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Medicinal Plants with Possible Anti- HIV Activities: A Review

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Abstract: *HIV is a virus that is widely transmitted along with the rise in viral infections. The majority of deaths worldwide are caused by this virus. Numerous treatments for this illness have been developed by scientists, but the outcomes are still uncertain. One of the responsible agents that authorized treatments can impact is the HIV-1 virus. One of the main ways to contract HIV and other STIs is through sexual contact. One promising preventative method that has been suggested is the use of microbicides. These microbicides can be administered directly to the vaginal or rectal surface and come in a variety of forms, including creams, gels, lubricants, and even tablets. The availability of a viable microbicide candidate would significantly increase women's power. (guys engaging in homosexual behavior) to shield themselves and their partners from HIV infection and other STIs. The availability of a microbicide will be crucial in situations involving several sexual partners. A perfect Microbicides should be used hours before intercourse, safeguard the natural vaginal micro-ecological system, avoid producing pro-inflammatory cytokines, and maintain the natural morphology of the female reproductive canal (without causing lesions or abnormalities in the epithelial layer). This review article will address medicinal plants that have been shown to have antiviral properties against HIV infection and lower the burden of sexually transmitted diseases in affected individuals.*

Keywords: Fungal infections

I. INTRODUCTION

With about 30,000 blooming plant species, or almost 10% of all higher plants worldwide, Southern Africa boasts an exceptionally rich plant variety (van Wyk, 2001). Utilizing plants for centuries, and the trade in medicinal plants is still very much alive today. Approximately 80% of the population of Africa, or over a half billion people, rely on traditional medicines for their primary medical requirements, according to the World Health Organization (WHO). However, the sector is not the same as utilized to the fullest extent possible. In South Africa, for instance, some 3,000 medicinal plant species are commonly utilized in plant-based medications; nevertheless, fewer than 40 native species have been made available for purchase. in part (van Wyk, 2008). disastrous consequences. 36.7 million persons were HIV positive in 2015. 2.1 million persons worldwide contracted HIV for the first time (UNAIDS, 2016). 70% of all newly infected individuals and 71% of all HIV-positive individuals lived in sub-Saharan Africa in 2012 (UNAIDS, 2013). Although eastern and southern Africa together make only 6% of the world's population, they are home to 52% of all HIV-positive individuals and nearly half of the estimated 2.3 million new HIV infections in 2012 (UNAIDS, 2013). For those with HIV, anti-retroviral therapy (ART) is a successful treatment. Suppressing the HIV replication cycle and stopping the disease's progression are the goals of standard treatment. The antiretroviral treatment is important in enhancing the quality of life for those with HIV, but the medications have a number of drawbacks, such as toxicity, resistance, restricted availability, and no curative impact (Chinsembu and Hedimbi, 2010a). Since it was first discovered decades ago, there has been growing concern about the possibility that HIV could develop resistance to anti-retroviral (ARV) therapy (De Clercq, 1995). Worldwide, the necessity for developing new medications is becoming more and more apparent as pathogens develop treatment resistance. These drawbacks create opportunities for the application of natural products in HIV treatment. **[1]**

THE HIV LIFE CYCLE: When the human immunodeficiency virus enters the body, it targets essential immune cells, such as T helper cells, for infection. (particularly CD4+ T cells), macrophages, and dendritic cells. The viral envelope glycoprotein fuses the virus with the membrane of the targeted cell.CD4+ T cells cause modifications in Ip120, which

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leads to the virus entering the host cell10, where interaction between CD4+ and gp120 occurs.Following the establishment of the ternary CD4 co-receptors gp120 complex, the membrane fusion is confirmed by gp41 conformational changes. Following receptor and CD4+ interaction, fusion took place at the low pH of the endosome compartment.The lipids that make up the targeted cells are crucial for membrane fusion. Lipid rafts, which are plasma membrane microdomains, replace the fusion of membrane in plasma membrane. These microdomains include glycosphingolipid and cholesterol.HIV or any disruption caused by cholesterol particles in the target cell may cause the membrane fusion to break. Amphotericin's role in HIV-fusion inhibition. B-methyl esters have a significant function. Reverse transcriptase transforms single-stranded HIV RNA into double stranded HIV DNA. Twelve The complex of ribonuclear proteins made up of NC, CA, RT, Vpr, and IN enters and fuses to form the complex of reverse transcription in the cytosol.RNA holds the dimerization initiation sequence (DIS) together at the 5′ end. Because retroviruses carry both strands of retroviral RNA, they are known as pseudodiploids. Once the virus has entered the target cell, the retroviral ribonuclease H (retroviral RNase H) begins the process of converting RNA into DNA. is the retroviral reverse transcriptase (RT) enzyme's catalytic domain. The retroviral RNA genome is converted into complementary DNA (cDNA) by the RT enzyme.We refer to this procedureas reverse transcription.

