocytopenia.

"The Label claims are based on global studies on API: PRPs (Radha108 as class of PRPs being part of it) for which we have sent and up loaded claims on various indications based on published data in first rate Medical Journals. BMJ has accepted our two articles and two more are likely to be in leading Science Journal like NATURE by end of 2014 since our Global Medical Advisory Board has recommended to wait for follow up of patients who tried the product over 6 to 7 years ago and still have not shown any sign of disease reappearance, indicating that all Hibernation Viruses (crossing a window period of 8 years), including HIV have been stopped its reproduction leading to a possible claim for treatment & cure of AIDS & other major immune disorders, for which we have just received an approval for new US Product Patent as well".

References:

1. Bovine neonatal pancytopenia--comparative proteomic characterization of two BVD vaccines and the producer cell surface proteome (MDBK). Euler KN, Hauck SM, Ueffing M, Deeg CA. BMC Vet Res. 2013 Jan 23;9:18. doi: 10.1186/1746-6148-9-18.

2. Reproduction of bovine neonatal pancytopenia (BNP) by feeding pooled **colostrum** reveals variable alloantibody damage to different haematopoietic lineages. Bell CR, Rocchi MS, Dagleish MP, Melzi E, Ballingall KT, Connelly M, Kerr MG, Scholes SF, Willoughby K. Vet Immunol Immunopathol. 2013 Feb 15;151(3-4):303-14. doi: 10.1016/j.vetimm.2012.12.002. Epub 2012 Dec 10.

3. Demonstration of early functional compromise of bone marrow derived hematopoietic progenitor cells during bovine neonatal pancytopenia through in vitro culture of bone marrow biopsies. Laming E, Melzi E, Scholes SF, Connelly M, Bell CR, Ballingall KT, Dagleish MP, Rocchi MS, Willoughby K. BMC Res Notes. 2012 Oct 30;5:599. doi: 10.1186/1756-0500-5-599.

4. Immunophenotyping and characterization of BNP colostra revealed pathogenic alloantibodies of IgG1 subclass with specifity to platelets, granulocytes and monocytes of all maturation stages.Assad A, Amann B, Friedrich A, Deeg CA. Vet Immunol Immunopathol. 2012 Jun 15;147(1-2):25-34. doi: 10.1016/j.vetimm.2012.04.012. Epub 2012 Apr 19.

5. An outbreak of late-term abortions, premature births, and congenital deformities associated with a bovine viral diarrhea virus 1 subtype b that induces **thrombocytopenia**. Blanchard PC, Ridpath JF, Walker JB, Hietala SK. J Vet Diagn Invest. 2010 Jan;22(1):128-31.

9.4.3 RECEPTOL® & Burns

What is a Burn?

A **burn** is a type of injury to flesh or skin causedby heat, electricity, chemicals, friction or Radiation. Burns that affect only the superficial skin are known as superficial or first-degree burns. When damage penetrates into some of the underlying layers, it is a partial-thickness or second-degree burn. In a full-thickness or third-degree burn, the injury extends to all layers of the skin. A fourth-degree burn additionally involves injury to deeper tissues, such as muscle or bone.

The treatment required depends on the severity of the burn. Superficial burns may be managed with little more than simple pain relievers, while major burns may require prolonged treatment in specialized burn centers. Cooling with tap water may help relieve pain and decrease damage; however, prolonged exposure may result in low body temperature. Partial-thickness burns may require cleaning with soap and water, followed by dressings. It is not clear how to manage blisters, but it is probably reasonable to leave them intact. Full-thickness burns usually require surgical treatments, such as skin grafting. Extensive burns often require large amounts of intravenous fluids because the subsequent inflammatory response will result in significant capillary fluid leakage and edema. The most common complications of burns are related to infection.

While large burns can be fatal, modern treatments developed since 1960 have significantly improved the outcomes, especially in children and young adults. Globally, about 11 million people seek medical treatment, and 300,000 die from burns each year. In the United States, approximately 4% of those admitted to a burn center die from their injuries. The long-term outcome is primarily related to the size of burn and the age of the person affected.

What are Symptoms of Burns?

Burn symptoms and signs vary depending on the type of burn.

Superficial Burn

Symptoms include:

- Burned area turns red and is painful
- The area blanches (turns white) when you press on it
- The area may swell, but it is dry and there is no blistering

Superficial Partial-Thickness Burn

Symptoms include:

- Blisters, the area is moist, red, and weeping
- The area blanches (turns white) when you press on it, painful to air and temperature

Deep Partial-Thickness Burn

Symptoms include:

- Blisters, usually loose and easily unroofed,the area can be wet or waxy dry
- The skin color can vary from patchy, to cheesy white, to red

- The area does not blanch (turn white) with pressure, may or may not be painful, can perceive pressure

Full-Thickness Burn

Symptoms include:

- Skin can appear waxy white, leathery gray, or charred and blackened
- May not be painful if nerves have been damaged, the only sensation may be to deep pressure

What Causes of Burns?

Burns can be caused by:

❖ **Heat or flame (thermal burns**)
- Hot foods or drinks such as boiling water, tea, or coffee
- Hot oil or grease
- Hot tap water
- Direct heat such as stoves, heaters, or curling irons
- Direct flame
- Flammable liquids such as gasoline
- Fireworks

❖ **Chemicals (chemical burn)-strong acids or strong bases such as:**
- Cleaning products, Battery fluid
- Pool chemicals, Drain cleaners

❖ **Sunlight (Sunburn)**

❖ **Electricity (electrical burn)**
- Damaged electrical cords, Electrical outlets
- High-voltage wires, Lightning

❖ **Radiation (radiation burn)**
- Nuclear radiation, X-rays
- Radiation therapy for cancer treatment, Tanning beds

9.4.4 RECEPTOL® & Insect bites

What are insect bites?

Insect bites are puncture wounds or lacerations made by insects. An insect may bite when it is agitated and defends itself, or when it wants to feed. Insects typically inject formic acid, which can trigger a reaction, including redness, swelling, pain or itching.

Fire ants, bees, wasps and hornets have a painful sting which can trigger a potentially dangerous allergic reaction (anaphylaxis) for some people. A wasp may either bite or sting. Bites from fleas, mites and mosquitoes tend to cause itching rather than pain.

The rest of this article is about insect bites, not insect stings. In northern countries, such as the UK, much of Europe, northern USA and Canada, biting insects include: Bedbugs, Fleas, Flies (such as horseflies), Gnats, Midges, Mosquitoes, Spiders, Ticks.

When insects bite they release a form of saliva that can cause inflammation, blisters and irritation. Insect bite signs and symptoms vary, depending on the type of insect and the individual's sensitivity. While one person may just have a small, itchy lump that clears away in a few days, somebody else can have a more serious reaction, such as papular urticaria - crops of small papules and wheals, which may become infected or lichenified (thickened and leathery) because of rubbing and excoriation.

