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HERBAL ANTIVIRALS: AN OVERVIEW

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ABSTRACT

Medicinal plants have long been employed in traditional medicine to treat viral infections, offering a rich source of chemically diverse compounds with potential therapeutic value. Interest in herbal antivirals has grown in recent years, particularly in the context of emerging infectious diseases and the limitations of current antiviral drugs. However, the transition of these remedies into evidence-based medicine is far from straightforward. Major challenges include variability in phytochemical content due to differences in cultivation, harvest seasons and processing methods, as well as safety concerns such as possible herb-drug interactions. The absence of validated analytical methods and robust pharmacological testing further complicates quality assurance. At the research level, progress is constrained by a lack of well-designed, large-scale clinical trials and by regulatory frameworks that are not fully adapted to the complexity of botanical mixtures. At the same time, important translational opportunities are emerging. Herbal antivirals may serve as valuable adjuncts to conventional therapies, providing complementary mechanisms of action and enhancing clinical outcomes. Advances in artificial intelligence, bioinformatics and network pharmacology are also opening new avenues for predicting plant–virus interactions and accelerating the discovery process. Moving forward, multidisciplinary collaboration between ethnobotanists, virologists and pharmaceutical scientists is essential, along with harmonized regulatory standards and investment in research infrastructure. With balanced attention to both potential and limitations, herbal antivirals can progress from traditional knowledge to scientifically validated contributions in global health.

KEYWORDS

Herbal antivirals, Phytochemical variability, Standardization, Clinical trials, Regulatory challenges, Drug–herb interactions, Bioinformatics and Multidisciplinary collaboration.

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INTRODUCTION

Viruses and the Need for Alternative Therapeutics

Global Burden of Viral Diseases

Viral infections continue to represent one of the foremost challenges to global health, exerting a

profound impact on populations across every continent. Unlike many bacterial diseases that can be effectively managed with antibiotics, viral infections often lack definitive cures and rely heavily on supportive care or prevention through vaccination. This gap in treatment options makes viral diseases a persistent source of morbidity and mortality. The global burden can be appreciated by examining specific case examples: HIV remains a lifelong condition requiring constant therapy, hepatitis B and C contribute significantly to liver-related deaths worldwide, and influenza causes seasonal epidemics that strain healthcare systems annually. In addition, viral oncogenesis-where persistent infections such as human papillomavirus (HPV), Epstein-Barr virus (EBV) and hepatitis viruses drive cancer development-adds another layer of complexity by linking viral burden to chronic diseases and malignancies[1,2].

Beyond these established threats, emerging and re-emerging viruses have become a hallmark of the 21st century. Outbreaks of Ebola in Africa, Nipah virus in South Asia, Zika in the Americas, and the global spread of SARS-CoV-2 highlight the unpredictable nature of viral emergence. Contributing factors include climate change, urbanization, migration, deforestation, and the ease of modern travel, all of which enable rapid transmission of novel pathogens. The social and economic costs of these outbreaks are immense. For example, the COVID-19 pandemic not only caused millions of deaths but also disrupted global economies, education and social structures, underlining the multifaceted impact of viral diseases.

It is also important to recognize that viral infections disproportionately affect vulnerable populations. Infants, the elderly, immunocompromised individuals, and those in resource-limited regions suffer the most severe consequences. In many low- and middle-income countries, where healthcare infrastructure is inadequate, viral infections such as rotavirus-induced diarrhea, measles and dengue continue to claim countless lives. Together, these factors illustrate that viral diseases remain one of the most significant public health burdens, and the need for more effective, accessible, and adaptable treatment options has never been greater[3,4].

Shortcomings of Current Synthetic Antivirals

The development of antiviral drugs marked a turning point in medicine, offering targeted therapies for conditions that were once fatal or untreatable. Agents such as acyclovir for herpesviruses, zidovudine for HIV, and direct-acting antivirals for hepatitis C have dramatically improved survival rates and quality of life for millions of patients. However, despite these advances, synthetic antivirals are far from perfect and face serious limitations. Perhaps the most pressing issue is the ability of viruses to rapidly develop resistance. Due to their high replication rates and error-prone polymerases, viruses accumulate mutations at a remarkable pace. These mutations can confer resistance to even the most potent drugs, as has been observed in influenza with resistance to neuraminidase inhibitors, or in HIV where multiple drug classes may fail due to viral evolution. Resistance undermines therapeutic efficacy, necessitating the constant development of new compounds, which is both time-consuming and costly[5].

Cost is another major obstacle in antiviral therapy. While high-income countries may afford the latest medications, access remains severely restricted in resource-limited settings. For example, the introduction of curative regimens for hepatitis C initially cost thousands of dollars per course, making them unattainable for the very populations most in need. Even today, the economic burden of lifelong therapy for HIV places immense strain on healthcare systems in developing nations. Without global initiatives to reduce costs and improve access, these disparities perpetuate cycles of illness and poverty[6].