The single strand of DNA synthesis takes place at the 3′-OH end of tRNA. Next, DNA synthesis proceeds in the direction of the 5′ end. tRNA is used by retroviruses to synthesize DNA.

The 3′ and 5′ ends have a virtual true repeating region, and this minus strand is transmitted for hybridization.

As the genome approaches its 5′ end, the RNA-DNA hybrid is generated that accompany the degradation of the RNAScH mediator.

The positive strand is PPT; the remaining hybridized RNA fragments can also be utilized for priming plus strand production.

The plus strand synthesizes the tRNA following the removal of RNase H.This enables the plus strand to hybridize with the 3′ end homologous region. One

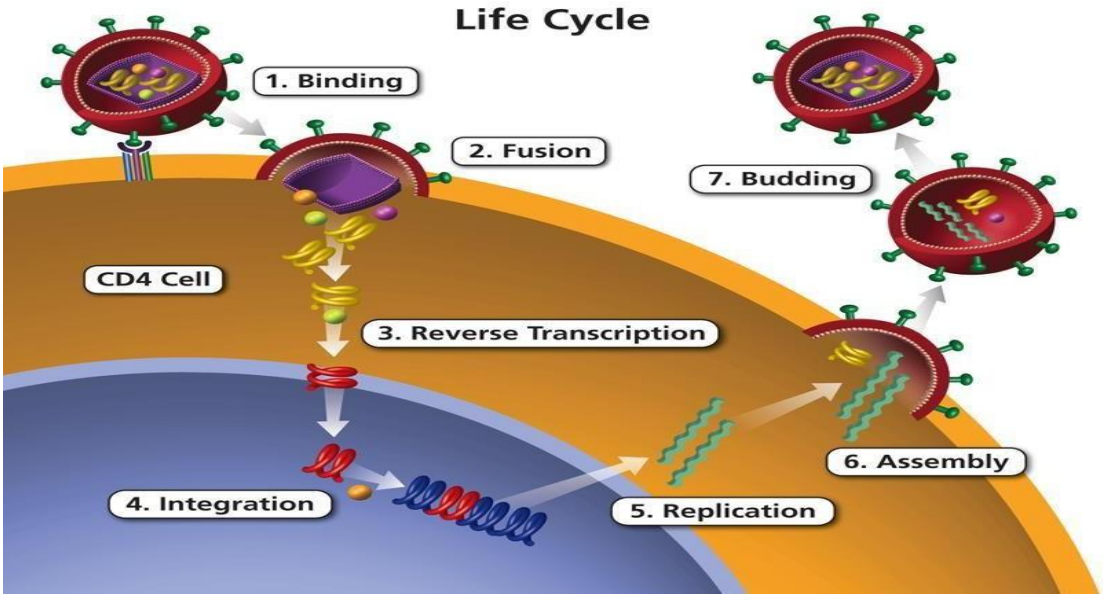

Figure 1.Life cycle**. [12]**

The RT creates additional templates from the two strands of RNA using a single template. Each infection may cause this to happen 30 times.Intermolecular leaps cause mutation by duplication and deletion. as well as insertions. Recombinants are produced via intermolecular jumps when two RNA packages are different. This recombinant gives HIV a quick way to fend off medications.The progenitors of retroviral gag proteins, such as PR55, are produced by polyproteins and give rise to a non-infectious virus-like particle. It is not necessary for pol-encoded enzymes, viral genomic RNA, or enclosed glycoproteins to generate non-infectious particles. The nascent particles that are expelled from the cell and form the structural virion's framework are targeted by retroviral Gag proteins.