People who work outdoors or regularly participate in outdoor activities are more likely to be bitten by insects. In countries far away from the equator, such as many parts of Europe, northern USA and Canada, the risk of catching diseases from insect bites is small. However, the nearer the equator you get, the higher the risk is for catching diseases, such as malaria, sleeping sickness or dengue fever.

What are the signs and symptoms of insect bites?

A symptom is something the patient feels and reports, while a sign is something other people, such as the doctor detect. For example, pain may be a symptom while a rash may be a sign. In most cases insect bites cause a small itchy lump to develop on the skin. Sometimes the bite itself may be visible (a tiny hole). The lump may be filled with fluid. The area around the lump is sometimes inflamed. In the majority of cases insect bites are successfully treated at home and clear up within a few days.

Allergic reactions - some people, unfortunately, react badly to insect bites. Even so, severe allergic reactions are extremely rare. Allergic reactions to insect stings are more common. It is useful to know what the signs and symptoms of a severe allergic reaction are:

- A rash, often blotchy, that spreads to other parts of the body
- Breathing difficulties
- Chest pain
- Cramps
- Faintness or dizziness

- Nausea
- Rapid heartbeat
- Severe swelling which may be far from the bite area, such as the tongue or lips.
- Very severe itching
- Wheezing

If an insect bite becomes infected, the following signs and symptoms are possible:

- Pus inside the bite
- Pus around the bite
- Swollen glands
- An elevated body temperature (fever)
- A feeling of not being well
- Flu-like symptoms
- Bite area becomes redder, swells more, and becomes more painful

Some people may have a stronger reaction when they are bitten by the same type of insect for the second time; this is called sensitization - the individual becomes more sensitive to the insect's saliva. In such cases an itchy papule or an itchy weal may develop and persist for several days. Eventually, most people become immune and insensitive to the saliva if they are bitten enough times.

In the vast majority of cases insect bite reactions do not last more than a few hours. Occasionally, however, they can linger for a long time; even months. Patients with persistent long-term signs and symptoms may need medical follow-up treatment.
Tick bites - if mouth parts remain on the skin, signs and symptoms can persist. In most cases tick bite signs and symptoms clear up within three weeks.

Ticks are commonly found where deer live and also in long grassy areas. Bites are not generally painful, but may sometimes cause a lump to develop where the bite occurred. However, ticks may cause Lyme disease, which is caused by Borrelia burgdorferi, a bacterium which ticks may carry.Midges, mosquitoes, and gnats - bites tend to cause small, itchy lumps (papules). Blisters (bullae) or weals may develop in sensitive individuals.

In warmer parts of the world mosquito bites may cause many diseases, such as malaria, dengue fever, yellow fever, and encephalitis.

Fleas - particularly sensitive people may develop papular urticaria. Fluid-filled blisters (bullae) may also develop.

Horseflies - bites may cause the following signs and symptoms:

- Dizziness
- Eyes and lips may be itchy, with pink or red swellings
- Fatigue
- General weakness
- Hives (urticaria, a rash of weals)
- Wheezing

Horsefly bites may take a long time to heal. This is because the insect cuts into the skin when it bites.

Bedbugs - initial bedbug bites do not generally present any signs or symptoms. However, sensitized individuals (sensitivity increases after subsequent bites) may develop weals or papules.

Spiders - All types of spider's bites and some of them can be quite dangerous to humans. The black widow is the most venomous spider in the USA. The brown recluse is another dangerous spider whose bite can be very damaging, causing tissue destruction and a great deal of pain.

The **female black widow spider**'s bite is more serious, but rarely deadly. When bitten the human feels a pinprick in the skin. At first there may only be slight swelling and faded red marks. However, within a few hours stiffness and extreme pain sets in.

Signs and symptoms of a black widow spider bite may also include:

- Chills
- Elevated body temperature
- Nausea
- Extreme abdominal pain
- The **brown recluse spider**'s bite produces a mild stinging. This is followed by redness in the bite area, and intense pain within about eight hours. A fluid-filled blister forms where the bite occurred. The blister then sloughs off, leaving a deep, enlarging ulcer. Patients may experience a mild fever, listlessness, nausea, and sometimes a rash. Death is rare, but may occur, especially in small children.

What are the causes of insect bites?

Pets - a common source of fleabites.

Crowded communities - crowded communities with low hygiene standards are common places for human flea infestations.

Birds' nests - if bird nests or bird boxes are too near a home there is a raised risk of household infestations of bird fleas.

Moving into a new home - fleas may survive for some time without hosts (animals or humans). Anybody who has recently moved house and has bites may have fleabites.

Old properties and furniture - old properties and furniture, especially with upholstery may be ideal environments for bedbugs.

Type of job - people who work outdoors have a higher risk of receiving tick bites. Mite dermatitis is more likely to be present among dockworkers, shopkeepers or warehouse workers.

Traveling - traveling from one country to another may raise the risk of being bitten by an insect.

References:

1. Seasonal differences in cytokine expression in the skin of Shetland ponies suffering from insect bite hypersensitivity.Meulenbroeks C, van der Meide NM, Zaiss DM, van Oldruitenborgh-Oosterbaan MM, van der Lugt JJ, Smak J, Rutten VP, Willemse T.Vet Immunol Immunopathol. 2013 Jan 15;151(1-2):147-56.
2. Skin-infiltrating T cells and cytokine expression in Icelandic horses affected with insect bite hypersensitivity: a possible role for regulatory T cells. Heimann M, Janda J, Sigurdardottir OG, Svansson V, Klukowska J, von Tscharner C, Doherr M, Broström H, Andersson LS, Einarsson S, Marti E, Torsteinsdottir S.Vet Immunol Immunopathol. 2011 Mar 15;140(1-2):63-74
3. Production of proinflammatory cytokines without invocation of cytotoxic effects by an Epstein-Barr virus-infected natural killer cell line established from a patient with hypersensitivity to mosquito bites.Suzuki D, Tsuji K, Yamamoto T, Fujii K, Iwatsuki K.Exp Hematol. 2010 Oct;38(10):933-44
4. Specific IgE and IgG responses and cytokine profile in subjects with allergic reactions to biting midge Forcipomyia taiwana.Chen YH, Lee MF, Tsai JJ, Wu HJ, Hwang GY.Int Arch Allergy Immunol. 2009;150(1):66-74.
5. Reduced incidence of insect-bit hypersensitivity in Icelandic horses is associated with a down-regulation of interleukin-4 by interleukin-10 and transforming growth factor-beta1.Hamza E, Wagner B, Jungi TW, Mirkovitch J, Marti E.Vet Immunol Immunopathol. 2008 Mar 15;122(1-2):65-75

9.5 GROUP: V

9.5.1 RECEPTOL® & Sickle Cell Anemia

What is Sickle cell anemia?

