Health for All

Via

Receptol ®

A Paradigm shift in Healthcare

Treatment to Prevention

Dr. Pawan Saharan

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NATIONAL HEALTH MISSION
राष्ट्रीय स्वास्थ्य मिशन

डॉ. हर्ष वर्धन
Dr. Harsh Vardhan



सत्यमेव जयते

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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.

Harsh

(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 Receptol s 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, Receptol s (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.

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 Receptol s, 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, Receptol s: 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 Receptol 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.

Receptol s
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. Receptol s are produced in the human body by the actions of the PRP proteins. Two main Receptol s that are produced by PRP include IFN-alpha and IFN-beta.

The function and applications of just these two Receptol s are described in the literature below. Receptol '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 Receptol s 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 Receptol s 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 Receptol , or immune Receptol s, 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 Receptol s 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 Receptol 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 Receptol actions see also: endocrine, paracrine, juxtacrine, retrocrine). Many growth factors and Receptol s 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 Receptol s, 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 Receptol 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: Receptol 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 Receptol s.

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 Receptol 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 Receptol s. 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 Receptol 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

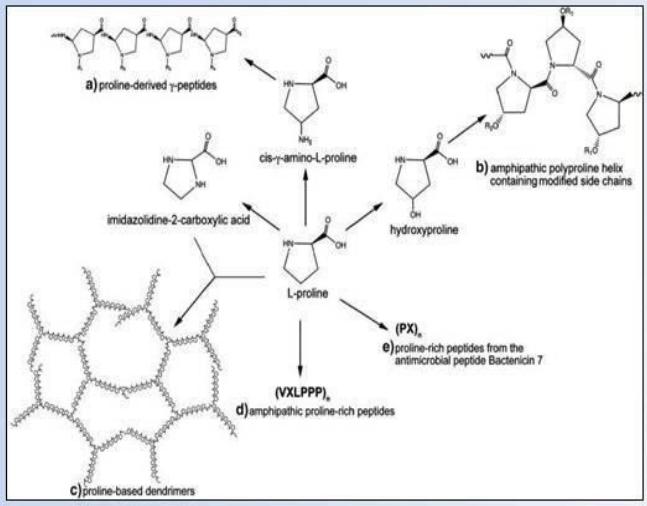
Radha 108 Active Pharmaceutical Ingredients (API)

- 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)

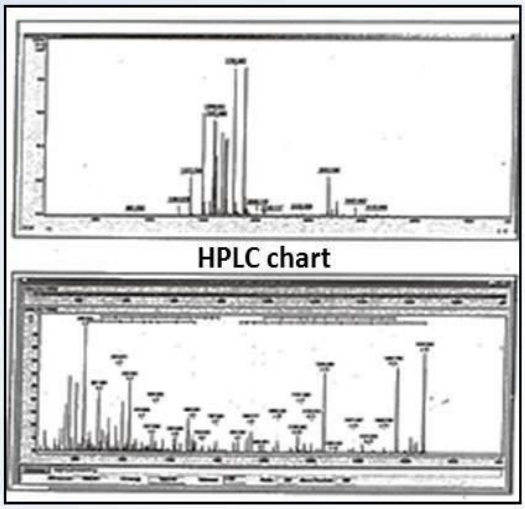
The 'Biggest' thing in Industry, just may be the 'Smallest' thing – Radha 108 Nanopeptides

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 Receptol modulators. Receptol s 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 Receptol '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 Receptol 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 Receptol 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 Receptol s:

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 Receptol s.

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 Receptol s 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 Receptol s 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 Receptol s. 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 & Receptol s 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 Receptol s 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 Receptol s 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.

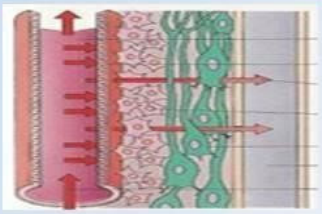
Radha 108 API containing SEQ ID1- 8 (With globally granted patent)