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Modeof transmission:- HIV is spread in a variety of ways, but most frequently through contaminated blood or blood components. Additionally, sexual contact can spread it, however there is a decreased risk of infection in Comparing heterosexuals to homosexuals (man to male).Additionally, blood, semen, vaginal secretions, breast milk, contaminated needles or syringes, pregnancy, and childbirth can all spread HIV infection.Additionally, it travels to the mucous membrane via a cut or injured tissue**. [3]**

ANTI-HIV AGENTS DERIVED FROM NATURE : Calanolides (Coumarins), betulinic acid (a triterpene), baicalin (a flavonoid), and polycitone are examples of natural compounds.

Coumarins

Calanolides are an example of a virus's non-nucleoside specific reverse transcriptase inhibitors (NNRTI). kind of coumarin that comes from various Calophyllum tropical tree species (Clusiaceae family; Dharmaratne et al., 2002). Calanolide A (Figure 1), Calanolide B (Vlietinck et al., 1998), and its derivative 7,8-dihydrocalanolide B are derived from Calophyllum lanigerum and can stop HIV-1's cytopathogenic effects on host cells. Similar in structure to calanolides, cordatolide A and B have the ability to prevent HIV-1 replication. Calophyllum cordato-oblongum is the source of these chemicals (Lee et al., 1994). Another substance that likewise inhibits the virus's ability to replicate in the T cell line is Suksdorfin (Yu et al., 2003), a pyrocoumarin.

Terpenes

Several triterpenoids have been shown to exhibit antiretroviral efficacy with a variety of modes of action. The acid betulinic , The leaves of Syzigium claviflorum contain platanic and oleanolic acid, which have been demonstrated to suppress HIV in H9 lymphocyte cells (Min et al., 1999). Oleanolic acid, which is obtained from the methanolic extract of the wood from the Sapindaceae family, Xanthoceras sorbifolia, was found to inhibit HIV1 replication in these cells (Kashiwada et al., 1998). Maslinic acid from the Geum japonicum has demonstrated strong inhibitory effect against HIV-1 protease (Xu et al., 1996). Celasdin B, which is made from an ethanolic extract of the Celastraceae plant Celastrus hindsii, exhibits anti-HIV replication activity in H9 cells. found with Celasdin B, which is made from an ethanolic extract of the Celastraceae plant Celastrus hindsii (YaoHaur and Li-Ming Yang, 1997). The garcisaterpenes and protostanes A and C, which are derived from the ethyl acetate extract of Garcinia speciosa stems and bark, have the ability to inhibit HIV-1 RTase activity (Rukachaisirikul et al., 2003). Lanostane-type triterpene, a suberosol made from an ethanolic extract of Polyalthia suberosa leaves and stems from the Annonaceae family, has also been demonstrated to inhibit HIV replication in H9 cells (Li et al., 1993). Another substance that inhibits HIV replication in these cells is triterpene lactone, lancilactone C, which is isolated from Kadsura lancilimba roots and stems (Chen et al., 1999). 13-acetate of 12-O-tetradecanoylphorbol (TPA),

Flavonoids

Flavonoids and related polyphenols have demonstrated favorable anti-HIV effects. They are renowned for possessingantiviral activity in several cell cultures and has antioxidant qualities (Orhan et al., 2010). Baicalin has a dose-dependent effect on HIV replication in PBMC. is derived from Scutellaria bailacalensis and is an anti-HIV flavonoid (Ohtake et al., 2004). The extract of Monotes africanus is the source of 6,8-diprenylaromadendrin's anti-HIV activity in the XTT-based, whole-cell screen (Meragelman et al., 2001). The ethanolic extract of Acer okamotoanum, a member of the Aceraceae family, yields the flavonoid gallate ester and quercetin 3-O-(2-galloyl) a-L-arbinopyranose, which can block HIV1's integrase activity (Kim et al., 1998). Methanolic extracts of Rhus succedanea leaves and branches from the Anacardiaceae family include robustaflavone and biflavonoids, which have been shown to inhibit the HIV-1 polymerase (Lin et al.