Sickle cell anemia is a disease passed down through families. The red blood cells that are normally shaped like a disc take on a sickle or crescent shape. Red blood cells carry oxygen throughout the body.

Causes

Sickle cell anemia is caused by an abnormal type of hemoglobin called hemoglobin S. Hemoglobin is a protein inside red blood cells that carries oxygen.

- Hemoglobin S changes the red blood cells. The red blood cells become fragile and shaped like crescents or sickles.
- The abnormal cells deliver less oxygen to the body's tissues.
- They can also easily get stuck in small blood vessels and break into pieces. This can interrupt healthy blood flow and cut down even more on the amount of oxygen flowing to body tissues.

Sickle cell anemia is inherited from both parents. If you get the sickle cell gene from only one parent, you will have sickle cell trait. People with sickle cell trait do not have the symptoms of sickle cell anemia.

Sickle cell disease is much more common in people of African and Mediterranean descent. It is also seen in people from South and Central America, the Caribbean, and the Middle East.

Symptoms

Symptoms usually do not occur until after the age of 4 months.

Almost all people with sickle cell anemia have painful episodes called crises. These can last from hours to days. Crises can cause pain in the lower back, leg, joints, and chest.

Some people have one episode every few years. Others have many episodes each year. The crises can be severe enough to require a hospital stay.

When the anemia becomes more severe, symptoms may include:

- Fatigue
- Paleness
- Rapid heart rate
- Shortness of breath
- Yellowing of the eyes and skin (jaundice)

Younger children with sickle cell anemia have attacks of abdominal pain.

The following symptoms may occur because small blood vessels become blocked by the abnormal cells:

- Painful and prolonged erection (priapism)
- Poor eyesight or blindness
- Problems with thinking or confusion caused by small strokes
- Ulcers on the lower legs (in adolescents and adults)

How RECEPTOL® Oral Spray can help people in Sickle cell Anemia

RECEPTOL® Oral Spray can have potential benefits for people with Sickle Cell Anemia Regulatory factors such as the Proline-Rich-Polypeptide (PRP) which is a powerful immune system regulator can help to calm down the over active immune system, cell and tissue repair growth factors which promote regeneration of damaged tissues and cells.

These mentioned components, as well as other factors in RECEPTOL® Oral Spray, are in a unique balance made by nature and therefore they have a significant beneficial for people suffering with Sickle Cell Anemia.

Routine utilization of a high quality colostrum product as a dietary supplement should prove very beneficial to an individual with sickle cell anemia. The condition results in a substantially accelerated degradation rate of tissue in comparison to non-afflicted persons. In addition, the associated anemia places a huge energy demand on normal metabolism and there is usually a large overall energy drain on the body.

Colostrum is an amazing resource of substances necessary to support the development and repair of cells and tissues, to assure the effective and efficient metabolism of nutrients and maintain a healthy immune system. This is not completely surprising when we consider that it is intended for consumption by a newborn calf that has received none of the substances in utero that will be required for its proper development outside of the uterus and that its growth will occur at a very rapid rate, creating a huge demand for energy. In addition, it is ideally suited for consumption by humans since most of its biologically active components have essentially the same chemical structure as the same components found in humans and there are no known negative side effects
to its routine consumption other than those that might be experienced by individuals who are sensitive to the lactose (milk sugar) normally found in dairy products.

There are very small quantities of growth hormone in complete first milking colostrum, but growth hormone is an extremely potent hormone and, thus, not much is required. It directly affects almost every cell in the body and significantly influences the development of new, healthy cells, causing them to generate at a more rapid rate when a sufficient quantity of the hormone is present. Scientific studies have shown that one of the benefits of ingesting even small
amounts of growth hormone is accelerated development and repair of damaged tissue. It is believed that this occurs through the growth hormone/insulin-like growth factor axis.

There are also 6 different proteins present inside the cell and on the surface of the cell that react to the attachment of IGF-1 to its receptor. These are called insulin-like growth factor binding proteins (IGFBPs) and they control the actions of IGF-1on the cell. In addition, inside the cell there are at least 87 other related proteins either capable of binding to IGF-1, altering its actions, or influencing the effects of the IGFBPs. These are called insulin-like growth factor binding protein-related proteins (IGFBP-rPs). The entire collection of these proteins is referred to as the Insulin-like Growth Factor Binding Protein (IGFBP) Superfamily.

9.5.2 RECEPTOL® & Crohn's disease

What is Crohn's disease?

Crohn's disease, also known as **Crohn syndrome** and **regional enteritis**, is a type of inflammatory bowel disease (IBD) that may affect any part of the gastrointestinal tract from mouth to anus, causing a wide variety of symptoms.

It primarily causes abdominal pain, diarrhoea (which may be bloody if inflammation is severe), vomiting, or weight loss, but may also cause complications outside the gastrointestinal tract such as anaemia, skin rashes, arthritis, inflammation of the eye, tiredness, and lack of concentration. Crohn's disease is caused by interactions between environmental, immunological and bacterial factors in genetically susceptible individuals. This result in a chronic inflammatory disorder, in which the body's immune system attacks the gastrointestinal tract possibly directed at microbial antigens.

While Crohn's is an immune related disease, it does not appear to be an autoimmune disease (in that the immune system is not being triggered by the body itself). The exact underlying immune problem is not clear; however, it may be an immune deficiency state.

There is a genetic association with Crohn's disease, primarily with variations of the NOD2 gene and its protein, which senses bacterial cell walls. Siblings of affected individuals are at higher risk. Males and females are equally affected. Tobacco smokers are two times more likely to develop Crohn's disease than nonsmokers. Crohn's disease affects between 400,000 and 600,000 people in North America. Prevalence estimates for Northern Europe have ranged from 27–48 per 100,000. Crohn's disease tends to present initially in the teens and twenties, with another peak incidence in the fifties to seventies, although the disease can occur at any age. There is no known pharmaceutical or surgical cure for Crohn's disease.

Treatment options are restricted to controlling symptoms, maintaining remission, and preventing relapse. The disease was named after gastroenterologist Burrill Bernard Crohn, who, in 1932, together with two other colleagues at Mount Sinai Hospital in New York, described a series of patients with inflammation of the terminal ileum of the small intestine, the area most commonly affected by the illness.

Sign and symptoms:

Many people with Crohn's disease have symptoms for years prior to the diagnosis. The usual onset is between 15 and 30 years of age, but can occur at any age.Because of the 'patchy' nature of the gastrointestinal disease and the depth of tissue involvement; initial symptoms can be more subtle than those of ulcerative colitis. People with Crohn's disease experience chronic recurring periods of flare-ups and remission.

