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Momordica charantia: A Natural and Safe Approach for the Treatment of HIV Infection

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Abstract: HIV belongs to a special class of viruses called retroviruses. A person is said to acquire AIDS if CD4+ count becomes less than 200 per microlitre of blood and body becomes weak in its immune response. The disease caused by HIV virus in human still remains a serious and major challenge to mankind in the history of human viral infection in view of its high mortality records. Antiretroviral therapy and HAART (HIGHLY ACTIVE ANTIRETROVIRAL THERAPY), both have certain side effects such as hypertriglyceridemia, hypercholesterolemia, and lipodystrophy. Herbal medicines are gaining popularity because of several advantages such as fewer side effects, better patient tolerance, relatively less expensive and acceptance . Traditionally *Momordica charantia* has been used widely as a medicine in diabetis, gout, jaundice, kidney stone, laxative, leucorrhea, piles, pneumonia, , purgative,worms,malaria,dysmenohorrhoea etc.

Recently momordica charantia has been explored for its new application as an anti cancer and anti HIV agent. MAP30 and alpha and beta momocharin obtained from Momordica charantia not only were found to be an effective anti HIV agents but also offered hope towards having a therapy with no toxic effects. Constituents of Momordica charantia can be used with HAART to give better results and patient compliance.

Key words: Momordica charantia, Treatment of HIV Infection.

INTRODUCTION:

IMMUNE SYSTEM:

The immune system is composed of many interdependent cell types that which help to protect the body from bacterial, parasitic, fungal, viral infections and from the growth of tumor cells. Many of these cell types have specialized functions. The cells of the immune system can engulf bacteria, kill parasites , tumor cells, or viral-infected cells[1] . The cells of the adaptive immune system are special types of leukocytes, called lymphocytes,which are of two types B cells and T cells and are derived from hematopoietic stem cells in the bone marrow[2] .B cells are involved in the humoral immune response, whereas T cells are involved in cell-mediated immune response. The two types of T cells involved in immunity are Killer T cells and Helper T cells[3, 4, 5].

- **Killer T cell :** Also called as CD4 cells are a sub-group of T cells that kill cells that are infected with viruses (and other pathogens), or are otherwise damaged or dysfunctional. These types of T-cells have a molecule called CD8 on their surface.

- **Helper T cells :**also called as CD8 cells regulate both the innate and adaptive immune responses and help determine which types of immune responses the body will make to a particular pathogen. These cells have no cytotoxic activity and do not kill infected cells or clear pathogens directly. They instead control the immune response by directing other cells to perform these tasks. These cells have molecules called CD4 on its surface.

HUMAN IMMUNODEFICIENCY VIRUS (HIV) [6,7,8]:

HIV belongs to a special class of viruses called retroviruses. HIV exists as roughly spherical particles (sometimes called virions). The surface of each particle is studded with lots of little spikes. HIV particles are too small to be seen through an ordinary microscope. However they can be seen clearly with an electron microscope.[1] The average Human Immunodeficiency Virus (HIV) is about 0.000031 inches (120 Angstroms) long and consists of a strand or strands of DNA (deoxyribonucleic acid) or a strand or strands of RNA (ribonucleic acid), coated with a layer of protein. Most known viruses have DNA cores but the Human Immunodeficiency Virus (HIV) has an RNA core.

The virus contains two identical copes of a positive sense (i.e. mRNA) single-stranded RNA strand about 9,500 nucleotides long. These may be linked to each other to form a genomic RNA dimer. The RNA dimer is in turn associated with a basic nucleocapsid (NC) protein. The ribonucleoprotein particle is encapsidated by a capsid made up of a capsid protein (CA), which also contains viral proteins such as integrase and reverse transcriptase and a wide variety of other macromolecules derived from the cell including tRNAlys3, which serves as a primer for reverse transcription. The capsid has an icosahedral structure which is encapsulated by a layer of matrix protein (MA), which is associated with a lipid bilayer or envelope. The matrix protein may be a continuous shell attached to the envelope as in HIV, noncontiguous but associated with envelope or separate from the envelope. The HIV envelope is derived from the host cell plasma membrane and is acquired when the virus buds through the cell membrane. In addition it also contains viral proteins often forming spikes or peplomers.

HIV has just nine genes. Three of the HIV genes, called gag, pol and env, contain information needed to make structural proteins for new virus particles. The other six genes, known as tat, rev, nef, vif, vpr and vpu, code for proteins that control the ability of HIV to infect a cell, produce new copies of virus, or cause disease. At either end of each strand of RNA is a sequence called the long terminal repeat, which helps to control HIV replication.