Alkaloids

Alkaloids of many kinds have demonstrated anti-HIV properties.One of the natural compounds on RT that exhibits intriguing activity is the aromatic alkaloid polycitone A , which was extracted from the marine ascidian Polycitor sp. Both DNA-directed and RNAdirected DNA polymerases are strongly inhibited by polycitone A (Loya et al., 1999). Papaverine, an alkaloid that is isolated from Papaver sominiferum, a member of the Papaveraceae family, has the ability to prevent HIV replication. Eodia roxburghiana is the source of the quinolone Buchapine, which has been demonstrated to reduce the cytopathogenic effects of HIV-1 (McCormick et al., 1996). Nitidine, which is derived from the roots of

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Toddalia asiatica, a member of the Rutaceae family, also exhibits anti-HIV action (Tan et al., 1991). O-demethylbuchenavianine, an alkaloid related to piperidine flavones, has a resistance to

Phenolics

Due to increased proliferation of lymphocytes generated by phytohaemagglutinin, extended administration of Fruit juices high in polyphenols are thought to hold promise for HIV-positive people. Numerous tannins and related phenolic compounds exhibit virucidal properties in a variety of viral systems. Salvia miltiorrhiza's lithospermic acid has potent anti-HIV action in H9 cells (Abd-Elazem et al., 2002). Terminalia chebula contains the hydrolyzable tannins punicalagin, chebulagic acid, and punicalin, which have anti-HIV properties (Lim et al., 1997). Extracted from Phyllanthus niruri, a member of the Euphorbiaceae family, repandusinic acid has demonstrated inhibition of HIV-1 RTase (Ogata et al., 1992). Monopotassium and monosodium salts of the isomeric caffeic acid tetramer, which are derived from the aqueous acetone extract of Arnebia euchroma, have demonstrated suppression of HIV replication**. [4]**

TECHNIQUES

We looked up "plants with anti-HIV activity" using the keywords in PubMed Central, the US National Library of The digital repository for biomedical and life sciences journal publications in medicine. Over the course of the three-month literature search, 224–250 journal publications were examined. Plant and other natural product families and species, along with their active ingredients and mechanisms of action, were, if feasible, included in tables arranged alphabetically by taxonomic families. **[5]**

The Structure of HIV :- The animal retrovirus known as HIV, which is prepared tomultiply and incorporate its infectious DNA into the healthy DNA of the host cell, is the driving force behind AIDS. The primary target of this animal virus is the body's helper T cells. The virus has a spherical shape and measures between 90 and 120 nm in diameter. Its genetic material typically consists of a single standard RNA fiber that is linked to an enzyme known as reverse transcriptase (RT) and metameric into two comparable fibers. The viral coating consists of spikes of glycoprotein that resemble protruding knobs and a lipid bilayer that is produced from the host cell membrane. It is made up of two protein coatings, as seen in On the inside, the virus It includes the essential nuclear material and proteins. Additionally, the virus has an enzyme called a protease that breaks down the viral polyproteins to create new, useful proteins. Reverse transcriptase is responsible for catalyzing the viral integrase, which permits viral DNA to enter the host nucleus, and RNA into viral DNA**. [6]**