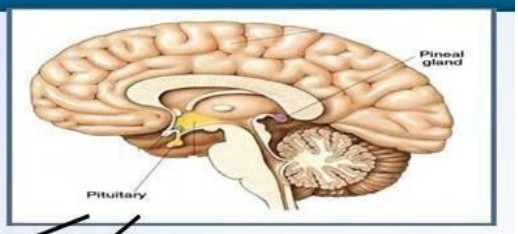
S. No.	Peptide Sequence	Spectral Count	Protein name
1	ELVPGVPRGTQL	27	DNA-binding protein inhibitor ID-3 **(MW – 1265.48)**
2	VAIIQHMIKKLR	24	Epstein-Barr virus induced gene 2 (Lymphocyte-specific G protein-coupled rec **(MW – 1449.86)**
3	LPQEVLNENLLRF	22	Alpha-S1-casein **(MW – 1584.84)**
4	RLNARMAELR	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

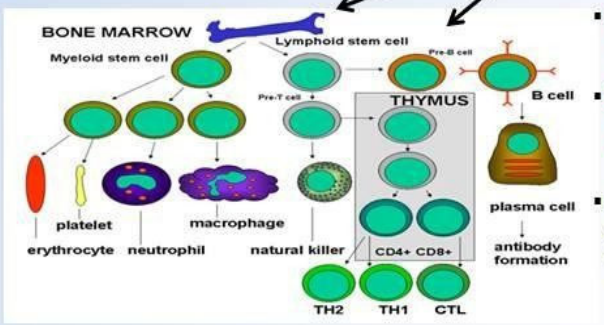


PRPs get absorbed in the blood through buccal mucosa and crosses BBB →





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

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

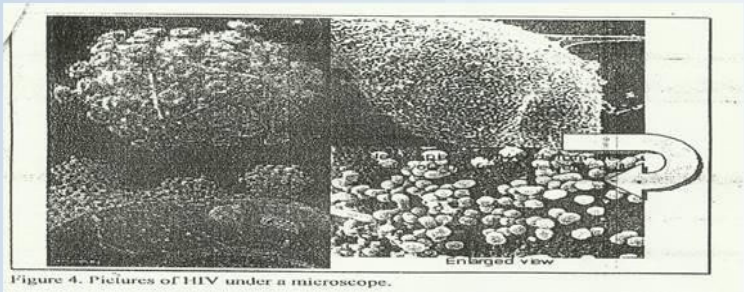


Figure 4. Pictures of HIV under a microscope.

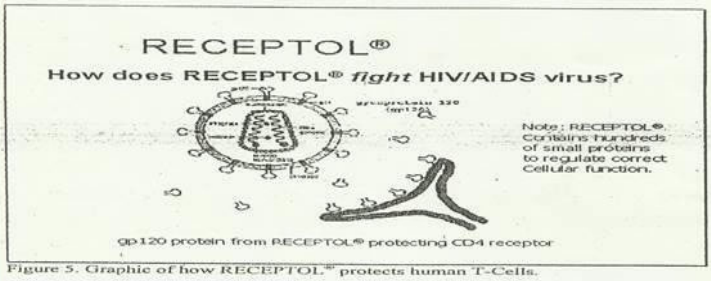
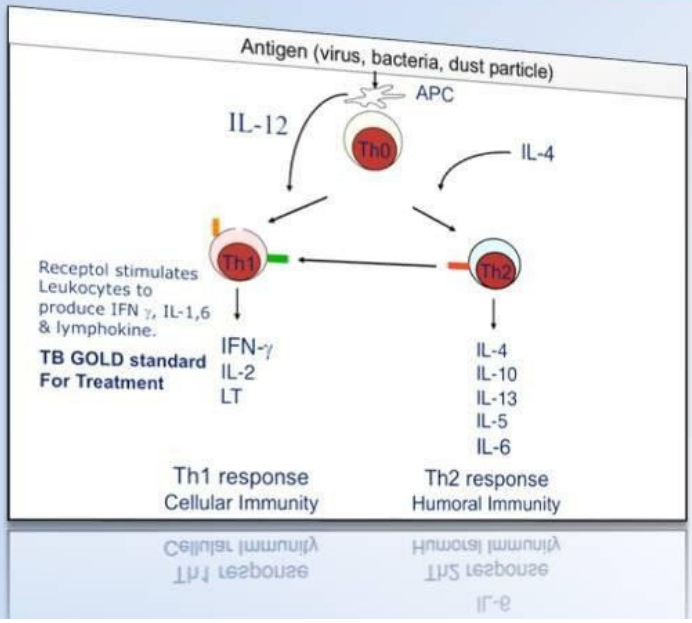