Abdominal pain may be the initial symptom of Crohn's disease. It is often accompanied by diarrhoea, especially in those who have had surgery. The diarrhoea may or may not be bloody. The nature of the diarrhoea in Crohn's disease depends on the part of the small intestine or colon involved. Ileitis typically results in large-volume, watery feces. Colitis may result in a smaller volume of feces of

higher frequency. Fecal consistency may range from solid to watery. In severe cases, an individual may have more than 20 bowel movements per day and may need to awaken at night to defecate.

Visible bleeding in the feces is less common in Crohn's disease than in ulcerative colitis, but may be seen in the setting of Crohn's colitis. Bloody bowel movements typically come and go, and may be bright or dark red in color. In the setting of severe Crohn's colitis, bleeding may be copious. Flatulence and bloating may also add to the intestinal discomfort.

Symptoms caused by intestinal stenosis are also common in Crohn's disease. Abdominal pain is often most severe in areas of the bowel with stenoses. Persistent vomiting and nausea may indicate stenosis from small bowel obstruction or disease involving the stomach, pylorus, or duodenum. Although the association is greater in the context of ulcerative colitis, Crohn's disease may also be associated with primary sclerosing cholangitis, a type of inflammation of the bile ducts.

Perianal discomfort may also be prominent in Crohn's disease. Itchiness or pain around the anus may be suggestive of inflammation, fistulisation or abscess around the anal area or anal fissure. Perianal skin tags are also common in Crohn's disease. Fecal incontinencemay accompany perianal Crohn's disease. At the opposite end of the gastrointestinal tract, the mouth may be affected by non-healing sores (aphthous ulcers). Rarely, the oesophagus, and stomach may be involved in Crohn's disease. These can cause symptoms including difficulty swallowing (dysphagia), upper abdominal pain, and vomiting.

Systemic

Crohn's disease, like many other chronic, inflammatory diseases, can cause a variety of systemic symptoms. Among children, growth failure is common. Many children are first diagnosed with Crohn's disease based on inability to maintain growth. As it may manifest at the time of the growth spurt in puberty, up to 30% of children with Crohn's disease may have retardation of growth. Fever may also be present, though fevers greater than 38.5 ˚C (101.3 ˚F) are uncommon unless there is a complication such as an abscess.

Among older individuals, Crohn's disease may manifest as weight loss, usually related to decreased food intake, since individuals with intestinal symptoms from Crohn's disease often feel better when they do not eat and might lose their appetite. People with extensive small intestine disease may also have malabsorption of carbohydrates or lipids, which can further exacerbate weight loss.

Extraintestine

In addition to systemic and gastrointestinal involvement, Crohn's disease can affect many other organ systems. Inflammation of the interior portion of the eye, known as uveitis, can cause blurred vision and eye pain, especially when exposed to light (photophobia). Inflammation may also involve the white part of the eye (sclera), a condition called episcleritis. Both episcleritis and uveitis can lead to loss of vision if untreated.

Crohn's disease that affects the ileum may result in an increased risk for gallstones. This is due to a decrease in bile acid resorption in the ileum and the bile gets excreted in the stool. As a result, the cholesterol/bile ratio increases in the gallbladder, resulting in an increased risk for gallstones.

Crohn's disease is associated with a type of rheumatologic disease known as seronegative spondyloarthropathy.

This group of diseases is characterized by inflammation of one or more joints (arthritis) or muscle insertions (enteritis). The arthritis in Crohn's disease can be divided into two types.

The first type affects larger weight-bearing joints such as the knee (most common), hips, shoulders, wrists, or elbows.

The second type symmetrically involves five or more of the small joints of the hands and feet. The arthritis may also involve the spine, leading to ankylosing spondylitis if the entire spine is involved or simply sacroiliitis if only the sacroiliac joint is involved. The symptoms of arthritis include painful, warm, swollen, stiff joints and loss of joint mobility or function.

Crohn's disease may also involve the skin, blood, and endocrine system. The most common type of skin manifestation, erythema nodosum, presents as raised, tender red nodules usually appearing on the shins. Erythema nodosum is due to inflammation of the underlying subcutaneous tissue, and is characterized by septal panniculitis.

Another skin lesion, pyoderma gangrenosum, is typically a painful ulcerating nodule. Crohn's disease also increases the risk of blood clots; painful swelling of the lower legs can be a sign of deep venous thrombosis, while difficulty breathing may be a result of pulmonary embolism. Autoimmune hemolytic anemia, a condition in which the immune system attacks the red blood cells, is also more common in Crohn's disease and may cause fatigue, a pale appearance, and other symptoms common in anaemia. Clubbing, a deformity of the ends of the fingers, may also be a result of Crohn's disease. Finally, Crohn's disease increases the risk of osteoporosis, or thinning of the bones. Individuals with osteoporosis are at increased risk of bone fractures.

People with Crohn's disease often have anaemia due to vitamin B12, folate, iron deficiency, or due to anemia of chronic disease. The most common is iron deficiency anemia from chronic blood loss, reduced dietary intake, and persistent inflammation leading to increased hepcidin levels, restricting iron absorption in the duodenum. As Crohn's disease most commonly affects the terminal ileum where the vitamin B12/intrinsic factorcomplex is absorbed, B12 deficiency may be seen. This is particularly common after surgery to remove the ileum. Involvement of the duodenum and jejunum can impair the absorption of many other nutrients including folate. If Crohn's disease affects the stomach, production of intrinsic factor can be reduced.

Crohn's disease can also cause neurological complications (reportedly in up to 15%). The most common of these are seizures, stroke, myopathy, peripheral neuropathy, Headache, depression.

People with Crohn's often also have issues with small bowel bacterial overgrowth syndrome, which has similar symptoms.

In the oral cavity people with Crohn's may develop cheilitis granulomatosa and other forms of orofacial granulomatosis, pyostomatitis vegetans, recurrent aphthous stomatitis, geographic tongue and migratory stomatitis in higher prevalence than the general population.

What Causes of Crohn's disease?

Crohn's disease seems to be caused by a combination of environmental factors and genetic predisposition. Crohn's is the first genetically complex disease in which the relationship between genetic risk factors and the immune system is understood in considerable detail.Each individual risk mutation makes a small contribution to the overall risk of Crohn's (approximately 1:200).

The genetic data, and direct assessment of immunity, indicates a malfunction in the innate immune system. In this view, the chronic inflammation of Crohn's is caused when the adaptive immune system tries to compensate for a deficient innate immune system.

Genetics

Crohn's has a genetic component.Because of this, siblings of known people with Crohn's are 30 times more likely to develop Crohn's than the general population.

