REVIEW OF LITERATURE

Plants are an important source of a variety of bioactive compounds with different modes of action. Anti-HIV agents from plant sources can be useful in developing a microbicide formulation with combination of compounds inhibiting HIV infection and transmission.

Donglei Yu et al (2007) have elaborately reviewed anti HIV agents from natural resources belonging to several classes including terpenoids, coumarins, alkaloids, polyphenols, tannins and flavonoids. Anti-HIV agents from these classes exhibit unique mechanism of action pertaining to their physicochemical properties. Structure activity relationship studies will help in transforming these leads into useful drugs. These natural product derived compounds can be used in conjunction with existing anti HIV agents and thus possibility of drug resistance could be minimized.

Inder Pal Singh et al discussed several anti-HIV compounds from plant sources, presently in different stages of development studies such as Buchapines, Harmines, Betulinic acid derivatives, Calliptin etc.

Hideo N et al showed that some phloroglucinol derivatives like mallotojaponin and mallotochromene had shown 70% RT inhibition while mallotophenone and mallotolerin exhibited weak RT inhibitory activity.

Chauthe et al recently reported anti-HIV-1 activity of dimeric phloroglucinol derivatives. Seven dimeric phloroglucinols had shown moderate to potent anti-HIV-1 activity in cell based assays, however only two derivatives inhibited HIV-1 transcription by inhibiting reverse transcriptase enzyme in vitro. For other five compounds, modifying side chains resulted in altered mechanism of action.

McCormick, J.L et al reported quinoline 2,4 diols from plant Euodia roxburghiana. ‘Quinoline 2,4-diol’ nucleus is abundantly present in various natural as well as synthetic molecules. The molecules containing this core have variety of pharmacological activities and therefore are of great interest to medicinal chemists as well as biologists. Buchapine is a quinoline alkaloid. In this paper anti-HIV-1 activity of buchapine and other quinoline diols was reported. Buchapine showed IC_{50} value 29µM and inhibited HIV RT with an EC_{50} of 12µM.
Nafees et al\textsuperscript{28} evaluated anti-HIV-1 activity of several derivatives of buchapine in CEMGFP cells. The unsubstituted ring B and free 2-OH group are essential for anti-HIV activity. Further, the chain length upto four carbons and prenyl group at C-3 and/or O-4 is required for HIV-1 inhibitory activity.

Buckheit,R.W et al\textsuperscript{29} discussed development in the area of topical microbicides. Topical microbicides represent an important strategy with clear potential for preventing the transmission of HIV through sexual intercourse, the predominant mode of HIV transmission worldwide. Thus, the dynamics of the epidemic demand the development of safe, effective, and acceptable female-controlled chemical and physical barrier methods including topical microbicides, to reduce HIV transmission. The development of microbicidal agents has gained significant focus and momentum during the past few years due to the realization that suppression of HIV transmission in the developing world can have a great impact on the HIV pandemic. It has been estimated that a single microbicide with 60% effectiveness could prevent millions of new cases of HIV infection each year throughout the world.

Balzarini,J. et al\textsuperscript{30} reviewed microbicide drug candidates and their classification. Microbicide is a formulation of one or more anti HIV agents that can prevent infection either by killing virus or preventing its entry or attachment to cells thereby preventing its infection. Microbides have been classified based on their mode of action.

Van Damme,L., et al\textsuperscript{31} and Fichorova R N et al\textsuperscript{32} studied the cytotoxicity and efficacy of nonoxynol 9. It is an anionic surfactant developed as spermicide. N9 disrupts viral envelop and thereby kills virus. Recent studies have indicated that presence of N9 actually enhances release of inflammatory cytokines and facilitates viral entry into the cells.

Charlene S. Dezzutti, et al\textsuperscript{33} have evaluated several potential microbicide candidates like CAP, Carraguard, PRO 2000, and cellulose sulphate along with their placebos for toxicity in epithelial and cervical cell lines. These compounds seemed to be relatively non toxic and efficacious against HIV infection in PBMCs and macrophages. Huskens,D et al\textsuperscript{34} found out mechanism of action of PRo2000. It blocks virus attachment to cell surface and thereby prevent infection.
Kilmarx, P.H., et al\textsuperscript{35} reported safety and efficacy of caraguard in phase III clinical trials. 

El Sadr, W.M et al\textsuperscript{36} Halpern, V et al\textsuperscript{37} evaluated safety and efficacy of cellulose sulphate as candidate microbicide. None of these agents showed promising results in the trials.

Patricia Fletcher et al\textsuperscript{38} evaluated UC781, a non-nucleoside reverse transcriptase inhibitor as a microbicide. It is a small molecule HIV-1 inhibitor. In human explant culture, UC781 inhibited infection of cervical tissue and prevented dissemination of virus by migratory cells.

Vermeire K et al\textsuperscript{39} reported anti-HIV activity of CADA (cyclotriazadisulfonamide). It is new class of compounds that down modulate cell surface expression of CD4 receptor in human cells. A gel formulation of CADA exhibited synergistic anti-HIV activity when used in combination with cellulose acetate phthalate.

Lanier, E.R. et al\textsuperscript{40} reported tenofovir a reverse transcriptase inhibitor, that had shown promising HIV-1 microbicidal activity.

Mayer, K.H., et al\textsuperscript{41} evaluated tenofovir for safety and efficacy in phase II clinical trials and its 1\% gel is presently being evaluated in phase III trials.

Based on previous studies, it appears that a single microbicidal agent will not be effective on its own but a combination of drugs targeting different steps in the viral infection process will provide effective protection.