REVIEW PAPER

Comprehensive review on herbal remedies treatment for acquired immune deficiency syndrome (AIDS)

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Abstract

This thorough review aimed to present critical examination of the literature on the subject, and assess the effectiveness of herbal medicines for the treatment of acquired immune deficiency syndrome (AIDS). This evaluation presented how herbal medications are used in conventional and alternative medical systems, investigated scientific data supporting their usefulness, and showed difficulties and potential benefits of incorporating herbal medicines into human immunodeficiency virus/AIDS treatment plans.

The analysis discovered that several herbal treatments were studied for their ability to cure AIDS, mostly as a complementary therapy to traditional antiretroviral medication. Studies demonstrated the immunomodulatory qualities of several herbs, including *Scutellaria baicalensis*, *Hypoxis hemerocallidea*, and *Sutherlandia frutescens*, which may help AIDS patients' immune systems function better.

Herbal medicines have a beneficial potential as adjunctive treatments for individuals with AIDS, mainly by strengthening immune function and improving general health. Patients should not, however, rely exclusively on herbal remedies, and their usage must be monitored by medical specialists. More investigations are needed to determine particular herbal ingredients and combinations, which may significantly improve the management of AIDS, taking into account possible drug interactions with antiretrovirals.

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Key words: human immunodeficiency virus, baicalein, *Hypoxis*, *Hemerocallis*, *Sutherlandia frutescens*, *Euphorbiaceae*, acquired immune deficiency syndrome.

Introduction

Human immunodeficiency virus (HIV) damages human CD4+ or T helper immune cells, which fight the virus, making HIV patients more susceptible to a wide range of illnesses and infections [1]. Sharing injectables, engaging in unprotected sexual activity, or contact with body fluids from an HIV-positive person, can all lead to infection [2]. The HIV/acquired immune deficiency syndrome (AIDS) epidemic has a terrible effect on people's health and quality of life [3]. There were 35 million HIV-positive people in the globe as of the end of 2013. Moreover, 78 million individuals have acquired HIV since the start of the pandemic, and 39 million have died from AIDS-related illnesses [4]. In 2021, 1.5 million people contracted HIV, and 650,000

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(range, 510,000-860,000) have died due to HIV-related causes. Recent data on the global spread of HIV and AIDS show that out of over 40 million people living with the virus, 2.5 million are youngsters under 15 years of age [5]. According to the Joint United Nations Programme on HIV/AIDS, more than 37 million individuals worldwide are HIV-positive and AIDS prevalence is fast increasing [6]. As the HIV/AIDS pandemic spreads, around 15,000 new infections are recorded daily.

Regarding the treatment, there are three main antiretroviral medication groups used in clinical settings, including nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and nucleoside analogs [7]. None of AIDS medications available on the market have the ability to completely cure and/or reverse the illness [8]. Several drugs employed for AIDS treatment have adverse effects, such as bone marrow cytopenia, kidney toxicity, and low platelet counts [9]. However, currently, many HIV-infected patients are moving towards herbal remedies due to lower side effects and abiding effects. In the last ten years, there have been an increase in using herbal remedies as common complementary and alternative medicines [10]. AIDS-infected individuals are particularly interested in herbal treatments, because of the chronic nature of the disease that impact their quality of life as well as the likelihood of fatal consequences. Due to the widespread use of herbal treatments for terminal illnesses, and the fact that there is no pharmacological treatment for HIV, many people are turning to alternative therapies and spiritual guidance [11]. Several clinical studies have revealed that herbal treatments may be able to reduce viral loads, alleviate symptoms, and increase CD4+ cells in persons with HIV and AIDS. The term "herbal medicines" refers to concoctions made from plants or plant components for curing illnesses [12]. Herbal medications may contain extracts from several different plants or just one herb. In the literature, they were compared with placebo, no treatment, and antiretroviral drug testing on herbal remedies (including highly active antiretroviral therapy, and both monotherapy and combination regimens) [13]. Nowadays, many countries no longer use this practice, but every nation has its own herbal medical system and history, such as traditional Chinese medicine (TCM) in China, Ayurveda in India, and allopathic medicine in ancient Greece [14]. According to Chinese medical texts, cordyceps, a kind of medicinal fungus, has a powerful immune-stimulating activity and function, possibly helpful in AIDS and HIV treatment [15]. There is significant potential for HIV/AIDS medication development in natural products [16]. Triterpenoids and their derivatives are significant sources of potential anti-HIV medication candidates, as demonstrated by a decade of comprehensive studies on natural compounds [17]. Pentacyclic triterpenes seem to be the most promising lead chemicals for the creation of new antiviral medications in the future [18].