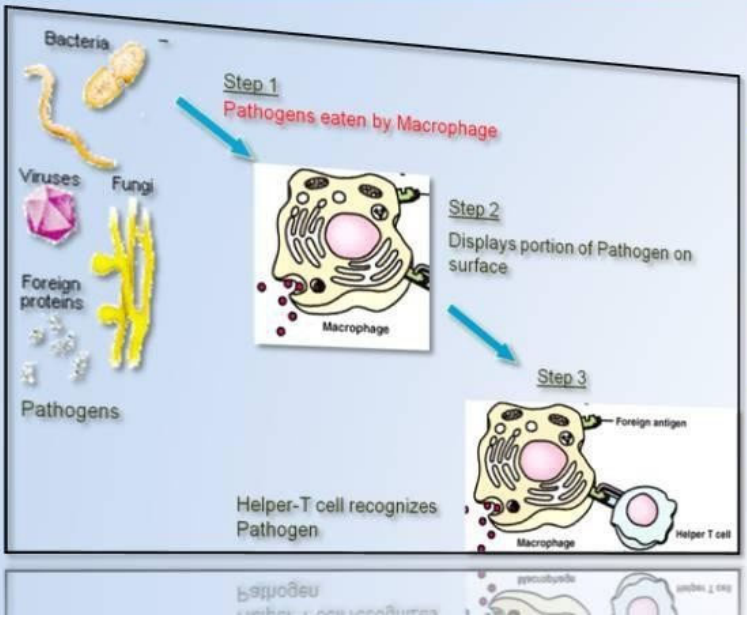
Figure 5. Graphic of how RECEPTOL® protects human T-Cells.

Mode of action



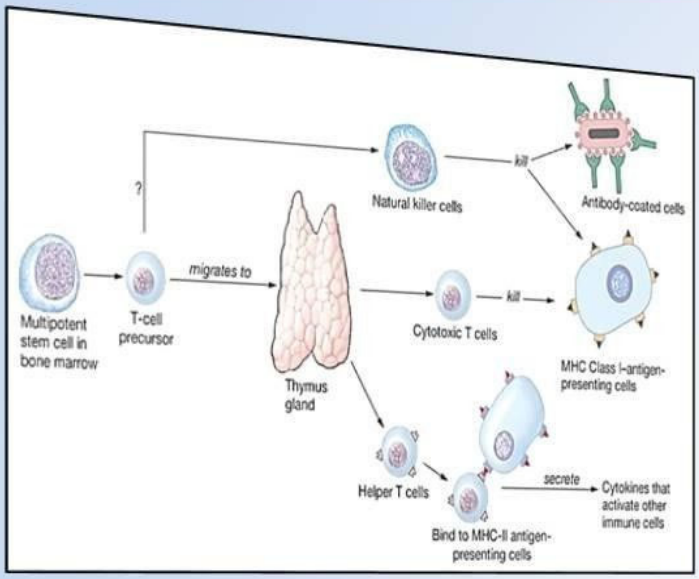
Mode of Action T Helper Cell Differentiation via Radha108 Nano Peptide®

