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Review Article

Pharmacognosy of Indian medicinal plants and their future aspects as an Anti-HIV agent: A review

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ABSTRACT

Along with increasing viral diseases, HIV is commonly transmitted virus. This virus is responsible for most of the deaths in the world. Scientist have been developing many methods to treat this disease but results are still doubtful. HIV 1 virus is one of the liable agents which can be affected by approved therapies. Sexual transmission is one of the major routes for HIV infection including other STIs. Microbicides have been proposed as a promising prevention strategy. These microbicides can be available either in the form of a cream, gel, lubricant or even in the form of a tablet and can be applied topically to the vaginal or rectal surface. Availability of a successful microbicide candidate would greatly empower women (men in homosexual act) to protect themselves and their partners from STIs including HIV infection. In cases where multiple sex partners are involved, availability of a microbicide will play an important role. An ideal microbicide should be applicable hours before sex, preserve the natural anatomy of female reproductive tract (does not lead to lesion and aberration in epithelial layer), protect the natural vaginal micro-ecological system and should not generate any pro-inflammatory cytokines. In this review article medicinal plants that are reported for antiviral activities against HIV infection and reduce the STD load in infected persons will be discussed.

1. Introduction

Worldwide around ~38.4 million people (both men and women equally affected) suffering from HIV infection with 1.5 million new cases and approx~0.65 million deaths.[1] Present condition in Indian scenario, 2.4 million people are seropositive, among them 1.05 million are female and 0.69 million were children.[2] Along with HIV infection reproductive tract infections (RTIs) and sexually transmitted infections (STIs) were also associated with large human suffering. According to data given by WHO 374 million new cases of syphilis, gonorrhoea, chlamydia, trichomoniasis and other HIV related STD's infect adults aged 15-49 years.[3] The use of 'condoms' has been proposed to prevent HIV and other STD transmissions along with resolving conception purpose. Reduction of sexual pleasure reduces its usage, however female condom has been developed to overcome this problem. High cost and objections from male partners also risks female life.[4] Anti-retroviral drug therapy has been used by several governmental programmes to combat transmission of HIV, reduce viral load and the chances of mother-to-child HIV infection. Several reports have been documented on the issue of drug resistance along with patient sufferings in the form of diarrhea, nausea, lipodistrophy, hyperglycemia, liver toxicity, pancreatitis and neuropathy.[5] To resolve these problems, the use of microbicides has recently been proposed.[6]

Microbicides may be available either in the form of a cream, gel, lubricant or even in the form of a tablet and can be applied topically to the vaginal or rectal surface.

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These microbicide should be applicable hours before sex, not lead to the lesion and aberration in epithelial layer, preserve natural vaginal environment and not show any allergic reactions.[7]

For the purpose of this study, ten Indian traditional medicinal plants, *Albizia procera* (Roxb.) Benth (fam. fabaceae), *Tridax procumbens* L. (fam. Asteraceae), *Achyranthes aspera* L. (fam. Amaranthaceae), *Ficus benghalensis* L. (fam. Moraceae), *Mallotus philippinensis* (Lam.) Muell. Arg. (Fam. Euphorbiaceae), *Rosa centifolia* L. (fam. Rosaceae), *Strychnos potatorum* L.f. (fam. Loganiaceae), *Annona reticulate* L. (fam. Annonaceae), *Ficus infectoria* Miq. (Fam. Moraceae) and *Annona squamosa* L. (fam. Annonaceae) were selected to investigate there *in vitro* inhibitory activity against entry inhibition/replication of HIV-1 as well as directly inactivating HIV or preventing HIV from attaching, entering or replicating in susceptible target cells.