The present review demonstrated critical examination of the literature on the above-mentioned subject as well as assessment of the effectiveness of herbal medicines in the treatment for AIDS. It provided a general review on how herbal medications are used in conventional and alternative medical systems, investigated scientific data supporting their usefulness, and showed difficulties and potential benefits of herbal treatments incorporated into HIV/AIDS treatment plans.

Types of HIV: HIV-1 and HIV-2

HIV is divided into two main varieties, i.e., HIV-1 and HIV-2. HIV-1 type was first discovered and is more widespread worldwide, whereas HIV-2 is less dangerous and most prevalent in West Africa. Both HIV-1 or HIV-2 can develop into AIDS [19]. Numerous aspects of the strains are comparable, including internal processes of replication, transmission routes (sexual contact, sharing of needles, and transfusion), and clinical outcomes. Patients with HIV-2 infection, as their illness worsens, are more prone to contracting individuals infected with HIV-1, and encounter the same range of opportunistic illnesses as people with HIV-1 type [20]. However, illnesses developed from both the viruses differ significantly from one another. These differences provide opportunities to explore immune factors associated with protection that can contribute to vaccine development, enhance the understanding of both specific disease mechanisms, and enquire about still not well-understood HIV pathogenesis [21]. The primary clinical distinction between the two infections is the rate of immunodeficiency development, where HIV-2 infection progresses more slowly than HIV-1, leading to a higher prevalence of long-term non-progressors in HIV-2 [22]. By contrasting these two infections, it is possible to generate and test hypotheses, and gain knowledge about the pathophysiology of immunodeficiency disorders caused by human retro-viruses [23]. In general, HIV-2 responds to ARV similarly as HIV-1; however, is naturally resistant to NNRTI, necessitating the use of alternate treatment algorithms. Complete review on treatment options is available in Campbell-Yesufu *et al*. study [24].

HIV infection's mechanism

HIV travels throughout the body once it first enters a person's blood circulation. A unique protein, called gp120, serves as a foundation for protective covering from HIV, with enzyme and viral RNA-containing capsid found in this protein, as shown in Figure 1. In addition, gp120 and a virus bond to CD4 receptors on the cell surface of macrophages and proteins. Endocytosis is also essential for viral entry into the cell. The second receptor protein, CCR5, is found in macrophages [25]. First strand of viral DNA and complementary DNA strand are produced by reverse transcriptase using viral RNA, when the viral RNA and enzyme are released into the cell cytoplasm. Viral DNA incorpo-

