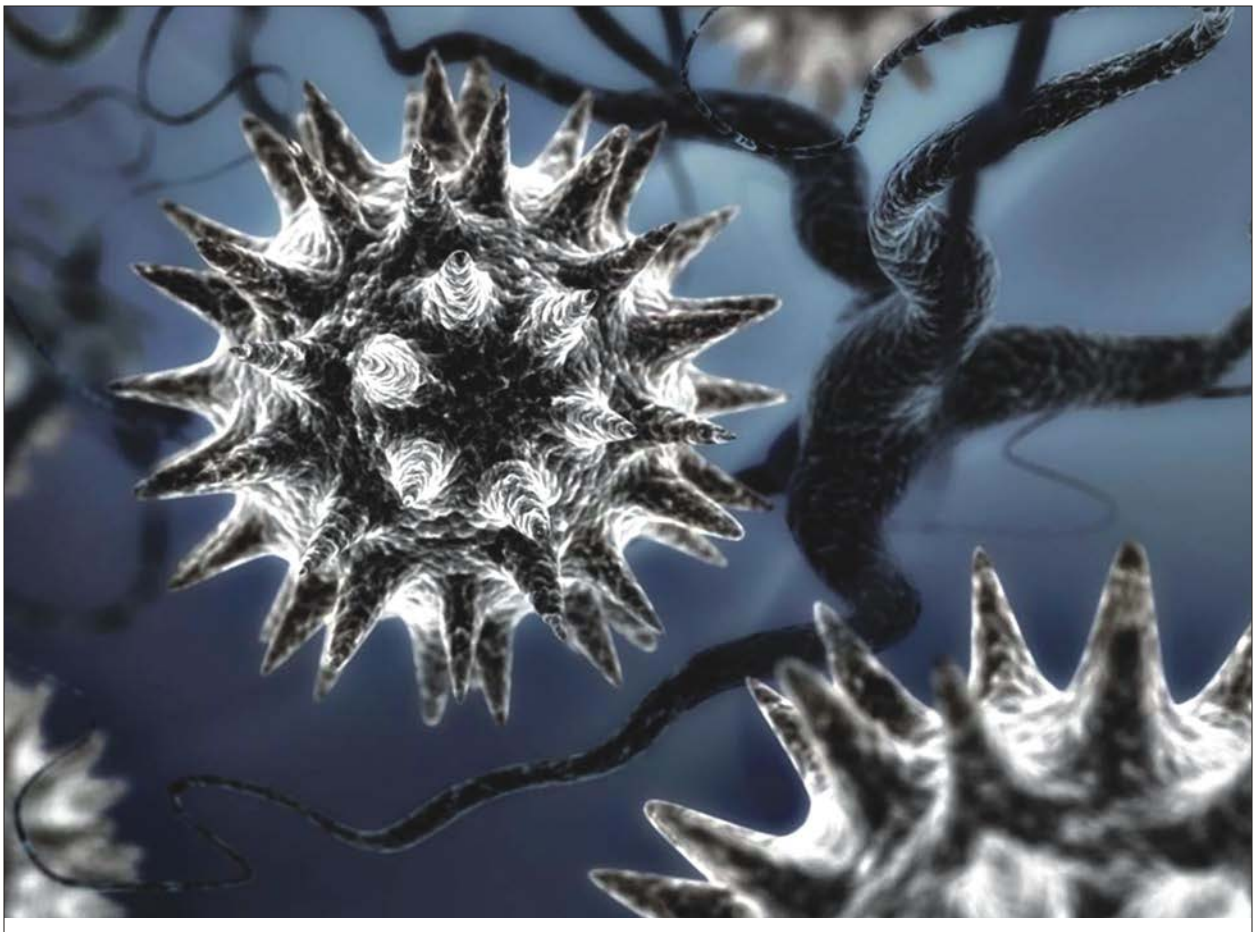

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De novo Combination Therapy in Retroviral Infection

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Abstract: Many plant-based medicines being used in treatment of HIV infections, but no scientific evidence are available to support their use. A number of synthetic, semi synthetic as well as drug of natural origin are reported to be active against HIV. In the present study, various drugs of plants and synthetic drugs have been discussed for some future beneficial combinations for formulations against viral infections. The combination therapy of the mentioned herbal agents with synthetic drugs might be beneficial for the treatment of retroviral infections in future due to better compatibility, potency and synergistic activities. New era of therapy can be developed by combination of synthetic, semi synthetic and natural drugs in pharmaceutical formulations.