2. Medicinal Plants

2.1. Strychnos potatorum

Strychnos potatorum L.f. (fam. Loganiaceae) used in gonorrhoea, leukorrhea[8] with suppressive effects on sperm motility.[9] *A. squamosa* fruit pulp with spermicidal properties significantly inhibit HIV replication in H9 lymphocytes.[10] This make it additional desirable attribute for a vaginal microbicide.[11] Methanolic extract of *S. potatorum* showed activity with preliminary IC_{80} in the range of 29.17–79.35 μg/ml giving estimated TI of 24 in cell free HIV-1_{Ada5} strain.[12]

Fig. 1: *Strychnos potatorum*

2.2. Rosa centifolia

Rosa centifolia L., a flowering plant of Rosaceae family, commonly known as Cabbage rose were also known for their antiviral activities. In chemistry, were Phenyl ethanol (43%), Geraniol (10.5%), Geranyl acetate (15.6%), Benzaldehyde (1.5%), Nerol (5-10%), Citronellyl acetate (0.3%), Linalool (6.9%), Benzyl alcohol (3.3%) have been isolated. Along with oils it also contains tannins, mineral salts, salt of mallic acid and tartaric acid.[13] Methanolic extract of the leaves of *R. centifolia* showed very low anti-HIV activities.[12]

Fig. 2: *Rosa centifolia*

2.3. Albizia procera

Albizia procera (Roxb.) Benth, a member of Fabaceae family is found all over Indian territories. Traditionally bark decoction used for the treatment of rheumatism, hemorrhage, and stomach-ache.[14] Laboratory analysis of bark ethanolic, ethyl acetate, aqueous, hexane-chloroform extracts inhibits the integrase enzyme with lower IC_{50} (19.5, 19.1, 21.3, and >100 μg/ml respectively). Major chemical constituents isolated from plant are catechin and protocatechuic acid. Catechin showed substantial activity against intergase enzyme with IC_{50} value of 46.3 μM, on the other hand protocatechuic acid showed lower protection.[15]

Fig. 3: *Albizia procera*

2.4. Achyranthes aspera

Achyranthes aspera L. (fam. Amaranthaceae), is a well-known folk medicine in Indian subcontinent. Oleanolic acid reported in the plant which demonstrated potential effects

against herpes simplex virus type-I, with EC50 6.8 μg/ml and type-II, HSV-2 with EC_{50} 7.8 μg/ml.[16] Oleanolic acid and crude ethanolic extract inhibit early stage of virus multiplication (2–6 h of post infection). methanolic extract of A. aspera which showed activity with preliminary IC_{80} in the range of 18–35 μg/ml giving TI of 14, 35 and 13 in cell free HIV-1_{IIIB}, HIV-1_{Ada5} and cell associated HIV-1_{IIIB} respectively.[12]

Fig. 4: Leaves of *Achyranthes aspera*

2.5. *Annona squamosa*

Annona squamosa L. (Annonaceae), known as the custard apple tree present throughout India. Annona squamosa used as insecticidal, anti-tumor, anti-diabetic, antioxidant, anti-lipidimic and anti-inflammatory agent.[17] A leaf decoction was taken in the case of dysentery. They possess a wide variety of compounds like acetogenins which were responsible for anti-feedant, anti-malarial, cytotoxic and the immunosuppressive activities.[18] Two diterpenes annosquamosins A and B demonstrated the anti-HIV activity and the anti-platelet aggregation activity.[19]

Fig. 5: Leaves of *Annona squamosa*

2.6. *Tridex procumbens*

T. Procumbens is a well-known Ayurvedic herb of Indian sub-continent with the history of traditional uses. Plant is widely to treat wounds, skin diseases and to stop blood clotting. It possesses anticoagulant, antileishmanial, antioxidants, anticancer, immunomodulatory agent, insecticidal, anthelmintic cardiovascular, antiseptic, antimicrobial, and insecticidal properties.[20] Methanolic extract of *T. procumbens* does not exhibit anti-HIV activity.[21]