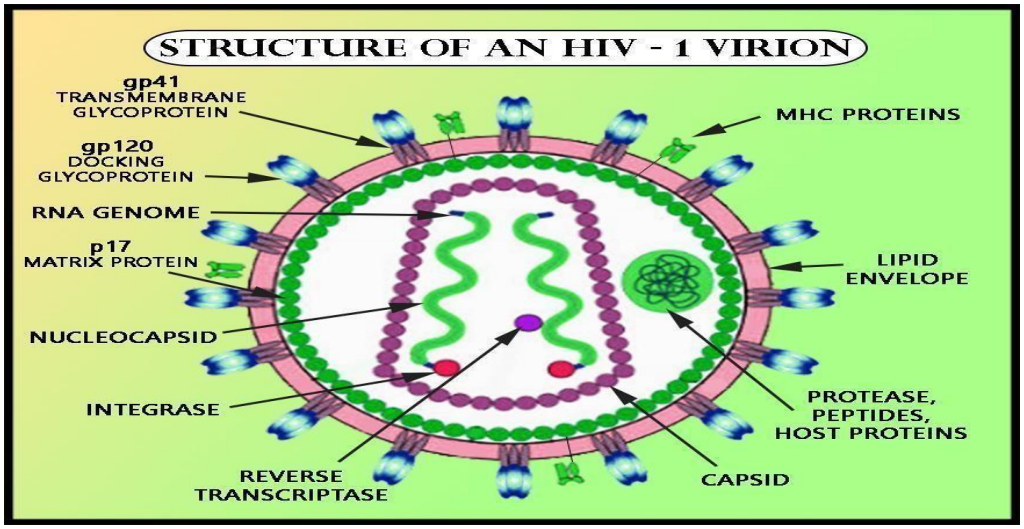

Figure 2. Structure of human immunodeficiency virus (HIV) virus-1 Virion **[7]**

HIV Replication Cycle Figure 2 depicts the entire HIV replication cycle. Once the virus has entered a person's body, it uses CCRS or CXCR4 receptors to infiltrate bodily cells. shown on top of monocytes, dendritic cells, and macrophages, also referred to as T- lymphocytes The virus interacts with cell membrane proteins and binds to chemokine receptors

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once it has entered the host cell. The reverse transcriptase (RT) enzyme is then released by the virus and used to synthesize viral DNA from its viral genome, or HIV RNA. This transformation enables the virus to reach the nucleus of the host cell, where the integrase enzyme releases and integrates the viral DNA into the DNA of the host cell. Viral RNA and freshly produced HIV proteins go toward the cell membrane and reconnect with immature HIV. The release of the protease enzyme from the viruses that cause the infection is then triggered when the new immature (non-infectious) virus buds off from the host cells. degradation of immature viral long-chain polypeptides. Small proteinparticles thathave just produced create mature viruses that infect new host cells and spread the infection. **[8]**