The first mutation found to be associated with Crohn's was a frameshift in the NOD2 gene (also known as the CARD15 gene), followed by the discovery of point mutations. Over thirty genes have been associated with Crohn's; a biological function is known for most of them. For example, one association is with mutations in the XBP1 gene, which is involved in the unfolded protein response pathway of theendoplasmatic reticulum.There is considerable overlap between susceptibility loci for IBD and mycobacterial infections.

Immune system

There was a prevailing view that Crohn's disease is a primary T cell autoimmune disorder, however a newer theory hypothesizes that Crohn's results from an impaired innate immunity.The later hypothesis describes impaired cytokine secretion by macrophages, which contributes to impaired innate immunity and leads to a sustained microbial-induced inflammatory response in the colon, where the bacterial load is high. Another theory is that the inflammation of Crohn's was caused by an overactive T_h1 cytokine response.More recent studies argue that T_h17 is more important.

The most recent gene to be implicated in Crohn's disease is ATG16L1, which may induce autophagy and hinder the body's ability to attack invasive bacteria. Another recent study has theorized that the human immune system traditionally evolved with the presence of parasites inside the body, and that the lack thereof due to modern hygiene standards has weakened the immune system. Test subjects were reintroduced to harmless parasites, with positive response.

Microbes

Current thinking is that microorganisms are taking advantage of their host's weakened mucosal layer and inability to clear bacteria from the intestinal walls, which are both symptoms of Crohn's. Different strains found in tissue and different outcomes to antibiotics therapy and resistance suggest Crohn's Disease is not one disease, but an umbrella of diseases related to different pathogens.

Some studies have suggested a role for Mycobacterium avium subspecies paratuberculosis (MAP), which causes a similar disease, Johne's disease, in cattle. NOD2, a gene involved in Crohn's genetic susceptibility, is associated with diminished killing of MAP by macrophages, reduced innate and

adaptive immunity in the host and impaired immune responses required for control of intracellular mycobacterial infection.Macrophages infected with viable MAP are associated with high production of TNF-α.

Other studies have linked specific strains of enteroadherent E. coli to the disease. Adherent-invasive Escherichia coli (AIEC), are more common in people with CD, have the ability to make strong biofilms compared to non-AIEC strains correlating with high adhesion and invasion indices of neutrophils and the ability to block autophagy at the autolysosomal step, which allows for intracellular survival of the bacteria and induction of inflammation.Inflammation drives the proliferation of AIEC and dysbiosis in the ileum, irrespective of genotype.AIEC strains replicate extensively into macrophages inducing the secretion of very large amounts of TNF-α.

Mouse studies have suggested some symptoms of Crohn's disease, ulcerative colitis and irritable bowel syndrome have the same underlying cause. Biopsy samples taken from the colons of all three patient groups were found to produce elevated levels of a serine protease. Experimental introduction of the serine protease into mice has been found to produce widespread pain associated with irritable bowel syndrome, as well as colitis, which is associated with all three diseases.[73] Regional and temporal variations in those illnesses follow those associated with infection with the protozoan Blastocystis.

The "cold-chain" hypothesis is that psychrotrophic bacteria such as Yersinia and Listeria species contribute to the disease. A statistical correlation was found between the advent of the use of refrigeration in the United States and various parts of Europe and the rise of the disease.

There is an apparent connection between Crohn's disease, Mycobacterium, other pathogenic bacteria, and genetic markers. In many individuals, genetic factors predispose individuals to Mycobacterium avium subsp. paratuberculosis infection. This bacterium then produces mannins, which protect both itself and various bacteria from phagocytosis, which causes a variety of secondary infections. Still, this relationship between specific types of bacteria and Crohn's disease remains unclear.

Environmental factors

The increased incidence of Crohn's in the industrialized world indicates an environmental component. Crohn's is associated with an increased intake of animal protein, milk protein and an increased ratio of omega-6 to omega-3 polyunsaturated fatty acids.Those who consume vegetable proteins appear to have a lower incidence of Crohn's disease. Consumption of fish protein has no association. Smoking increases the risk of the return of active disease (flares).

The introduction of hormonal contraception in the United States in the 1960s is associated with a dramatic increase in incidence, and one hypothesis is that these drugs work on the digestive system in ways similar to smoking.Isotretinoin is associated with Crohn's.Although stress is sometimes claimed to exacerbate Crohn's disease, there is no concrete evidence to support such claim.Dietary microparticles, such as those found in toothpaste, have been studied as they produce effects on immunity, but they were not consumed in greater amounts in patients with Crohn's.

References:

1. Effect of exclusion diet with nutraceutical therapy in juvenile Crohn's disease.Slonim AE, Grovit M, Bulone L.J Am Coll Nutr. 2009 Jun;28(3):277 85.

2. Milk-derived proteins and peptides in clinical trials. Artym J, Zimecki M.Postepy Hig Med Dosw (Online). 2013 Aug 6;67:800-16.

3. Rapid and sensitive method to identify Mycobacterium avium subsp. paratuberculosis in cow's milk by DNA methylase genotyping. Mundo SL, Gilardoni LR, Hoffman FJ, Lopez OJ.Appl Environ Microbiol. 2013 Mar;79(5):1612-8. doi: 10.1128/AEM.02719-12. Epub 2012 Dec 28.

4. Complementary and alternative therapies for inflammatory bowel disease.Langmead L, Rampton DS.Aliment Pharmacol Ther. 2006 Feb 1;23(3):341-9

5. A 60-day probiotic protocol with Dietzia subsp. C79793-74 prevents development of Johne's diseaseparameters after in utero and/or neonatal MAP infection.Virulence. 2011 Jul-Aug;2(4):337-47. Epub 2011 Jul 1.

6. Cytokines in inflammatory bowel disease.Neurath MF.Nat Rev Immunol. 2014 Apr 22.

7. Multigene Analysis Unveils Distinctive Expression Profiles of Helper T-cell-related Genes in the Intestinal Mucosa that Discriminate Between Ulcerative Colitis and Crohn's Disease.Iboshi Y, Nakamura K, Ihara E, Iwasa T, Akiho H, Harada N, Nakamuta M, Takayanagi R.Inflamm Bowel Dis. 2014 Apr 15.

8. Interleukin-19 impairment in active Crohn's disease patients.Cantó E, Garcia Planella E, Zamora-Atenza C, Nieto JC, Gordillo J, Ortiz MA, Metón I, Serrano E, Vegas E, García-Bosch O, Juárez C, Vidal S.PLoS One. 2014 Apr 9;9(4):e93910

9. Crohn's disease complicated by hepatitis B virus successfully treated with the use of adsorptive depletion of myeloid lineage leucocytes to suppress inflammatory cytokine profile.Yokoyama Y, Fukunaga K, Kamikozuru K, Sato T, Kawai M, Nogami K, Nagase K, Nakamura M, Immured M, Hida N, Nakamura S. Cytotherapy. 2014 Apr 5.