Toxicity and adverse effects further complicate the long-term use of antivirals. Many nucleoside analogues can cause mitochondrial toxicity, bone marrow suppression, or renal impairment. Protease inhibitors used in HIV therapy are associated with metabolic syndromes, including lipodystrophy and

dyslipidemia, which increase cardiovascular risk. These side effects often limit adherence, reduce quality of life, and may require additional supportive therapies. In the case of chronic infections, patients are exposed to these toxicities for decades, compounding their long-term health risks.

Collectively, these shortcomings reveal a paradox: while synthetic antivirals are powerful tools, their real-world utility is constrained by resistance, cost, and toxicity. As a result, there is a growing recognition that alternative or complementary therapeutic approaches are urgently required to broaden the arsenal against viral diseases[7,8].

Renewed Scientific Interest in Botanicals as a Therapeutic Reservoir

In the face of the challenges posed by synthetic antivirals, natural products and botanicals are gaining renewed scientific attention as promising alternatives or adjuncts. Plants have been used in traditional medicine for centuries to treat fevers, respiratory infections, and skin ailments-many of which are now understood to have viral origins. The empirical knowledge passed down through Ayurveda, Traditional Chinese Medicine, Unani, and other ethnomedical systems provides a vast reservoir of leads for modern pharmacological exploration. Unlike single-target synthetic drugs, botanical preparations often contain complex mixtures of phytochemicals that can act synergistically, producing broad-spectrum antiviral effects and reducing the likelihood of resistance[9].

Research has already identified numerous plant-derived compounds with demonstrated antiviral properties. Flavonoids, terpenoids, alkaloids, tannins, and saponins have shown activity against a wide array of viruses, including influenza, herpes simplex, hepatitis, HIV, and coronaviruses. Some of these compounds inhibit viral entry into host cells, others interfere with replication or protein synthesis, and still others enhance host immune responses. This multiplicity of mechanisms highlights the potential advantage of botanicals over narrowly focused synthetic agents. Furthermore, plants offer an accessible and renewable resource, particularly relevant for low- and middle-income countries where pharmaceutical access is limited[10].

The recent resurgence of interest in botanicals is not merely anecdotal; it is supported by scientific advances in pharmacognosy, biotechnology and drug delivery systems. Techniques such as high-throughput screening, bioinformatics, and molecular docking are being applied to evaluate phytochemicals systematically. Additionally, modern formulation strategies-such as incorporating herbal extracts into nanoparticles, liposomes, or niosomes-are being investigated to enhance bioavailability and therapeutic efficacy. These approaches bridge traditional medicine with modern science, providing a rational framework for the development of safe, effective, and standardized herbal antivirals[11].

Of course, the potential of botanicals is not without challenges. Issues of standardization, quality control, and safety must be addressed through rigorous pharmacological and clinical studies. Nevertheless, the growing body of evidence suggests that botanicals represent an invaluable therapeutic reservoir. As viral threats continue to evolve and test the limits of synthetic antivirals, plant-derived agents are emerging as vital candidates in the ongoing search for sustainable and globally accessible antiviral therapies[12].

Historical Roots and Ethnomedicinal Evidence

Traditional Systems (Ayurveda, TCM, Unani, Folk Medicine)

The development of traditional medicine reflects humanity's earliest efforts to understand and respond to illness through observation, experience, and symbolic interpretation of the natural world. In the Indian subcontinent, Ayurveda emerged as an organized medical tradition at least two millennia ago, although oral transmission of remedies predates the classical texts. Its central doctrine emphasized that health depends on maintaining equilibrium among three governing principles, the *doshas-vata* (air and movement), *pitta* (fire and metabolism) and *kapha* (water and structure). When epidemic fevers or respiratory disorders struck, physicians (vaidyas) classified these as disruptions

in *pitta* and *kapha* and employed herbs to restore harmony. Plants like *Tulsi* (*Ocimum sanctum*), *Guduchi* (*Tinospora cordifolia*), and *Neem* (*Azadirachta indica*) became indispensable in managing fevers, throat infections, and skin eruptions. Remedies were not purely curative; many were taken as *rasayana* (rejuvenators) intended to fortify the body against future outbreaks, suggesting an early recognition of preventive medicine[13,14].

In Traditional Chinese Medicine (TCM), which traces its mythology to the Divine Farmer Shen Nong, herbal knowledge was framed through the cosmological principles of yin-yang and the Five Phases (wood, fire, earth, metal, water). Epidemic and febrile illnesses were understood as invasions of external pathogenic forces such as "wind-heat" or "damp-heat". Treatments were designed to expel these evils while simultaneously strengthening the vital energy, *qi*. During outbreaks resembling influenza, classical physicians prescribed combinations of herbs including *Isatis root* (*Ban Lan Gen*), *Honeysuckle* (*Jin Yin Hua*), and *Forsythia* (*Lian Qiao*). These plants were said to clear heat and resolve toxicity, a concept that mirrors modern ideas of antiviral and anti-inflammatory activity. Unlike Western pharmacology, which privileges reductionist explanations, TCM incorporated dietary adjustments, breathing exercises, and acupuncture alongside herbal prescriptions, providing a holistic framework for epidemic control[15,16].