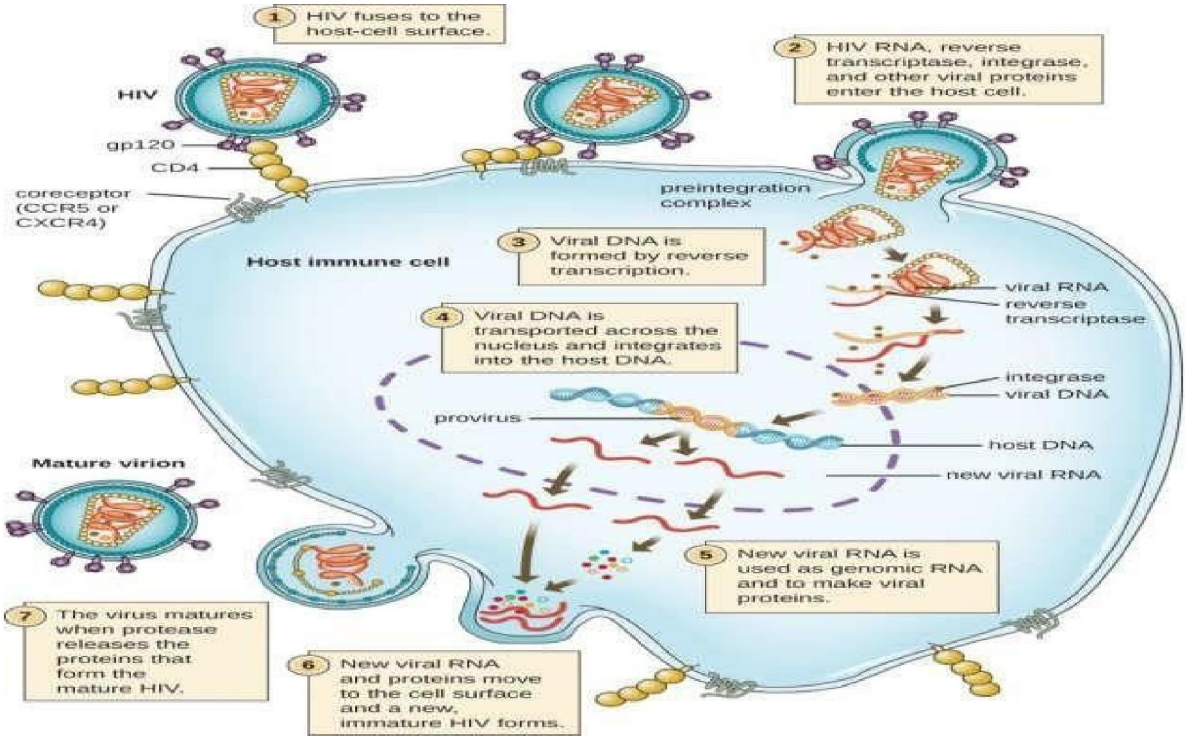

Figure 3. The HIV replication cycle . Image was originally published within Open Access license**. [9]**

The diagnosis : Viral RNA mass estimation from the host's blood plasma is used to determine the degree of HIV infection. Acute symptoms have been linked to the illness, specifically symptoms such as lymphadenopathy, fever, fatigue, weight loss, pharyngi.tis, rashes, headache, nausea, myalgias, meningitis, and general malaise **[10-11].** Viral RNA is most abundant in the plasma during an acute HIV infection. The quantity and properties of the virus are thought to reveal its pathogenicity and reproduction. Therefore, in addition to the viral genotype, host features also influence the clinical details and infection development **[12-13].** Western plotting and ELISA were the two primary tests used for the AIDS diagnoses in the past. Western Blotting was used to validate ELISA positive tests, while ELISA is used to detect and measure the antibodies generated against a particular pathogen **[14].** It is employed to verify the certain proteins found in the blood. Following protein denaturation, the samples undergo gel electrophoresis. It is discovered that the combined effect of both tests is 99% correct. These days, there are a number of beneficial substitutes for Western Blotting.Among the benefits connected to such alternative. **[15]**

Potential Anti-HIV Plants Currently, the development of multidrug resistance limits the strategies available to combat AIDS. Therefore, new targets and effective medications are needed to accomplish the objective of a complete elimination of AIDS. Additionally, infected cells endure and serve as a fundamental obstacle to HIV-1 eradication. The way the virus spreads has made it necessary to develop newer medication compounds that effectively combat HIV without stimulating the immune system's T cells during the last ten years **[16-17**]. The WHO has advised that ethnomedicines and other natural components be further examined to prevent HIV in order to achieve this goal. Remarkably, natural compounds that work against HIV-1 enzymes such as reverse transcriptase, integrase,

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protease, and certain fusion inhibitors were found in the 1990s. The chemical variety of natural medications results in increased hit rates at high throughput. screening and excellent ability to go to the intended location **[18–19].** Numerous plant-derived alkaloids, flavonoids, coumarins, terpenoids, and polyphenolic compounds were discovered, along with well-known medicinal substances with a range of biological properties like antiinflammatory, anti-cancer, analgesic, and anti-HIV properties **[20–21]**. The anti-HIV potential of components of Dioscorea bulbifera **[22],** Euphorbia sikkimensis **[23],** Culendula officinalis [**24**], Sceletium tortuosum **[25],** Brazilian propolis, Kadsura lancilimba, Lithocarpus litseifolius, and Ocimum labiatum [**26-27**]

Herbal Remedies :-

Potatorum Strychnos:The Loganiaceae family's Strychnos potatorum L.f. is utilized in Sperm motility is decreased by leukorrhea and gonorrhea**[28-29]** Fruit pulp from A. squamosa that has spermicidal qualities dramatically reduces HIV replication in H9 cells. **[30**] For a vaginal microbicide, this makes it an extra attractive feature**.[31]** In cell-free HIV-1Ada5 strains, methanolic extract of S. potatorum demonstrated action with preliminary IC80 in the 29.17–79.35 µg/ml range, resulting in an estimated TI of 24**.[32]**

Fig. 4: Strychnos potatorum **[33]**

Centifolia Rosa:- The blooming plant Rosa centifolia L., which belongs to the Rosaceae family, is also referred to as the cabbage rose.due of their antiviral properties. Benzaldehyde (1.5%), Nerol (5–10%), Citronellyl acetate (0.3%), Linalool (6.9%), Phenyl Ethanol (43%), Geraniol (10.5%), and Geranyl Acetate (15.6%) were found in chemistry. In addition to oils, it also contains mineral salts, tannins, tartaric acid, and mallic acid salt. **[34]** A methanolic extract of R. centifolia leaves exhibited negligible anti-HIV properties