10. A CD3-specific Antibody Reduces Cytokine Production and Alters Phospho- protein Profiles in Intestinal Tissues from Patients with Inflammatory Bowel Disease.Vossenkämper A, Hundsrucker C, Page K, van Maurik A, Sanders TJ, Stagg AJ, Das L, Macdonald TT.Gastroenterology. 2014 Apr 1

11. Effect of interleukin-17 on gene expression profile of fibroblasts from Crohn's disease patients.Kerami Z, Duijvis NW, Vogels EW, van Dooren FH, Moerland PD, Te Velde AA.J Crohns Colitis. 2014 Mar 14.

12. T2 enhances in situ level of Foxp3+ regulatory cells and modulates inflammatory cytokines inCrohn's disease.Li G, Ren J, Wang G, Gu G, Hu D, Ren H, Hong Z, Wu X, Liu S, Li J.Int Immunopharmacol. 2014 Feb;18(2):244-8.

13. Oral vitamin D3 supplementation reduces monocyte-derived dendritic cell maturation and cytokine production in Crohn's disease patients.Bartels LE, Bendix M, Hvas CL, Jørgensen SP, Agnholt J, Agger R, Dahlerup JF.Inflammopharmacology. 2014 Apr;22(2):95-103.

14. S-nitrosothiols, nitric oxide and proinflammatory cytokines in children with inflammatory boweldisease.Kolesov SA, Korkotashvili LV, Yazykova AB, Fedulova EN, Tutina OA, Tolkacheva NI.Clin Lab. 2013;59(9-10):953-7
15. Polymorphisms of the cytokine genes TGFB1 and IL10 in a mixed-race population with Crohn's disease.Almeida NP, Santana GO, Almeida TC, Bendicho MT, Lemaire DC, Cardeal M, Lyra AC.BMC Res Notes. 2013 Sep 27;6:387. doi: 10.1186/1756-0500-6-387.

16. Th17 cytokines in inflammatory bowel diseases: discerning the good from the bad.Troncone E, Marafini I, Pallone F, Monteleone G.Int Rev Immunol. 2013 Oct-Dec;32(5-6):526-33

17. Interleukin-17 immunity in pediatric Crohn disease and ulcerative colitis.Hölttä V, Klemetti P, Salo HM, Koivusalo A, Pakarinen M, Westerholm-Ormio M, Kolho KL, Vaarala O.J Pediatr Gastroenterol Nutr. 2013 Sep;57(3):287-92

18. Treatment of inflammatory bowel disease by chemokine receptor-targeted leukapheresis.Eberhardson M, Marits P, Jones M, Jones P, Karlen P, Karlsson M, Cotton G, Woznica K, Maltman B, Glise H, Winqvist O.Clin Immunol. 2013 Oct;149(1):73-82.

9.5.3 RECEPTOL® & Diabetes type II

What is Diabetes type II?

Diabetes mellitus type 2 (formerly noninsulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes) is a metabolic disorder that is characterized by hyperglycemia (high blood sugar) in the context of insulin resistance and relative lack of insulin.[2]This is in contrast to diabetes mellitus type 1, in which there is an absolute lack of insulin due to breakdown of islet cells in thepancreas.[3] The classic symptoms are excess thirst, frequent urination, and constant hunger. Type 2 diabetes makes up about 90% of cases of diabetes, with the other 10% due primarily to diabetes mellitus type 1 and gestational diabetes. Obesity is thought to be the primary cause of type 2 diabetes in people who are genetically predisposed to the disease.

Type 2 diabetes is initially managed by increasing exercise and dietary changes. If blood sugar levels are not adequately lowered by these measures, medications such as metformin or insulin may be needed. In those on insulin, there is typically the requirement to routinely check blood sugar levels.

Rates of type 2 diabetes have increased markedly since 1960 in parallel with obesity. As of 2010 there were approximately 285 million people diagnosed with the disease compared to around 30 million in 1985. Long-term complications from high blood sugar can include heart disease, strokes, diabetic retinopathy where eyesight is affected, kidney failure which may require dialysis, and poor blood flow in the limbs leading to amputations. The acute complication of ketoacidosis, a feature of type 1 diabetes, is uncommon; however hyperosmolar hyperglycemic state may occur.

Sign and symtoms

The classic symptoms of diabetes are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss. Other symptoms that are commonly present at diagnosis include a history of blurred vision,itchiness, peripheral neuropathy, recurrent vaginal infections, and fatigue.Many people, however, have no symptoms during the first few years and are diagnosed on routine testing.People with type 2 diabetes mellitus may rarely present withhyperosmolar hyperglycemic state (a condition of very high blood sugar associated with a decreased level of consciousnessand low blood pressure)

Complications

Type 2 diabetes is typically a chronic disease associated with a ten-year-shorter life expectancy.This is partly due to a number of complications with which it is associated, including: two to four times the risk of cardiovascular disease, includingischemic heart disease and stroke; a 20-fold increase in lower limb amputations, and increased rates of hospitalizations. In the developed world, and increasingly elsewhere, type 2 diabetes is the largest cause of nontraumatic blindness and kidney failure. It has also been associated with an increased risk of cognitive dysfunction and dementia through disease processes such as Alzheimer's disease and vascular dementia. Other complications include acanthosis nigricans, sexual dysfunction, and frequent infections.

What causes of diabetes type II?

The development of type 2 diabetes is caused by a combination of lifestyle and genetic factors. While some of these factors are under personal control, such as diet and obesity, other factors are not, such as increasing age, female gender, and genetics. A lack of sleep has been linked to type 2 diabetes.This is believed to act through its effect on metabolism. The nutritional status of a mother during fetal

development may also play a role, with one proposed mechanism being that of altered DNA methylation.

Lifestyle

A number of lifestyle factors are known to be important to the development of type 2 diabetes, including obesity and overweight (defined by a body mass index of greater than 25), lack of physical activity, poor diet, stress, and urbanization.Excess body fat is associated with 30% of cases in those of Chinese and Japanese descent, 60-80% of cases in those of European and African descent, and 100% of cases in Pima Indians and Pacific Islanders.Those who are not obese often have a high waist–hip ratio.

Dietary factors also influence the risk of developing type 2 diabetes. Consumption of sugar-sweetened drinks in excess is associated with an increased risk. The type of fatsin the diet are also important, with saturated fats and trans fatty acids increasing the risk, and polyunsaturated and monounsaturated fat decreasing the risk.[10] Eating lots ofwhite rice appears to also play a role in increasing risk. A lack of exercise is believed to cause 7% of cases.