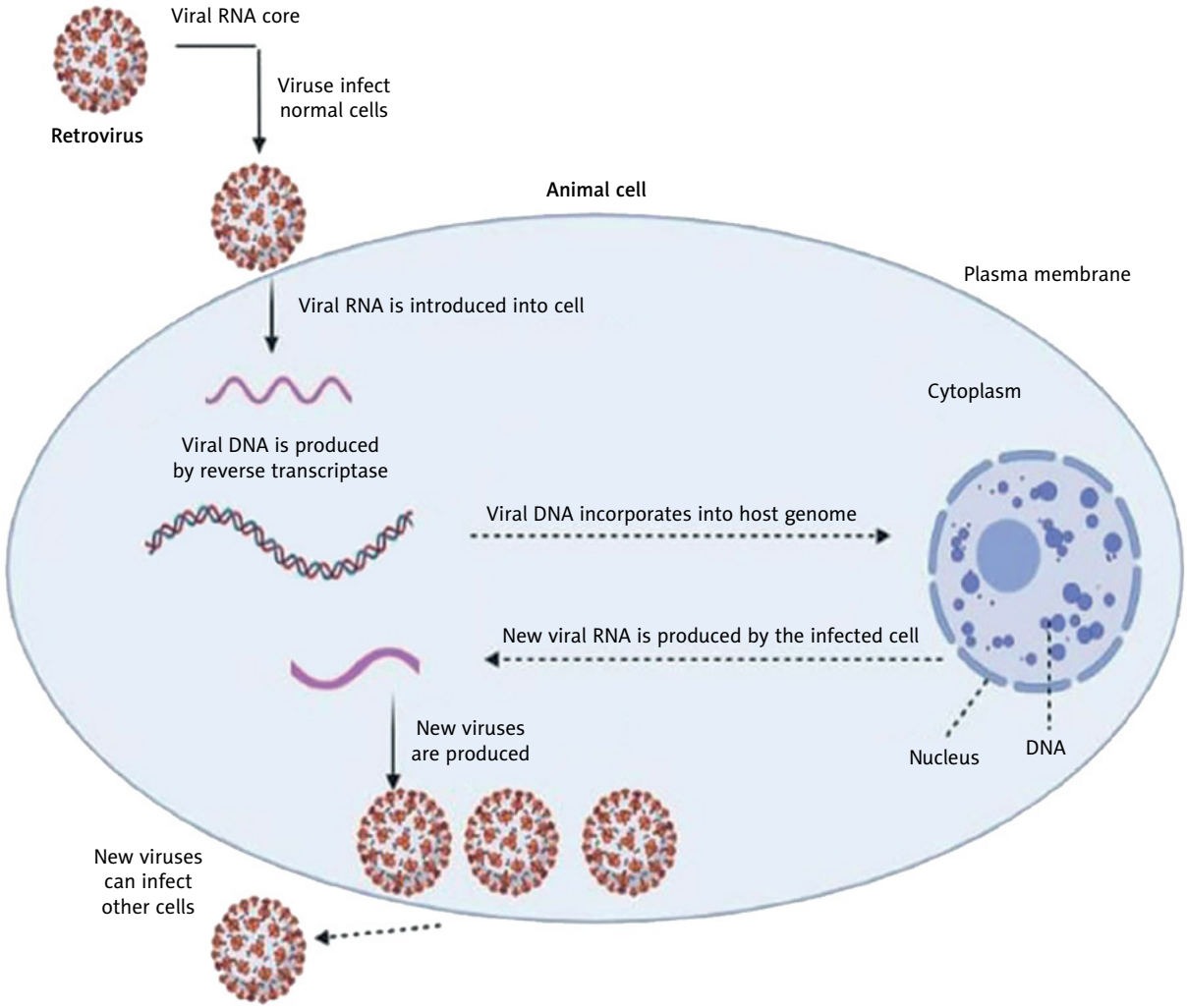

Figure 1. Mechanism of HIV infection

rates host cell DNA as it travels to the cell's nucleus in DNA. Following the transcription of DNA inside the nucleus, the viral RNA is produced. This RNA virus functions as both the RNA messenger that ribosomes utilize to transcribe RNA into viral proteins, and DNA for new viruses. Exocytosis is employed to construct viruses, which are then discharged from the cell without harming macrophages. HIV travels in the body by macrophages repeatedly over several years, replicating, and appearing not harming the host [26]. A mutation exists in the gp120 protein's gene; the changed gp120 protein modifies amino acid of its co-receptor. The same mechanism produces new virus particles within T cells, but these novel viruses enter T cell, and cross-kill the cell and plasma membrane. The body's immune system is weakened by these recently released viruses, which attack and destroy additional T cells, resulting in the emergence of AIDS [27].