TYPES OF HIV:

There are two type of HIV , HIV-1 and HIV-2 , both are infectious and causing agent of AIDS. Development of disease results from lack of control of HIV replication by the host immune system.

LIFE CYCLE OF HIV VIRUS [9]

A brief description of HIV's life cycle can be given as follows.

Binding: Once in the body, HIV needs a *host* to help it reproduce. The host in the case of HIV is the T-cell or CD4 cell. The process typically begins when a virus particle bumps into a cell that carries on its surface a special protein called CD4. The spikes on the surface of the virus particle stick to the CD4.

Fusion: The virus then fuses with the host cell. After fusion, the virus releases RNA, its genetic material, into the host cell leaving the envelope behind.

Reverse Transcription: In the next step an HIV enzyme called reverse transcriptase converts the single- stranded HIV RNA to double-stranded HIV DNA. This HIV DNA is compatible with human genetic material.

Integration: The newly formed HIV DNA enters the host cell's nucleus, where an HIV enzyme called integrase integrates the HIV DNA within the host cell's own DNA. The integrated HIV DNA is called provirus. The provirus may remain dormant for several years.

Transcription: When the host cell receives a signal to become active, it treats HIV genes in much the same way as human genes. First it converts the provirus using a host enzyme called RNA polymerase to create copies of the HIV genomic material, as well as shorter strands of RNA called messenger RNA (mRNA). Then the messenger RNA is transported outside the nucleus, and is used as a blueprint for producing new HIV proteins and enzymes.

Assembly: An HIV enzyme called protease cuts the newly formed long chains of HIV proteins into smaller individual proteins. These smaller HIV proteins come together with copies of HIV's RNA genetic material, to assemble a new virus particle.

Budding: The newly assembled virus pushes out ("buds") from the host cell. During budding, the new

virus steals part of the cell's outer envelope. This envelope, which acts as a covering, is studded with protein/sugar combinations called HIV glycoproteins. These HIV glycoproteins are necessary for the virus to bind CD4 and co- receptors. The newly matured HIV particles are ready to infect another cell and begin the replication process all over again. In this way the virus quickly spreads through the human body. And once a person is infected, they can pass HIV on to others in their bodily fluids.

If after an HIV infection the CD4+ lymphocyte count per microlitre of blood becomes less than 200 then person is said to acquire AIDS, due to such low CD4+ count body becomes weak in its immune response . Certain germs take advantage of this opportunity when defenses are down and may cause what we term "opportunistic infections" (OIs). Examples of such opportunistic infections are respiratory infections like tuberculosis and pneumocystis carnii pneumonia,toxoplasmosis,Kaposi sarcoma and other infections and cancers involving multiple systems of the body such as immune, gastrointestinal, genitourinary, endocrine, dermatologic, and nervous systems [10] .

TRANSMISSION OF HIV

The Human Immunodeficiency Virus (HIV) travels from the inside of one person to the inside of another person, arriving with its RNA strands intact, which then successfully find and enter a T-cell. With AIDS, the major infection sites are the bloodstream and the central nervous system. HIV-carrying macrophages are also found in very less number in the connective tissues of the lung and in oral and mucous membranes. In an infected person, HIV is found in any body fluid or substance which contains lymphocytes which include: blood, semen, vaginal and cervical secretions, mother's milk, saliva, tears, urine, and feces.

As a group, retroviruses can live in their hosts for a long period of time without causing any sign of illness. In most animals, retrovirus infections last for life. Retroviruses die when exposed to heat, are killed by many common disinfectants, and usually do not survive well if the tissue or blood they are in dries up. However, retroviruses have high rates of mutation and, as a result, tend to evolve very quickly into new strains.

The disease caused by HIV virus in human still remains a serious and major challenge to mankind in the history of human viral infection in view of its high mortality records [11]. The only reliable option for its prevention and control is to avoid risky behaviours such as those that tend to promote exchange of blood, or body fluids containing HIV virus and/or HIV infected cells [11, 12.] In patients infected with HIV-1, there exists a significant and steady decline in CD4+ lymphocytes (helper/inducer) that correlates with progression to disease. The steady decline in CD4+ cells is related to the trophism of HIV-1 for the CD4 receptors.