Fig.5: Rosa centifolia **[35]**

Procera albizia:- Across Indian territories, Albizia procera (Roxb.) Benth, a member of the Fabaceae family, is found. Conventionally A bark decoction is used to cure stomachaches, rheumatism, and bleeding. **[36]** According to laboratory analysis, the integrase enzyme is inhibited by bark ethanolic, ethyl acetate, aqueous, and hexane-chloroform extracts

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with lower IC50 values (19.5, 19.1, 21.3, and >100 µg/ml, respectively). Protocatechuic acid and catechin are the two main chemical components that were extracted from the plant. With an IC50 value of 46.3 µM, catechin shown strong action against the intergase enzyme; protocatechuic acid, however, demonstrated less protection**. [37]**

Fig. 6: Albizia procera **[38]**

Aspera Achyranthes:-In the Indian subcontinent, Achyranthes aspera L. (family Amaranthaceae) is a popular folk remedy. The plant's stated oleanolic acid showed possible impacts. Against type I herpes simplex virus (EC50 = 6.8 µg/ml) and type II HSV-2 (EC50 = 7.8 µg/ml). **[39]** Crude ethanolic extract and oleanolic acid prevent the virus in its early stages. multiplication between two and six hours after infection. The methanolic extract of A. aspera provided TIs of 14, 35, and 13 in cell-free HIV-1I I B, HIV-1Ada5, and cell-associated HIV1I I B, respectively, with preliminary IC80 in the 18–35 µg/ml range.

Fig.7: Leaves of Achyranthes aspera **[40]**

Squamosa Annona:- The custard apple tree, Annona squamosa L. (Annonaceae), is found all over India. Squamosa Annona used as an anti-inflammatory, anti-tumor, anti-diabetic, antioxidant, and antilipidimic substance**. [41]** When dysentery was present, a leaf decoction was taken. They include a large range of substances, such as acetogenins, which have cytotoxic, immunosuppressive, anti-feedant, and anti-malarial properties. **[42]** Anisquamosins A and B, two diterpenes, showed anti-HIV and anti-platelet aggregation properties. **[43]**

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Fig. 8: Leaves of Annona squamosa **[44]**

Procumbens tridex :-A popular Ayurvedic plant from the Indian subcontinent, T. procumbens has a long history of traditional applications. Plant is frequently used to prevent blood clotting, treat wounds, and cure skin conditions. It has antiseptic, antibacterial, anticoagulant, antileishmanial, antioxidant, anticancer, immunomodulatory, insecticidal, and anthelmintic cardiovascular qualities**. [45]** T. procumbens methanolic extract has no anti-HIV properties**. [46]**

Fig. 9: Tridex procumbens **[47]**

Reticulata Annona The plant has long been used to cure heart issues, worm infestation, diarrhea,and epilepsy.symptoms such as fever, ulcers, dysuria, hemorrhage, antimicrobial infections, and constipation. It also possesses antitumor, antifertility, and abortifacient qualities. The bark of A. reticulata has yielded a bioactive acetogenin and a tetrahydroisoquinoline alkaloid with cardiotonic action in its leaves. Leaves have strong antidiabetic effects. Flavonoids were extracted from leaves by some workers. It has been reported that an ethanol extract of the leaves and stem has anti-cancer properties. **[48]** High antiviral activity was demonstrated by extracts from A. reticulata peels, with HIV-1 reverse transcriptase inhibition values of 78.63 ± 0.97%. **[49]**

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Fig. 10: Annona reticulate **[50]**

II. CONCLUSION

Research on microbicides is rapidly evolving at the moment. Creation of secure and efficient microbicides appears to be one of the major public health issues in developing nations. These microbicides will be one of the most important components of any allencompassing HIV response whenever they are produced. The creation of goods that are not required to be used in a manner that is dependent on the coast will be a crucial step. In addition to being essential for enhancing women's health, microbicides will also lessen the burden of illness and death on women and assist end poverty in developing nations.

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