Different classes of HIV drugs

Treatment for HIV/AIDS frequently involves the use of allopathic medications, generally referred to as conventional or Western medicine. The following is the list of common allopathic drug classes for HIV/AIDS treatment and possible adverse effects.

Nucleoside reverse transcriptase inhibitors

NRTIs were the first class of ARV drugs to be approved by the FDA. NRTIs are given as pro-drugs, which need to enter the host cell. To have an antimicrobial impact, pro-drugs must first enter the target cell and be phosphorylated by cellular kinases, which are used to deliver NRTIs [28].

Examples: tenofovir, zidovudine (AZT), lamivudine, and emtricitabine. Side effects: anemia, neuropathy, nausea, vomiting, and mitochondrial toxicity.

Non-nucleoside reverse transcriptase inhibitors

These non-uncompetitive inhibitors do not prevent the replication of HIV-2 and the simian immunodeficiency virus, in contrast to NRTIs [29].

Examples: rilpivirine, nevirapine, and efavirenz. Side effects: rash, liver damage, and adverse effects on the central nervous system, such as vivid nightmares, vertigo, and mood swings.

Integrase inhibitors

In addition to the nucleoside backbone, the most widely used class at the moment is integrase strand transfer inhibitors (INSTIs). They are effective against both HIV-1 and HIV-2, and work by preventing viral DNA fusion to the host [30].

Examples: elvitegravir, dolutegravir, and raltegravir. Side effects: sleeplessness, headaches, and seldom allergic responses.

Protease inhibitors

Protease inhibitors (PIs) are frequently used in NRTI-sparing regimens or in combination with nucleoside backbones. They work by preventing the gag-pol polyprotein from being cleaved, which causes the development of immature virions. They are effective against both HIV-1 and HIV-2 [31].

Examples: lopinavir/ ritonavir, darunavir, and atazanavir. Side effects: gastrointestinal problems (diarrhea, nausea), metabolic alterations (lipodystrophy, elevated cholesterol/ triglycerides), and drug interactions.

Entry inhibitors

This type of medications prevents HIV from attaching to its target cells. Drugs called, co-receptor antagonists, particularly block the chemokine co-receptors CCR5 or CXCR4 [32].

Examples: maraviroc. Side effects: liver and cardiovascular issues.

Fusion inhibitors

The fusion-active version of gp41 was discovered by analyzing molecular structures of ectodomain, and the ectodomain in combination with inhibitory peptide [33].

Examples: enfuvirtide. Side effects: injection site reactions.

Treatment of HIV/AIDS by using herbal remedies

Scutellaria baicalensis

Scutellaria baicalensis is a plant used in TCM. It is often referred to as Chinese skullcap or Baikal skullcap. Originating from Eastern Asia, specifically China and Russia, it has been utilized for millennia due to its potential medicinal properties. The part of *Scutellaria baicalensis* plant that is most frequently utilized for therapeutic reasons is the root. Herbal formulations are frequently made in traditional medicine systems, such as TCM, by mixing many plants to accomplish certain medicinal outcomes. Herbs can be combined to enhance their particular effects, and treat variety of health issues. Herbal synergy is the term for this strategy.

Ginseng root, bupleurum root, *Pinellia tuber*, jujube fruit, *Scutellaria* root, and ginger rhizome refer to a blend of herbs or a herbal composition used with *Scutellaria baicalensis*.