Mode of action



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

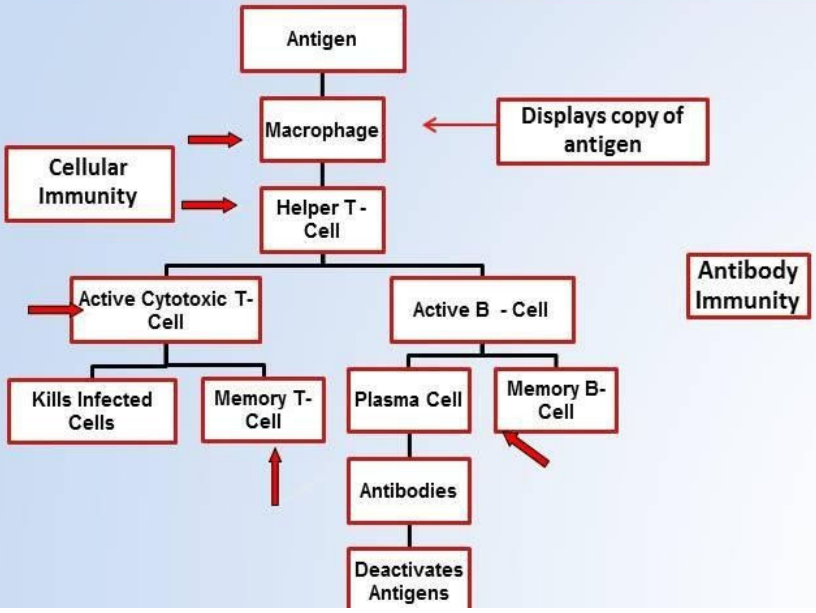
Mode of action



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

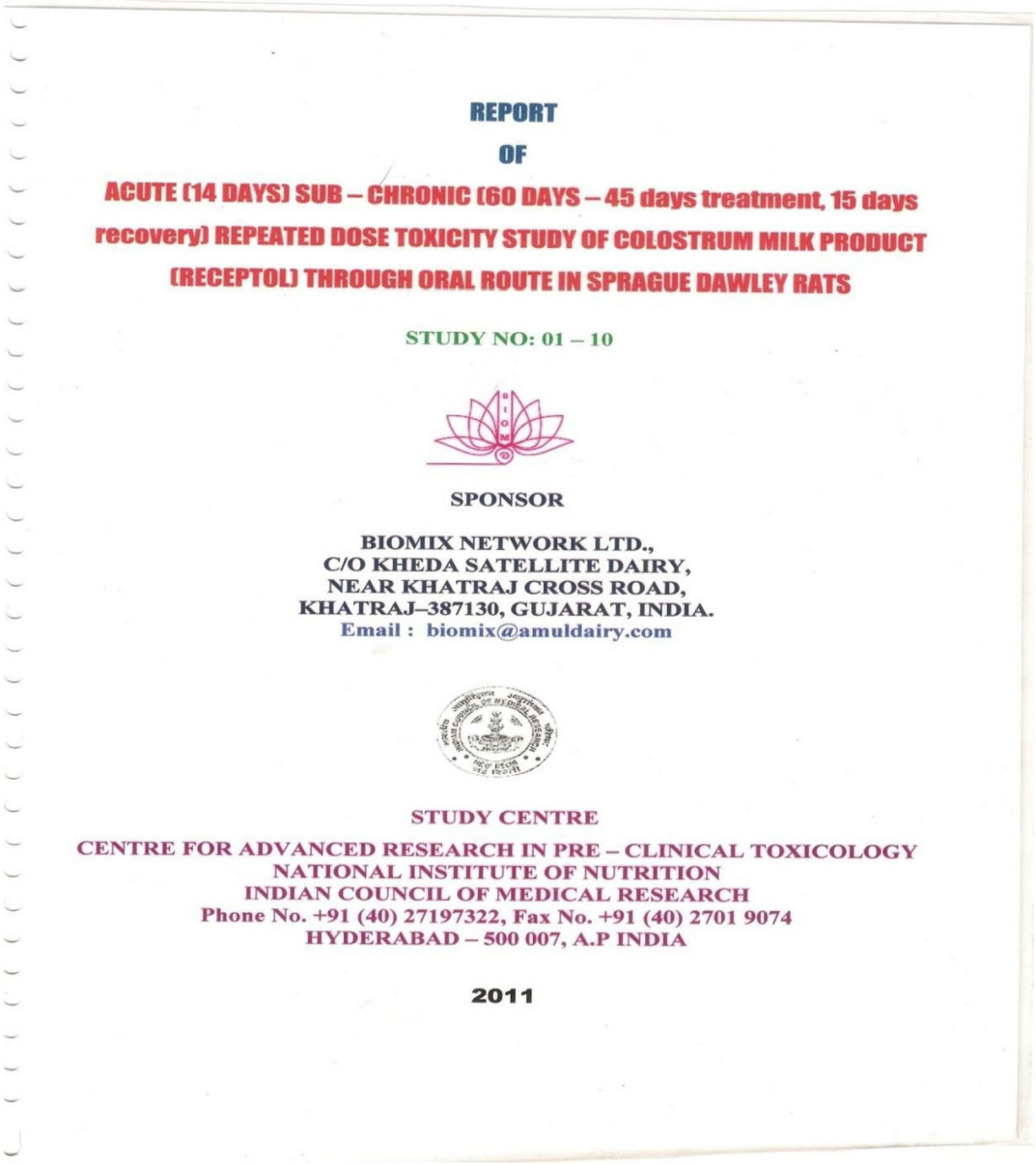
1.	No. of Rats used	48
2.	Categories	Vehicle control (VC), Therapeutic dose (TD – 1.08ml), Average dose (AD – 5XTD), (five times of TD) and High Dose (HD – 10XTD), (ten times of TD)
3.	Days of trial	45
4.	Period of Observation	Biweekly for live phase, cage side, physical and neurological parameters. 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