Key words: Combination therapy, retroviral infection, natural products, Nucleosidase RT-inhibitor

INTRODUCTION

Viral infections are the challenging area because of lacking of specific treatment. Human Immunodeficiency Virus (HIV) is a retrovirus and the causative agent for Acquired Immunodeficiency Syndrome (AIDS). Retrovirus is one, which utilizes the enzyme Reverse Transcriptase (RT) for the conversion of its RNA in to DNA, in this way enabling it to become incorporated in to the DNA of host. This virus can be divided in to HIV-1, HIV-2. Both deplete the helper T-lymphocytes, which results in continued destruction of immune system and also leads to opportunistic infections and malignancies. At present, most commonly used anti-HIV therapy is through the concomitant use of drugs that belong either to the class of nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs/NTRIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease or entry inhibitors (PIs), and HIV integrase inhibitors (Pawar *et al*., 2010). The global HIV epidemic kills around 3 million people annually and attempts to control further spread have been of limited success. The efficacy of antiviral drug therapy has been limited by toxicity and viral resistance. Thus, alternative therapies need to be explored. Many plant-based medicines being used in treatment of HIV infections, but no scientific evidence are available to support their use. Non-selectivity of natural products against viruses is another problem. Formulations based on plant products shall not only serve as effective one in combating with these viral

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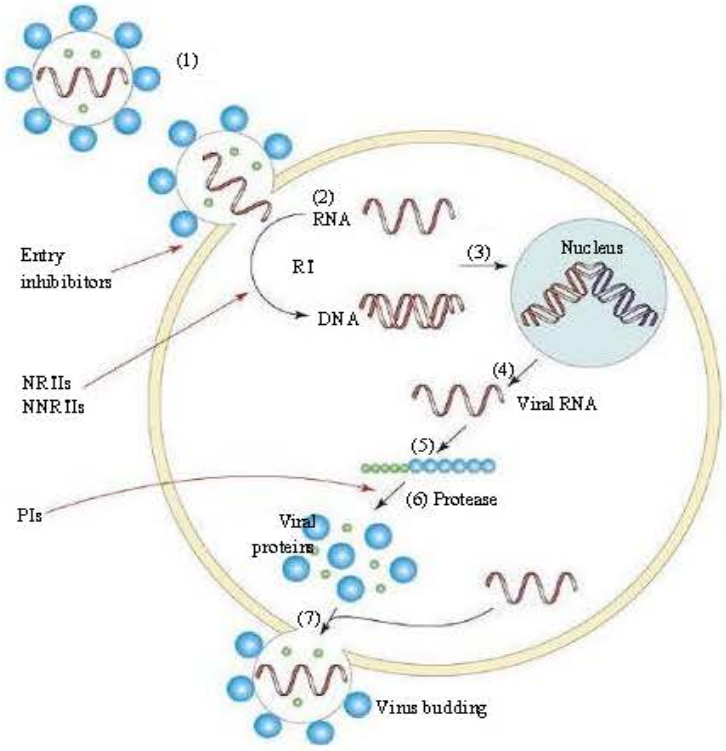

Fig. 1: The life cycle of HIV and the targets of antiretroviral drugs (ARV) drugs. (1) The HIV life cycle begins with binding and fusion of the virus to the CD4 T lymphocyte cell membrane, followed by the release of the viral core contents into the target cell. (2) Viral RNA is transcribed to DNA by the viral enzyme reverse transcriptase (RT). (3) Viral DNA is then integrated into the host cell genome to form provirus with subsequent transcription (4) and translation (5) to generate viral polypeptides. (6) Post-translational cleavage of viral polypeptides by the protease enzyme follows with subsequent particle assembly and (7) budding of new virions. The sites of action of currently used drugs are depicted in figure, including blocking entry of virion, transcription arrest, inhibition of the enzyme in cleaving viral polyproteins, inhibition of budding

infections (Sharma *et al.*, 2006). There are so many new herbal agents having antiretroviral activity with no or less adverse effects. The combination therapy of these herbal agents with synthetic drugs might be beneficial for the treatment of retroviral infection in future due to better compatibility. The success may be achieved in taking viral infection by the use of natural herbal agents derived from various species in combination with synthetic agents might be paralleled in the quest for antiviral therapy (Fig. 1).

Goals of Therapies Used

- To decrease the symptoms from HIV infection and delay the disease progression to AIDS

- To reduce AIDS induced severe side effects
- To prolong survival
- To maintain durability of viral suppression
- To eliminate resting reservoir of HIV
- To increase CD4 lymphocyte count
- To decrease viral resistance and drug failure
- To re-constitute the immune system
- To prevent transmission from mother to fetus
- To prevent HIV infection from high-risk occupational or non-occupational exposures