A blend of water, and 7.5 grams of extracts from 7 different plants make up the product. This mixture includes 4.5 g of dry extract obtained by extracts of 7 herbs combined in boiling water, including ginseng root (4.0 g) (*Zingiber officinale*) from *Zingiberaceae* family, jujube fruit (4.0 g) (*Ziziphus jujuba*) from *Rhamnaceae* family, *Pinellia* tuber (5.0 g) (*Pinellia ternate*) from *Araceae* family, *Scutellaria* root (4.0 g) (*Scutellaria baicalensis*) from *Lamiaceae* family, bupleurum root (7.0 g) (*Bupleurum chinese*) from *Apiaceae* family, and ginger rhizome (1.0 g) (*Zingiber officinale*) from *Zingiberaceae* family [34]. According to various studies, baicalein and baicalin are the key active ingredients in Sho-saiko-to (TJ-9), and reported to have antioxidative, anti-tumor, anti-proliferative, and anti-HIV properties. Worth noting is the similarity of the findings regarding using methanol extracts, in which antioxidative activity was found in Sho-Saiko-to and *Scutellaria* root. The aqueous extracts of *Scutellaria* root exhibit substantial antioxidant activity, according to our group and other studies [35]. Moreover, antioxidant activity was observed in four main components, such as baicalein, baicalin, wogonin, and wogonoside. The anti-HIV actions of baicalin and baicalein may be due to pathways involving antioxidants and other factors. Sho-saiko-to oral dosage toxicity research in rats has been published. Animals were given two oral doses of Sho-saiko-to (2 and 6.4 g/kg each) following an overnight fast, and no signs of mortality were noticed [36].

Baicalein and baicalin are two bioactive compounds found in *Scutellaria baicalensis*, commonly known as Chinese skullcap or Baikal skullcap. Baicalein is a flavone, a type of plant pigment found in many herbs and fruits. It is well-known for having anti-inflammatory and antioxidant qualities. According to research, baicalein may provide several possible health advantages, including anti-inflammatory, anti-cancer, and neuro-protective properties. Baicalin is a glycoside, which indicates that it is a substance with a flavone (baicalein) and a sugar molecule (glucose). It is common to find this glycoside form in *Scutellaria baicalensis*. The above substances are some of the main ingredients of *Scutellaria baicalensis*, with possible therapeutic benefits.

Mechanisms of action

Baicalin and baicalein were both shown to have an inhibiting impact on variety of cellular DNA and RNA polymerases, which is thought to be the way of these drugs anti-HIV-1

activity [37]. Baicalein may also inhibit HIV-1 reverse transcriptase function by preventing viral RNA from the active site. Baicalein demonstrated competitive inhibition towards both HIV-1 reverse transcriptase and murine leukemia virus (MLV), displayed in mixed-type inhibition [38]. Baicalin does not inhibit the reverse transcriptases of murine leukemia virus or HIV-2. Also, Baicalin does not affect OKT4A mAb's ability to bind to CD4+'s gp120 binding site or its ability to bind to CD4 in general. This firmly invalidates the hypothesis that baicalin affects the viral adsorption phase (step 1 of the replicative cycle). It was discovered that flavonoids, such as gardenin, myricetin, and baicalein, block HIV-1 protease. Gardenin IC50 value of 11 M was outperformed by baicalein LC50 value of 480 M by a factor of almost 44 [39].

Effects of baicalein and baicalin

The impact of baicalein on different reverse transcriptases' activity was observed. Baicalein was shown to block 90% of MLV reverse transcriptase activity at 1 g/ml of the concentration, and 90% of HIV reverse transcriptase activity at 2 g/ml of the concentration [40]. It was reported that baicalin from *Scutellaria baicalensis* had an IC_{50} value of 22 M and inhibited HIV reverse transcriptase. According to certain pharmacological test results, the expression of HIV-1-specific core antigen p24, concentrated syncytium development on CEM-SS mono-layer cells, and a decrease in the activity of retroviral reverse transcriptase in H9 cells infected with HIV-1 were quantified and observed. The decrease in reverse transcriptase activity occurred non-competitively. Baicalin and its derivative 5, 6-dihydroxy-7-glucuronic acid were similarly effective in inhibiting the reverse transcriptase of other retro-viruses [41]. Baicalein and baicalin's differences in HIV-1 reverse transcriptase inhibitory activity have been studied. According to the findings, baicalein had four times inhibitory effect of baicalin against HIV-1 reverse transcriptase [42]. In another report, baicalein's IC_{50} value for inhibiting HIV integrase was 4.3 [43]. A recently published study on baicalin's metabolism demonstrated results of comparing the final metabolite's retention time in electrospray ionization mass spectra (ESI-MS)/MS, and outcomes of comparing baicalin with a genuine sample using HPLC (high-performance liquid chromatography), and revealed that baicalin was first converted into baicalein [44].