Genetics

Most cases of diabetes involve many genes, with each being a small contributor to an increased probability of becoming a type 2 diabetic. If one identical twin has diabetes, the chance of the other developing diabetes within his lifetime is greater than 90%, while the rate for nonidentical siblings is 25–50%. As of 2011, more than 36 genes had been found that contribute to the risk of type 2 diabetes. All of these genes together still only account for 10% of the total heritable component of the disease. The TCF7L2 allele, for example, increases the risk of developing diabetes by 1.5 times and is the greatest risk of the common genetic variants. Most of the genes linked to diabetes are involved inbeta cell functions.

There are a number of rare cases of diabetes that arise due to an abnormality in a single gene (known as monogenic forms of diabetes or "other specific types of diabetes").These include maturity onset diabetes of the young (MODY), Donohue syndrome, and Rabson-Mendenhall syndrome, among others.Maturity onset diabetes of the young constitute 1–5% of all cases of diabetes in young people.

9.5.4 RECEPTOL® & Fibromyalgia

Fibromyalgia

Fibromyalgia is not yet officially classed as an autoimmune disorder, but studies strongly suggest that it involves deregulation of the immune system. It is also known as fibrositis, it is a chronic condition which causes pain, stiffness and tenderness of the muscles, tendons and joints. Other symptoms are restless sleep, waking feeling tired, fatigue, anxiety, depression and disturbances in the function of the bowel. The cause of fibromyalgia is not yet fully understood. The pain is not associated with tissue inflammation, tissue damage or deformity. Fatigue occurs in 90% of individuals with the disorder.

Immune dysfunction and fibromyalgia

A number of studies have shown, that fibromyalgia is caused by an irregular function of the immune system. "Researchers in Poland found that individuals with fibromyalgia have similarities in leukocyte (white blood cell) activity to individuals with allergies. They reported that allergy symptoms were been found in about 50% of individuals with fibromyalgia.

"Studies on sleep disorders and the symptoms of fibromyalgia showed a link between IL-1, immune-neuroendocrine- thermal systems and the sleep-wake cycle which results in non-restorative sleep, pain, fatigue, cognitive and mood symptoms with patients with fibromyalgia. (Moldofsky)"

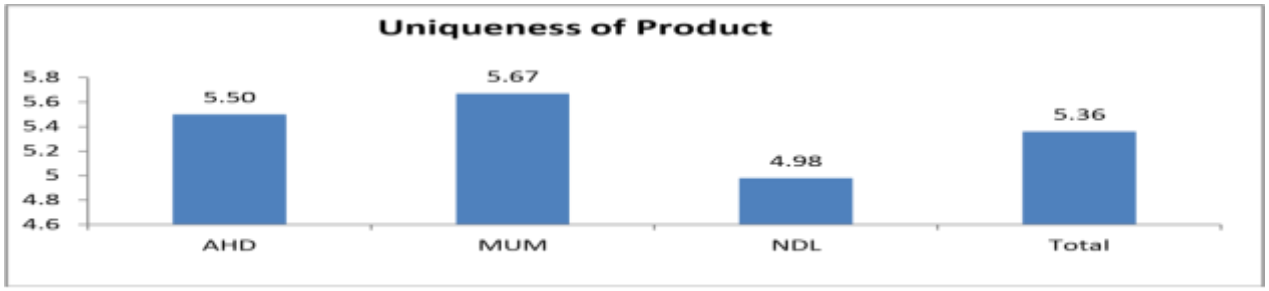
This further supports the statement that fibromyalgia is caused by irregular function of the immune system.

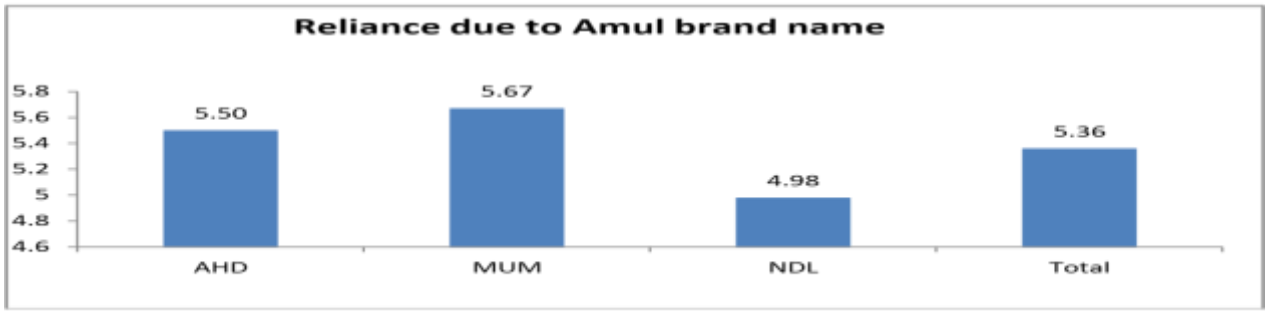
How RECEPTOL® Oral Spray can help people with fibromyalgia

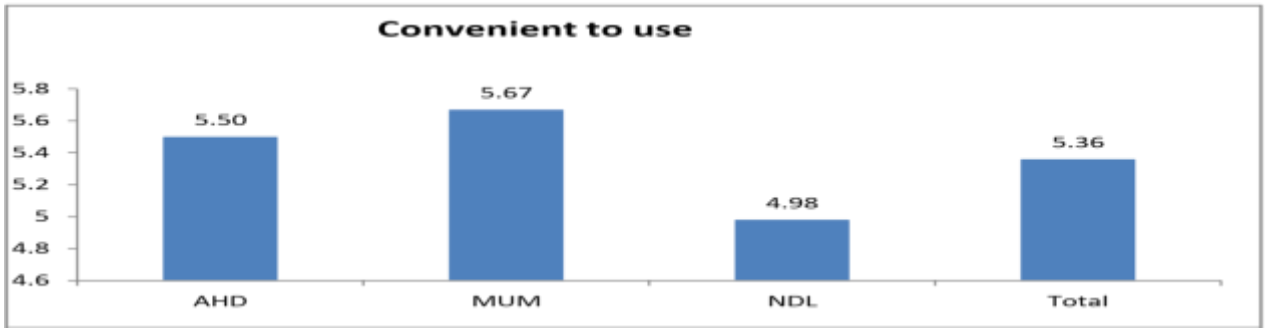
RECEPTOL®'s powerful immune regulatory components (Proline-Rich-Polypeptide – PRP) may be of benefit to people with fibromyalgia because it can regulate the immune system.