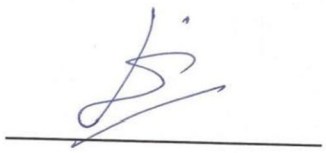
STUDY CENTRE

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

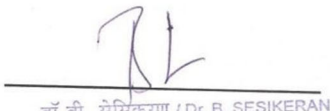


Dr. B. Dinesh Kumar, PhD
National Institute of Nutrition

13/06/2011

Date

Director & Coordinator PCT



डॉ बी. सेसिकरण / Dr. B. SESIKERAN
DIRECTOR
National Institute of Nutrition
भारत आयुर्विज्ञान अनुसंधान परिषद
Indian Council of Medical Research
जाम उस्मानिया पोस्ट, हैदराबाद-500 604
Jamai Osmania P.O. Hyderabad - 500 604

Dr. B. Sesikeran, MD
National Institute of Nutrition

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

S. No.	Unique Id.	product x	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.

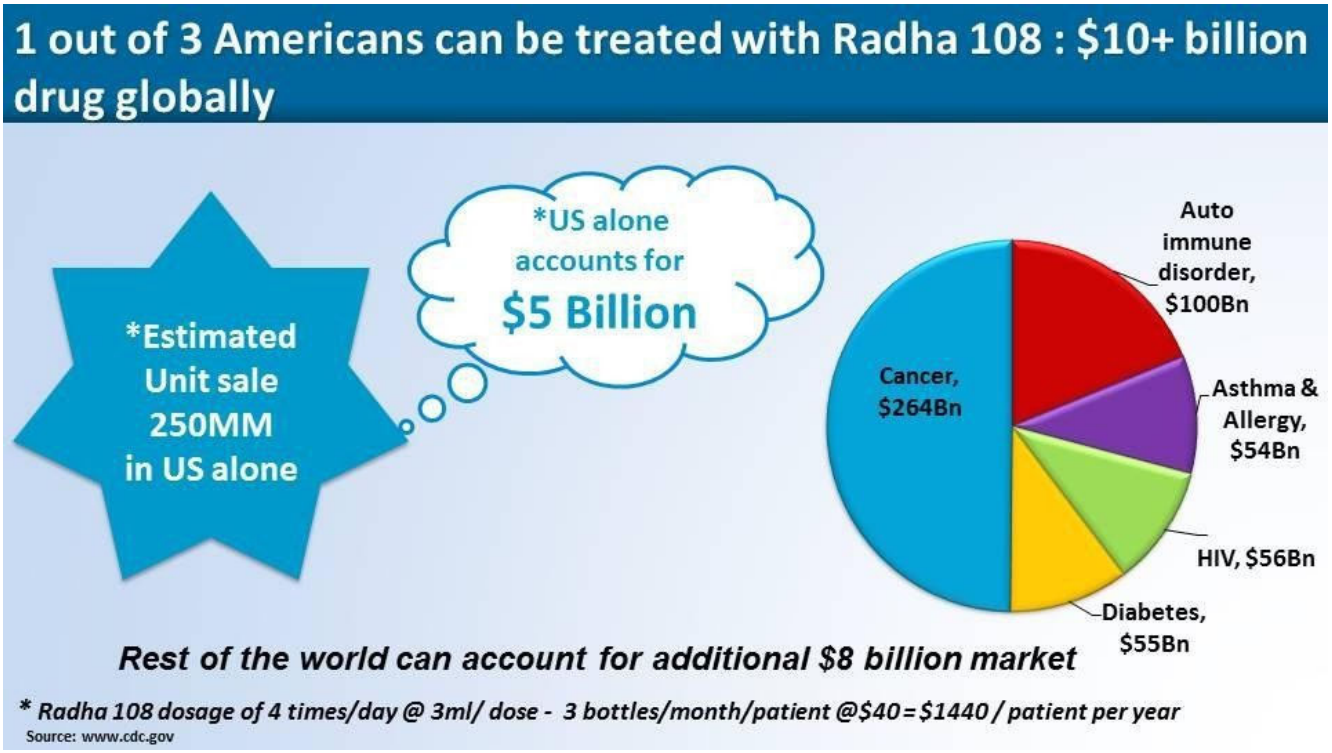
NIN Study - Sub acute data : No sub chronic toxicity found