ANTIRETROVIRAL THERAPY[13]-

Antiretroviral drugs are medications for the treatment of infection by retroviruses, primarily HIV**.** The current guidelines for antiretroviral therapy (ART) from the World Health Organization reflect the changes to the guidelines and recommend that in resource-limited settings, HIV-infected adults and adolescents should start ART when HIV infection has been confirmed and one of the following conditions is present World Health Organization. Reverse transcriptase is virus-specific enzyme and an important target for antiviral drug therapy.

- Clinically advanced HIV disease;
- WHO Stage IV HIV disease, irrespective of the CD4 cell count;
- WHO Stage III disease with consideration of using CD4 cell counts less than 350/µl to assist decision making;
- WHO Stage I or II HIV disease with CD4 cell counts less than 200/µl.

Drugs used for the treatment of HIV can be divided into four categories [14-20]:

Nucleoside Reverse Transcriptase Inhibitors (Nrtis)	Zidovudine, Lamivudine, Didanosine, Stavudine, Abacavir, Emtricitabine, Zalcitabine
Nucleotide Reverse Transcriptase Inhibitors (Ntrtis)	Tenofovir
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Nevirapine, Delavirdine, Efavirenz
Protease inhibitors (PIs)	Saquinavir, Ritonavir, Indinavir, Nelfinavir, Amprenavir, Lopinavir, Atazanavir.

HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART):

A combination of three or more drugs from at least two different classes to suppress the replication process of the virus in at least two different ways is known as Highly Active Antiretroviral Therapy, or HAART.most commonly used combinations are of nucleoside analog reverse transcriptase inhibitors (NRTI) plus a protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) [21] .Using this method the replication process is slowed down and the rate at which drug resistance can develop is vastly reduced because HIV finds it more difficult to overcome this combined attack. Treatment of HIV-1 infection with highly active antiretroviral therapy (HAART) has resulted in major improvements in survival, immune function and decrease in the incidence of opportunistic infections[22].HAART is complicated with metabolic complications including hypertriglyceridemia, hypercholesterolemia, and lipodystrophy[23, 24].

Current chemotherapeutic medication and therapy suffers from issues of cost, patient compliance, deleterious acute and chronic side effects, emerging single and multi drugs resistance and generalized treatment and economic issue. Therefore, expansion of current therapeutic options calls for an urgent need for an effective chemotherapy for the Acquired Immuno Deficiency Syndrome (AIDS), which is caused by Human Immuno Virusv[11, 12].

HIV-1 infection is found to be associated with an atherogenic lipid profile [25]. Use of some Antiretroviral drugs such as ritonavir and lopinavir reported to accentuates these lipid abnormalities[26]. Such an atherogenic profile is likely to increase the risk of cardiovascular complications including myocardial infarction and premature atherosclerosis[27,28]. Management of HAART-associated hyperlipidemia include switching drugs, exercise or conventional use of anti hyperlipidemic drugs like statins or fibrates [29]. Unfortunately statins reduces the efficacy of HAART [30] while other lipid-lowering drugs can cause adverse drug–drug interactions[31]. HAART-associated metabolic disorders have a tremendous negative impact on quality of life among HIV-1-infected patients, leading to decreased HAART compliance and ultimately virological failure [32] .Hence, there is an urgent need to develop new therapeutic approaches that are equally or more effective, and have minimal side effects.

ALTERNATE MEDICINES:

Herbal medicines for therapeutic purposes have been explicitly used since the dawn of human civilization to maintain health and to treat diseases. WHO estimates that about three-quarters of the world's population currently uses herbs and other forms of traditional medicines for mitigation and/cure of various ailments.

Medicinal plants have a long history of use and their use is widespread in both developing and developed countries. Herbal medicines provide rational means for the treatment of many diseases that are obstinate and incurable in other systems of medicine. These are gaining popularity because of several advantages such as often fewer side effects, better patient tolerance, relatively less expensive and acceptance due to long history of use. Medicinal effects of plants tend to normalize physiological function and correct the underlying cause of the disorder [33].

MOMORDICA CHARANTIA:

Momordica Charantia is an economically important medicinal plant belonging to the family cucurbitaceae known as balsam pear or Karela. It is a Tropical vegetable which is a common food in Indian cusine and has been used extensively in folk medicine as a remedy for a number of diseases and disorders. The Latin name Momordica means “to bite” which referred to the jagged edges of the leaf, which appear as if they have been bitten. Since ancient times, Ayurveda has considered the *Momordica Charantia* to be tonic, stomachic, stimulant, emetic, antibilous, laxative and alterative.