Hypoxis hemerocallidea

The common names of *Hypoxis hemerocallidea* include sterretjie, Afrika patat (Afr.), African potato (English), magic muthi, yellow stars, star lilies, inkomfe, ilabatheka, sterblom, gifbol, lotsane, and molikharatsa [45].

The *Hypoxidaceae* family includes the well-known genus *Hypoxis*, and it is easily recognized by its bright yellow strap-like leaves and star-shaped blooms. Throughout Africa, it has been used for remedial purposes for a long time. Presently, *Hypoxis* is being utilized as an immunostimulant by primary healthcare providers in South Africa for HIV/AIDS-positive individuals [46]. Two species in the genus, *H. colchicifolia* and *H. hemerocallidea*, are particularly used as ingredients for herbal teas, tinctures, and traditional African medicines. Zulu traditional healers have historically employed the rootstocks of this plant to treat internal tumors, heart weakness, urinary infections, and neurological disorders [47]. The plant is also associated with potential uses in cancer, mild prostatic hypertrophy, and hyperglycemia, although evidence supporting these claims is uncertain. *H. hemerocallidea* corms are utilized for the treatment of immune-related conditions, such as HIV, flu, arthritis, cold, and cancer [48]. Hypoxis preparations are being sold in South Africa as a medication that can benefit those with HIV/AIDS by enhancing their immunity. This claim has received backing from several websites, well-known periodicals, and even the Health Ministry of South Africa. Despite the lack of supporting data, many Africans declare that consuming the root of *H. hemerocallidea* has health benefits [49].

Chemical ingredients

Hypoxoside (Figure 2A) is a nor-lignan glycoside that, after entering the human gastrointestinal system, is a key component of the plant, and easily transforms into aglycone, rooperol (Figure 2B), a physiologically active substance with potential therapeutic benefits [50]. Additionally, the plant has several sterols, such as sitosterol and stigmasterol (Figure 2C), along with its sterolins, which have been demonstrated to have substantial biological action. Moreover, it contains stanols-like sitostanol, also known as stigmastanol and sterolin glycosides-like sitosterol glycoside [45].

Sutherlandia frutescens

Sutherlandia frutescens is also known as cancer bush, kankerbos, kankerbossie, insiswa, unwele, mukakana, phetola, and lerumo-lamadi [51]. *Sutherlandia frutescens* is a flowering shrub related to *Fabaceae* family, and the genus is *Sutherlandia*. *Sutherlandia*'s 9 mg/kg/day therapeutic dosage for people is advised. This herb has been used to treat various conditions, such as cancer, HIV infection, diabetes, peptic ulcers, gastritis, reflux esophagitis, rheumatoid arthritis, chronic fatigue syndrome, and menopausal symptoms [52]. There is not much information in the scientific literature about how *Sutherlandia* affects the immune system. The plant's ability to scavenge superoxide and hydrogen peroxide in hot water extracts may be responsible for the plant's anti-inflammatory effects. Even though there was no obvious antioxidant activity in several human tumor cell lines, it was revealed that ethanolic extracts have an anti-proliferative effect [53]. The efficacy of this plant in treating HIV/AIDS has been investigated using both the encapsulated and powdered forms of *Sutherlandia frutescens*.