VC - Vehicle control TD -Therapeutic dose Average dose

HD -High dose

S. 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

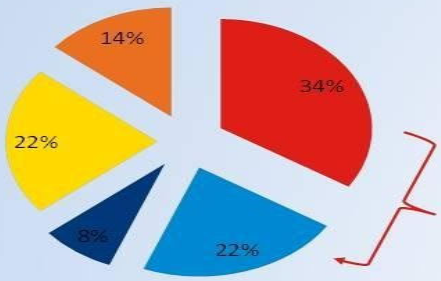
6.2. RECEPTOL INTERNATIONAL CLINICAL STUDY





Radha 108 in NCDs : Rheumetoid Arthritis Study

Reporting Patients* : 63
Duration of Treatment : 6 months

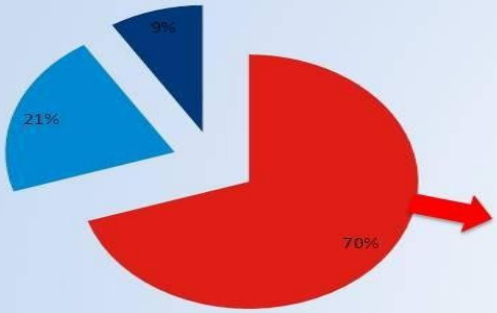


- Complete resolution of symptoms
- Significant benefits
- Some benefit
- Did not exhibit the same benefit
- Inconclusive

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

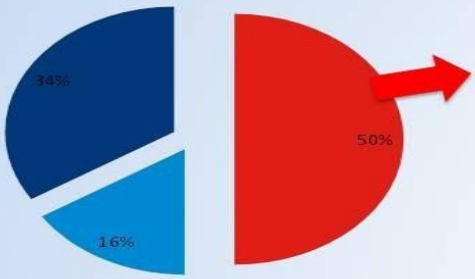


- Significant benefit
- Some Benefit
- Did not exibit the same benefit

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

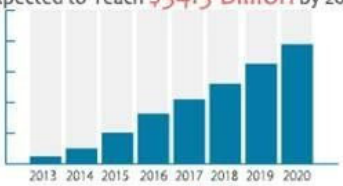
25MM alone in US

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

- Inhalers
  - Drug powder inhalers (DPIs)
  - Metered Dose Inhalers (MDIs)
  - Soft Mist Inhalers (SMIs)
- Nebulizers
  - Compressor nebulizer
  - Ultrasonic nebulizer
  - Mesh nebulizer

Global COPD and Asthma Devices Market By Geography

Asia-Pacific, North America,LAMEA

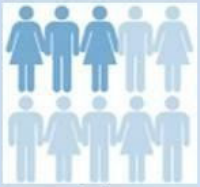
Europe

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.

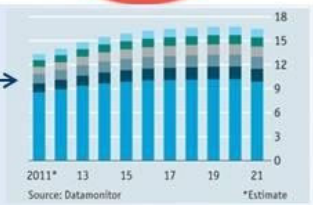


2.6 MILLION CHILDREN

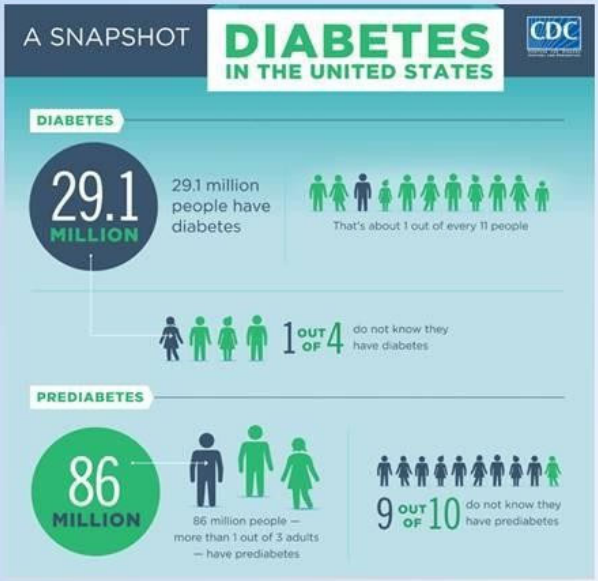
worldwide are living with HIV. Most of these children were infected by their HIV-positive mothers during pregnancy, childbirth or breastfeeding.



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 4th 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