Fig. 6: *Tridex procumbens*

2.7. *Annona reticulata*

The plant is traditionally used for the treatment of epilepsy, dysentery, cardiac problems, worm infestation, constipation, haemorrhage, antibacterial infection, dysuria, fever, ulcer etc. It also has antifertility, antitumour and abortifacient properties.[21] The leaves of *A. reticulata* tetrahydroisoquinoline alkaloid with cardiotonic activity and a bioactive acetogenin from its bark have been isolated. Leaves shows potent antidiabetic activity. Some workers isolated flavonoids from leaves. Ethanol extract of the leaves and stem is reported to have anti-cancer.[22] Extracts from the peels of *A. reticulata* showed high antiviral activity, with HIV-1 reverse transcriptase inhibition values of 78.63 ± 0.97%.[23]

Fig. 7: *Annona reticulata*

2.8. *Ficus infectoria*

The plant demonstrated a wide spectrum of *in vitro* and *in vivo* pharmacological activities like, antidiabetic, cognitive enhancer, wound healing, anticonvulsant, anti-inflammatory, analgesic, antimicrobial, antiviral, hypolipidemic, antioxidant, immunomodulatory, antiasthmatic, parasympathetic modulatory, esterogenic, antitumor, antiulcer, antianxiety, antihelmintic, endotheilin receptor antagonistic, apoptosis inducer and hypotensive.[24]

F. infectoria exhibited activity in both laboratory adapted strains with estimated IC_{80} in the range of 18–73 μg/ml giving therapeutic index between 12–32.[12]

Fig. 8: *Ficus infectoria*

2.9. *Mallotus philippinensis*

Mallotus (family: Euphorbiaceae) is a large genus of trees and shrubs distributed in subtropical regions of the Old World with about 20 species in India. It is a tree species with the height of 1500 m. Mature fruits hairs The collected material is fine, granular powder, dull red, or madder red-colored and floats on water. This plant is traditionally used for antifilarial, antibacterial, anti-inflammatory, and immune-regulatory activity.[23] Plant extract does not showed any anti-HIV activity in aqueous as well as in methanolic extract.[12]

Fig. 9: *Mallotus philippinensis*

2.10. *Ficus benghalensis*

Ficus is a large tree, 20–30 m high, with wide-spreading branches bearing aerial roots. The root extract used to boost the immunity. Plant is extensively used in folklore medicines for its vermicidal, astringent, hypotensive, and antidysenteric propertis.[25] The active components isolated from *F. benghalensis* were glucosides flavonoids[26,27] etc.

Aqueous extract of *F. benghalensis* exhibited activity in both laboratory adapted strains with estimated IC_{80} in the range of 18–35 μg/ml giving TI between 12–32.[12]

Fig. 10: *Ficus benghalensis*

Methanolic extracts of *Tridax procumbens*, *Mallotus philippinensis*, *Annona reticulate*, aqueous extract of *Ficus benghalensis* and hydroalcoholic extract of *Albizzia lebbeck* did not exhibit anti-HIV activity in all the tested strains.[12]

3. Microbicides

A combination of anti-retroviral drugs has been used successfully to treat HIV infected humans and their introduction has prolonged their life span. Anti-retroviral drug therapy has been found to be useful to combat blood-to-blood transmission of HIV due to use of contaminated needles in drug addicted cases or transfusion of infected blood. These drugs also reduce the viral load and hence minimize the chances of mother-to-child HIV transmission. Long-term usage of available anti-retroviral drugs leads to the issue of drug resistance, and severe side effects such as diarrhea, nausea, lipodistrophy, hyperglycemia, liver toxicity, pancreatitis & neuropathy.

Microbicides are prophylactic agents, applied to the vagina or rectum to protect against sexually transmitted infections (STIs) including HIV. They can be in the form of gels, creams, films, or suppositories.