Combination Therapy-I

Pesticidal non-protein amino acids discovered in seeds of *Castanospermin australe* (Leguminaceae) new alkaloid of tetrahydroxyindolizidine named as castanospermine (Taylor *et al*., 1992; Walker *et al*., 1987). It has usual solubility and isolated by experiments designed for separation of amino acids rather than alkaloids. It acts on insect larvae and inhibits the carbohydrase enzyme, which is essential for the elaboration of the oligosaccharide side chain on glycoprotein. This action lead to the testing of alkaloid against HIV because the compound inhibits α-glucosidase I and II and this controls the formation of glycoproteins in the viral coat. Thus without essential envelop structure the virus would be unable to infect healthy white blood cells. O-acyl derivatives having 20 times more activity than castanospermin. Though toxicity levels are unsatisfactory for clinical use. But it provides lead to development of other α-glucosidase inhibitors (Castanospermine) might be beneficial because one can inhibit the formation of glycoproteins and other can inhibits the protein synthesis. Due to this synergistic activity can be obtained and dosing frequency as well as adverse effects of both can be reduced.

Combination Therapy-II

Roots of *Tripterygium wilfordii* (Celastracae) gives salaspermic acid, pentacyclictriterpine, tripterifordin, kaurene type diterpene lactone having inhibitory action on HIV RT and virus replication in HG-lymphocyte cells (Matthee *et al*., 1999; Vlietinck *et al*., 1998). The commercial tannic acid contains tetragalloylquinic acid having HIV RT inhibitory activity. Combination of these drugs with Nucleosidase RT-inhibitor (Volberding *et al*., 1995; Hammer *et al*., 1996; Hilts and Fish, 1998; Meruelo *et al*., 1988) (Zidovudine, Dideoxycytidine, Stavudine) can be helpful in decreasing the adverse drug reactions like hepatitis, hyperglycemia, peripheral neuropathy which might hinders the therapy. Roots of Tripterygium wilfordii also having inhibitory action on viral replication and it can be given with Amantidine which is a virus penetration inhibitor.

Combination Therapy-III

Ipomoea cairica (convolvulacae) containing (-)-Trachelogenin suppresses the integration of proviral DNA in cellular genome and acting as an integrase inhibitor. It can be given as a supportive treatment with RT-inhibitors (Vlietinck *et al*., 1998; Hilts and Fish, 1998; Volberding *et al*., 1995; Hammer *et al*., 1996; Meruelo *et al*., 1988) this combination might be lead to positive result. Lycopyranocoumarin, Glycycoumarin from Glycyrrhiza glabra inhibits integrated provira DNA formation in HIV infected cell cultures. Coumarines and flavonides can also act as anti-AIDS. This drug therapy can combined with Hypericin (Hilts and Fish, 1998) form *Hyperecium* sp. having anti-retroviral activity (Matthee *et al*., 1999; Vlietinck *et al*., 1998). This combination is combined with Rt-inhibitors to increase the potency.

Combination Therapy-IV

Calophyllum lanigerum (Guttiferae) contains calanolide-A and B in the leaves and fruits acting as an anti-HIV. Some related compounds from *C. inaphyllum*, which have C-4 position propyl side chain, replaced with phenyl ring. At least 27 coumarines from Sumbul root (*Feruls sambul*) having anti-HIV activity, with stimulant and antispasmodic activity (Matthee *et al*., 1999; Vlietinck *et al*., 1998). Michellamines-A,B,C (naphthyl isoquinoline dimmers) from Ancistrocladus korupensis (ansistrocladacae), out of michellamines-B has potent antiviral activity. Podophylotoxin lignan, Xypodophylotoxin from *Thuja accidentalis* having action against Herpes simplex (Matthee *et al*., 1999; Vlietinck *et al*., 1998). Both hesepharmacognostic agents might be significant in combinational therapy.

Combination Therapy-V

Oleane type of saponins inhibits the viral sysnthesis can be given with Acyclovir. Ursen type of saponins that interfere with capsidal protein formation can be given with Castanospermin and Amantidine. This combination will become a promising research view for anti-HIV activity.

CONCLUSION

A number of synthetic and natural drugs available can become beneficial combinations for formulation against viral infection as mentioned above. The combination therapy of these herbal agents with synthetic drugs might be beneficial for the treatment of retroviral infection in future due to better compatibility. New therapy can be developed by combination of Protease inhibitors with α-glucosidase beneficial because one can inhibit the formation of glycoproteins and other can inhibits the protein synthesis. Due to this synergistic activity can be obtained and dosing frequency as well as adverse effects of both can be reduced. The commercial tetragalloylquinic acid having HIV RT inhibitory activity. The combination of these drugs with Nucleosidase RT-inhibitor can be helpful in decreasing the adverse drug reactions like hepatitis, hyperglycemia, peripheral neuropathy. Coumarines, flavonoids, Hypericin can be combined with RT-inhibitors to increase the potency. Michellamines-B, Podophylotoxin lignan and Xypodophylotoxin against Herpes simplex might be significant in combinational therapy.

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