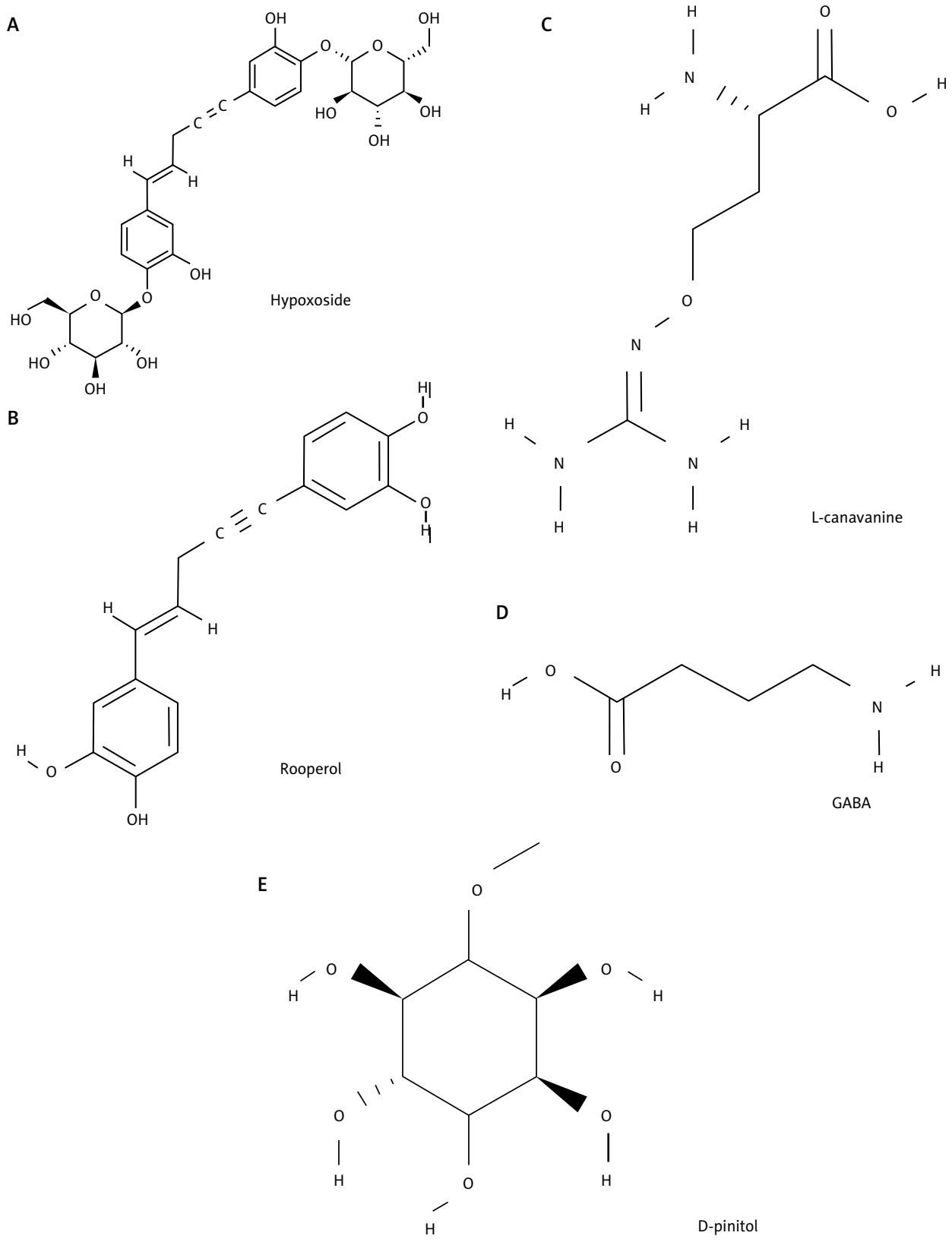

Figure 2. (**A**) Hypoxoside. (**B**) Aglycone, rooperol. (**C**) L-canavanine. (**D**) GABA. (**E**) D-pinitol