An ideal microbicide should be applicable hours before sex, preserve the natural anatomy of female reproductive tract (does not lead to lesion and aberration in epithelial layer), protect the natural vaginal micro-ecological system and should not generate any pro-inflammatory cytokines. Microbicides may act by

1. Virucidal activity

2. Inhibiting HIV entry/fusion by preventing (i) attachment of the viral gp120 to the CD4 T cell receptor, (ii) binding of the gp120 to CCR5 or CXCR4 co-receptors, and (iii) fusion of the viral and cellular membranes.
3. Inhibiting HIV reverse transcriptase (RT) activity
4. Inhibit HIV protease activity
5. Inhibit HIV integrase activity
6. Unique mechanism of action like inhibiting the gene expression in HIV (e.g. Tat inhibitors), compounds with immunomodulatory properties, etc.

An ideal microbicide should possess the following qualities:

Should be safe: It should preserve the natural anatomy of female reproductive tract; absence of pro-inflammatory response; protect natural vaginal micro-ecological system including lactobacilli

Should be acceptable: Applicable hours before sex; not messy or 'leaky'; rapid and even spreading property; long acting; not smelly and 'taste' OK

Should be effective against HIV and a wide range of pathogens causing STIs e.g. *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, T*reponema pallidum*, *Chlamydia trichomati*s and Herpes Simplex virus

Should be cost effective and affordable: The Phase-III clinical trials of microbicides in humans based on cellulose sulfate (Ushercell),[28] Carrageenan (Caraguard)[29,30] and Buffer Gel (PRO2000)[31] have not yielded the promising results to prevent HIV infection. However, recent results on Phase-III clinical trials of microbicide based on tenofovir showed that HIV incidence was 54% lower in high adherers(gel adherence >80%), in the tenofovir gel arm as compared to placebo control.[32,33] However, this study (VOICE) of oral Tenofovir pre-exposure prophylaxis has been terminated because oral oral intake of tenofovir has not shown any benefit as compared to placebo pills (wwww.aidsmap.com/Tenofovir-PrEP-arm-dropped-in womems-HIV-prevention-trial). However, the trial will continue to test Tenofovir microbicide gel and Truvada (an oral tablet with Tenofovir plus emtricitabine). The findings of VOICE clinical trials warrant an urgent need of active participation of various investigators engaged in the development of microbicides and arrives at more stringent preclinical evaluation criteria. A better understanding of the mechanisms involved in HIV transmission had helped us in designing appropriate and more effective strategies for vaccine and microbicide development. Sexually transmitted infections, leading to genital ulcers, have been strongly associated with an increased risk for HIV infection. STIs also increase viral shedding in the genital tract of HIV-infected individuals. It may be due to STIs-related ulcers, which can serve as portals for viral entry across the mucosal layer of vagina. Non-ulcerative infections increase susceptibility to HIV infection by triggering the pro-inflammatory responses that enhance viral replication or by increasing the number of activated $CD4^+$ T cells and DCs trafficking from the genital mucosa to the lymph nodes. HIV infects several cell types such as $CD4^+$ T cells, DCs and macrophages that are present in the vaginal mucosa. In addition to CD4, HIV uses a variety of co-receptors to enter the cells, including CXCR4 and CCR5. Recently, it has been shown that compounds, may block co-receptors, provide incomplete protection from infection via migratory DCs might still proceed.[34]