TRADITIONAL USES OF *MOMRDICA CHARANTIA:*

Momordica charantia is a plant used since centuries in traditional Indian culture as a remedy for for tumors, wounds, rheumatism, malaria, vaginal discharge, inflammation, menstrual problems, diabetes, colic, fevers, worms. It is also used to induce abortions,contraceptive and as an aphrodisiac. It is prepared into a topical remedy for the skin to treat vaginitis, hemorrhoids, scabies, itchy rashes, eczema, psoriasis, leprosy and other skin problems. The entire plant is used for diabetes and dysentery; the root is a reputed aphrodisiac the leaf or aerial parts of the plant are used to treat measles, malaria, and all types of inflammation. the leaf is commonly used for abdominal pain, diabetes, fevers, colds, coughs, headaches, malaria, skin complaints, menstrual disorders, aches and pains, hypertension, infections, and as an aid in childbirth.

Momordica charantia has also been used widely as a medicine as an anthelmintic, emmenagogue, galactagogue, gout, jaundice, kidney stone, laxative, leucorrhea, piles, pneumonia, ,

purgative. It has also been used in treating peptic ulcers and various cancers such as lymphoid leukemia, lymphoma, choriocarcinoma, melanoma, breast cancer, skin tumor, prostatic cancer, squamous carcinoma of tongue and larynx, human bladder carcinomas and Hodgkin's disease [34].

ROLE OF *MOMORDICA CHARANTIAIA* IN HIV INFECTION:

Momordica charantia contains three anti-HIV proteins: alpha- and beta momorcharin, and MAP-30, and charantin, These proteins known as alpha- and beta-momorcharin are present in the seeds, fruit, and leaves have been reported to inhibit the HIV virus.MAP-30 is a chemical analog of alpha momocharin and beta momocharin . MAP 30 (Momordica Anti-HIV Protein), is a basic protein of about 30 kDa. It exhibits dose-dependent inhibition of cell-free HIV-1 infection and replication [35]. It has been isolated and purified to homogeneity from the seeds and fruits of the Momordica charantia MAP30 (Momordica Anti-HIV Protein), alpha- and beta-momorcharins inhibit HIV replication in acutely and chronically infected cells and thus are considered potential therapeutic agent in HIV infection and AIDS

MECHANISM OF ACTION OF MAP 30:

MAP30 antiviral agent is capable of inhibiting infection of HIV type 1 (HIV-1) in T lymphocytes and monocytes as well as replication of the virus in already-infected cells. MAP30 being unable to enter healthy cells it is not toxic. MAP30 also possess an N-glycosidase activity on 28S ribosomal RNA and a topological activity on plasmid and viral DNAs including HIV-1 long terminal repeats (LTRs). LTRs are essential sites for integration of viral DNA into the host genome by viral integrase. It has been reported that this antiviral agent exhibit inhibition of HIV-1 integrase too. Integration of viral DNA into the host chromosome is a vital step in the replicative cycle of retrovirus. The inhibition of HIV-1 integrase by MAP30 suggests that obstruction of viral DNA integration may play a key role in the anti-HIV activity of this protein[36].

***MOMORDICA CHARANTIA* IN HAART ASSOCIATED HYPERLIPIDEMIA:**

Momordica charantia has found to reduce cellular TG synthesis and secretion as well as apoB secretion in HepG2 cells [37]. Juice of fruits of Momordica charantia has been found to reduce adiposity in rats fed a high-fat diet (HFD), lower serum insulin and leptin levels and normalize glucose tolerance [38]. Further, MAP30 improved the efficacy of anti-HIV therapy when used in combination with other anti-viral drugs. MAP30 holds therapeutic promise over other RIPs because not only it is active against infection and replication of both HSV and HIV but is non toxic to normal cells[39].

CONCLUSION:

Momordica charantia not only exhibits inhibition of HIV virus but also reduce cellular TG synthesis and secretion as well as apoB secretion in HepG2 cells. Juice obtained from momordica charantia reduces adiposity in rats fed a high-fat diet (HFD), as well as lowers serum insulin and leptin levels and normalizes glucose tolerance.

Thus we can say that *Momordica charantia is offering more promising antiretroviral therapy because it shows anti HIv activity without any toxic effect as well as it has also shown to solve the problem of* HAART-associated hyperlipidemia.

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