Chemical ingredients

L-canavanine (Figure 2C), GABA (Figure 2D), and D-pinitol (Figure 2E) are three of the main components of *Sutherlandia frutescens*, which are thought to be active. An alternative structural form of L-arginine L-canavanine is L-2-amino-4-guanidinooxy, a non-protein amino acid. Approximately 30-40 mg of L-canavanine are present in of *S. frutescens* leaf. A chiro-inositol, D-pinitol, which may be found in many different kinds of legumes, is a form of sugar [54], with inhibitory neuro-transmitter (GABA) as well as amino acid. *In vitro*, the destruction of 95% of HIV-infected cells was reported in a US study in 1988. Unfortunately, no more research investigating the impact of this plant on HIV has verified this assertion. Although there is limited data, in order to destroy cancer cells and AIDS, D-pinitol has been recommended, a significant component of *S. frutescens* [55].

The role of conventional remedies in the advancement of anti-HIV drugs

The use of conventional therapies in the treatment of HIV/AIDS focuses on three primary areas, i.e., direct impact on the virus, stimulation of the immune system, and treatment of opportunistic infections [56]. Through random screening or conventional medical practices, numerous plant species have been discovered to disrupt various stages of the viral life cycle. Some examples include substances, which hinder reverse transcription, viral attachment, fusion with cells, and proteolytic cleavage [57]. Two conventional medications, *Aspilia pluriseta* (ASPILIA. pluriseta) from *Asteraceae* family, and *Rumex bequaertii* from *Polygonaceae* family, have shown effectiveness against HIV [58]. Research focusing on plants used in traditional remedies from different countries has revealed promising anti-HIV properties. Calanolide A has demonstrated efficiency against several mutations, which are resistant to NNRTIs, such as the very resistant Y181C mutation, and even nucleoside analogue-resistant clinical virus isolates have displayed sensitivities to its antiviral activities [59]. In laboratory tests, Calanolide A has also exhibited a synergistic effect when combined with other anti-HIV medications. Phase III clinical trials for such medication, developed by Sarawak MediChem Pharmaceutical Inc., are currently underway [60]. *Lobostemon trigonu* and *Sutherlandia frutescens* are plants both sold in South Africa, believed to have curative properties for HIV/AIDS patients. A recent research has indicated that these plants possess inhibitory effects on HIV-1 reverse transcriptase activity [61]. Clinicians using *Sutherlandia* pills observed increases in CD4+ counts and decreases in viral loads of HIV-positive patients. Furthermore, *Sutherlandia* reportedly can induce apoptosis in human cancer cell lines [62].

Conclusions

Herbal remedies have the potential to be included in HIV/AIDS treatment as a complementary therapy. Further studies are needed to determine their possible antiviral and immunomodulatory effects. However, to determine their efficacy, safety, and best use in conjunction with conventional antiretroviral medication, rigorous trials are required. To produce evidence-based recommendations and include herbal treatments in comprehensive HIV/AIDS therapy, traditional medicine systems and contemporary medical practices must work together. Despite the potential of herbal medicines as HIV/AIDS medications, collaborative efforts and clinical trials are required to determine their place further in all-encompassing care and treatment regimens.

Future prospectives

Although there is beneficial potential of herbal remedies to cure HIV/AIDS in the future, it will require coordinated efforts from the scientific community and healthcare. Key areas for further research are proposed as follows:

- Consistency in herbal treatments' composition, efficacy, and safety will be ensured through the development of standardized methods for the manufacturing, quality control, and regulation of herbal products.
- Mechanistic research: Additional investigations are required to fully comprehend the mechanisms of action of herbal HIV therapies, including their effects on viral replication, immunological response, and possible interactions with antiretroviral medicines.
- Trials: The efficient use of herbal medicines in HIV/AIDS treatment will be demonstrated by conducting well-designed clinical studies, which conform to strict scientific criteria.
- Herb-drug interactions: To prevent negative effects and guarantee the best possible treatment results, it is crucial to investigate any possible interaction between herbal treatments and antiretroviral medications.

Disclosures

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3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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