Thus, there is an urgent need for novel prophylactic methods, called microbicides. These topical products, had to be applied to the genitalarea, with the capacity to prevent transmission of STDs, particularlythe HIV and with or without sperm-inhibitory activity, therebyserving as both contraceptives and non-contraceptive modes.[35] Topical microbicidescan provide excellent potential for a female-controlled, preventiveoption, which would not require negotiation, consent or evenknowledge of the partner. Both women and men would benefited.[36] Substantial amount of research has been done and a lot more is in progress to isolate the active leads from plants for prevention of transmission of HIV and treatment of AIDS. These natural compounds and their synthetic derivatives may act by different mechanisms, targeting critical steps within the replication cycle of HIV. Given the successful history of natural product based drug discovery, a library of close to one thousand plant and fungal extracts was screened for antiretroviral activity by Adeleke and Babalola.[37] A review[38] on natural products under development for anti-HIV activity has been published by National Cancer Institute (USA). An Indian group on the anti-HIV activity of the medicinal plants has also published an extensive review. Several natural products acting as anti-HIV surface-active agents, reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, integrase inhibitors and protease inhibitors have been reported. Vlietinck[39] have summarized many compounds of plant origin that inhibit HIV during various stages of life cycle. These include several alkaloids, carbohydrates, coumarins, flavonoids, lignans, phenolics, proteins, quinines/xanthones, phospholipids, tannins, and terpenes from various plants. Given the successful history of natural product based drug discovery, a library of close to one thousand plant and fungal extracts was screened for antiretroviral activity several studies have been conducted to screen the plants used in folk medicine for anti-HIV activity. These include plants from Panama,[40] Indonesia,[41] Egyptian folk medicine,[42] Ayurvedic medicine[43] and traditional Chinese herbs.[44]

For compounds that act directly against the virus—for example, before integration of the virus into genetic material—it will be vital to check that drug resistance does not emerge, and for those that block cell surface receptors it will be necessary to ensure that they are not circumvented by the virus interacting with other receptors. Defensins and

maganins are examples of this class. Other compounds with encouraging antimicrobial profiles include cellulose acetate phthalate (CAP) and CTC-96, an organocobalt compound. CAP has shown virucidal activity against HIV-1, HSV-1 and HSV-2[45] CAP blocks infection by both cell free and cell associated HIV as well as blocks CXCR4 and CCR5-tropic virus types in tissue explant.[46] Preclinical evaluation to till date these microbicides does not increase in the production of proinflammatory mediators during or after exposure and not modify the epithelial resistance to leukocyte.[47] The micronised form of CAP (~1μm diameter) leads to disintegration and loss of infectivity of HIV-1 and its lack of systemic absorption increases its bioavailability to the topical surface. Due to heavy vaginal discharges in CAP based microbicide, the clinical trials were aborted.[48] The combination of CAP and UC781 (a tight-binding HIV-1 reverse transcriptase inhibitor) has resulted in significant synergistic and complementary effects against HIV-1 infection and its evaluation is under progress.[49]

Several research institutions including Talwar Research Foundation, New Delhi; National AIDS Research Institute (NARI), Pune; National Center for Cell Science, Pune; National Institute of Research in Reproductive Health, Mumbai; National Institute of Pharmaceutical Education and Research (NIPER), etc are actively involved in basic, pre-clinical as well as clinical research to facilitate development of microbicides. Microbicide Praneem-prepared from the neem *(Azadirachta indica*), *Sapindus mukorossi*, and citrate oil has been developed. Talwar.[50] Praneem has shown wide-spectrum antimicrobial activity against reproductive tract infections, including anti-retroviral properties[50] and has undergone Phase-I and -II safety and acceptability studies[51–53] with the help of National AIDS Research Institute (NARI), Pune. Along with polyherbal cream Basant has been proposed which has curcumin, *Emblica officinalis* (Amla) and *Sapindus mukorossi* purified extract (*Aloe vera* and rose water used as preservatives). Basant inhibits the growth of WHO strains and clinical isolates of *Neisseria gonorrhoeae*, *Candida glabrata*, *Candida albicans*, *Candida tropicalis* and Chlamydia and displayed a high virucidal action against HIV.[54]

4. Conclusion

Microbicide research is undergoing a period of rapid evolution. Development of safe and effective microbicides in developing countries promises to be one of the great public health concerns. Once developed these microbicides will be one of the crucial elements in any comprehensive response to HIV. Critical step will be to develop products that do not have to be used in a coastally dependent fashion. Microbicides will not only be integral to improving women's health but also will help reduce the burden of death and disease in women and eradicate poverty in the developing world.

5. Source of Funding & Conflict of Interest

None.

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