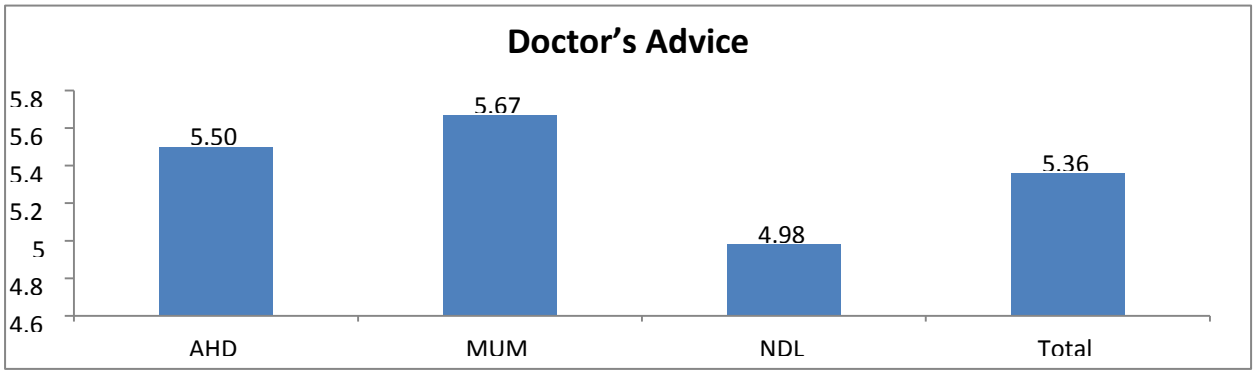
RECEPTOL® Oral Spray can offer protection against viruses and infections, support digestion and digestive immunity and help to improve sleep and energy levels."The Label claims are based on global studies on API: PRPs (Radha108 as class of PRPs being part of it) for which we have sent and up loaded claims on various indications based on published data in first rate Medical Journals. BMJ has accepted our two articles and two more are likely to be in leading Science Journal like NATURE by end of 2014 since our Global Medical Advisory Board has recommended to wait for follow up of patients who tried the product over 6 to 7 years ago and still have not shown any sign of disease reappearance, indicating that all Hibernation Viruses (crossing a window period of 8 years), including HIV have been stopped its reproduction leading to a possible claim for treatment & cure of AIDS & other major immune disorders, for which we have just received an approval for new US Product Patent as well".

10. Consumer opinion about RECEPTOL®









Expected Usage pattern:

*Consumer opinion is from source data Market Research conducted by Institute of Rural Management and IPSOS, USA

11. Granted Global Product Patents & Inventor' Brief Biography

Entry barrier via global patent exclusivity

1.	USA	13/142,327 DT. 27.06.2011	Mammalian Colostrum Derived Nanopeptides For Broadspectrum Viral And Recurrent Infections With A Method Of Isolation Thereof	GRANTED (PATENT# US8518454) on date August 27,2013
2.	USA	13/845,577 DT. 22.12.2015	"Mammalian Colostrum Derived Nanopeptides for Broadspectrum Viral and Recurrent Infections with a Method of Isolation Thereof **(Approved 58 indications for Radha 108)**	GRANTED (PATENT# 9,249,188) on date February 02, 2016
3.	SOUTH AFRICA	2011/4687 DT. 24.06.2011	Mammalian Colostrum Derived Nanopeptides For Broadspectrum Viral And Recurrent Infections With A Method Of Isolation Thereof	GRANTE (PATENT # 2011/04687) on date February 29, 2012
4.	SINGAPORE	201104717.2 DT. 29.12.2009	Mammalian Colostrum Derived Nanopeptides For Broadspectrum Viral And Recurrent Infections With A Method Of Isolation Thereof	GRANTED (PATENT #172793 on date March 7, 2014
5.	INDIA	1353/MUM/08 DT. 27/06/2008	Mammalian Colostrum Derived Nanopeptides For Broadspectrum Viral And Recurrent Infections With A Method Of Isolation Thereof	Approved
6.	EUROPE	EP 09827010.1 DT. 30.06.2011	Mammalian Colostrum Derived Nanopeptides For Broadspectrum Viral And Recurrent Infections With A Method Of Isolation Thereof	Approved
7.	CANADA	2478449 DT. 29.12.2009	Mammalian Colostrum Derived Nanopeptides For Broadspectrum Viral And Recurrent Infections With A Method Of Isolation Thereof	Approved
8.	PCT	PCT/IN09/749 DT. 29.12.2009	Mammalian Colostrum Derived Nanopeptides For Broadspectrum Viral And Recurrent Infections With A Method Of Isolation Thereof	Entered into National Phase-South Africa, Europe, USA, Canada & Singapore

Inventor's biography

Dr. Pawan Saharan, MS., Ph.D. (West Virginia Medical Center)
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- Dr. Pawan Saharan, with a vision to provide Health for all globally, Invented World's 1st solution to H1N1, HIV and host of other problems via Broad Spectrum Antiviral and New Generation Immuno-modulator- **RECEPTOL®**: **Recipe for all** that was recently launched at the International and Domestic Airports in Mumbai, India on August 25th 2009.

- Prestigious Who's Who American Historical Society (Boston) nominated Dr. Saharan as a World Leader in healthcare industry responsible for changing the destiny of nations & human race via the creative contribution in the healthcare sector via Receptol that builds body's own immune system naturally, providing hope to most disenchanted terminally ill patients globally.

- Dr. Saharan has global experience in running healthcare industry, including the Pharmaceuticals MNCs and hospitals at the top management level in USA & India

- Dr. Saharan created the first truly Nano-Bio-IT Helix via inventing Radha 108 Nano-Peptides for AIDS therapy : **RECEPTOL®** along with reusable micro-chip diagnostics for AIDS, Cancer, TB and other infections, costing a fraction of current tests creating a paradigm shift in healthcare & bringing smile on Billion Faces who could not afford modern treatment.

- Late Dr. Abdul Kalam, former President of India, nominated Dr. Saharan for India's new drug discovery with a funding of Rs 120MM (US$ 3MM), by department of science & technology, Govt. of India.

- Dr. Saharan has a Ph.D. Major in Medicine & topped First Rate University- JNU in India while pursuing Master in Life Sciences and has several International Publications / Presentations including in Top Scientific Journal_ Nature. Dr. Saharan has organized several global conferences and lead the Global Impact of Nano-biotechnology in Healthcare.

- Canadian and UK Govt. invited Dr. Saharan as the state guest in recognition for his contribution to healthcare and technological alliances between North America and India via Canada India Business Council that has generated Billions of dollars of business. UK Prime Minister invited Dr. Saharan in March, 2011 as a key note speaker at the UK India Business Council for the key note address on affordable health care.

- American Association for the Advancement of Science (AAAS), Washington DC nominated Dr. Saharan for the best US Graduate Student Scientist Award.