Unani medicine, derived from Greco-Arabic traditions, reached its maturity under the influence of Persian and Arab scholars such as Avicenna (Ibn Sina). Rooted in the humoral theory of Hippocrates and Galen, Unani classified illness as imbalances of blood, phlegm, yellow bile and black bile. Epidemic fevers were interpreted as "humoral excess of heat" and remedies emphasized cooling, demulcent and detoxifying qualities. Herbal preparations using *Viola odorata* (banafsha), *Coriander seeds* (*Coriandrum sativum*), and *Rose petals* were common prescriptions for patients with cough, sore throat and fever. When transplanted to South Asia, Unani medicine absorbed local plants from Ayurveda and folk practices, producing a hybrid pharmacopoeia where Mediterranean species coexisted with Indian botanicals[17,18].

Meanwhile, folk medicine-the everyday knowledge of villagers, midwives and shamans-remained a critical layer of healing traditions. Unlike codified systems, folk remedies relied on empirical trial-and-error, often bound to ritual practices or seasonal cycles. During epidemic outbreaks, people turned to simple yet widely available plants: neem leaves were hung at doorways to ward off "bad air," garlic was chewed raw for its protective effect and decoctions of ginger and black pepper were consumed to relieve fever and chills. These practices, while framed within local cosmologies of contagion and spirit affliction, in many cases aligned with pharmacological activities later confirmed by modern science.

Together, Ayurveda, TCM, Unani and folk traditions formed overlapping yet distinct frameworks of medical reasoning. Each identified viral-like syndromes centuries before the concept of viruses was articulated, and each built extensive pharmacopoeias through accumulated clinical experience. Their persistence into the present attests to their practical utility and cultural authority.

Examples of Plants Long Associated with Viral Ailments

One of the most striking features across traditional systems is the consistent identification of certain plants as remedies for fevers, respiratory illnesses, and epidemic outbreaks-conditions now understood as viral in origin. In India, Tulsi (Ocimum sanctum) was hailed as a sacred plant with both spiritual and medicinal significance. Its leaves were chewed fresh, brewed into teas, or burned as fumigants during epidemics. In *Indian Materia Medica*, Tulsi is described as a febrifuge, expectorant, and immune supporter, employed for conditions ranging from influenza-like illness to chronic bronchitis. Equally valued was Guduchi (*Tinospora cordifolia*), named "Amrita" or nectar of immortality, which was prescribed for persistent fevers, jaundice, and convalescence after infectious diseases. Its reputation as an immunomodulator has led to

modern studies on its antiviral and hepatoprotective effects.

In China, Isatis root (Ban Lan Gen, Isatis tinctoria) gained prominence during dynastic epidemics. Physicians considered it indispensable for sore throat, swollen glands, and febrile illnesses. Similarly, Honeysuckle (Lonicera japonica) became part of the classic formula *Yin Qiao San*, still prescribed for influenza, common cold, and viral sore throat. Honeysuckle flowers were classified as "cold" in nature, able to counteract "heat toxins," aligning well with its observed anti-inflammatory and antimicrobial actions. Another widely used TCM herb, Forsythia fruit (Lian Qiao), was paired with honeysuckle to create a synergistic effect against epidemic heat diseases.

Plants that transcend cultural boundaries illustrate the convergent wisdom of ethnomedicine. Garlic (Allium sativum) is a prime example: used in folk medicine across Asia, Europe and the Middle East, it was consumed raw, crushed into tonics, or infused in oils as a preventive measure against epidemics. Its pungent odor was believed to repel "miasmas," yet its modern recognition as a broad-spectrum antimicrobial validates the tradition. Licorice root (Glycyrrhiza glabra), another trans-cultural herb, was described in both TCM and Unani texts. In TCM it harmonized complex formulas and soothed inflamed throats, while in Unani it was a demulcent for respiratory infections. Contemporary studies highlight its active compound, glycyrrhizin, which shows antiviral properties against hepatitis viruses.

Indian folk medicine also emphasized Neem (Azadirachta indica), whose bitter leaves were used in decoctions to lower fever and purify blood during outbreaks. Beyond ingestion, neem twigs and smoke were employed for environmental cleansing. Black pepper (Piper nigrum) and ginger (Zingiber officinale) were likewise household remedies for colds and fevers, their pungency thought to stimulate circulation and expel phlegm.

Taken together, these examples reveal a mosaic of plant remedies that span geography yet converge in application. They illustrate how different cultures, observing patterns of disease and recovery, arrived at parallel solutions. This convergence suggests that ethnomedicine was not arbitrary but grounded in empirical evidence accumulated over centuries. Many of these plants remain in use today, either as home remedies or as leads for modern pharmaceutical research.

Lessons Modern Pharmacology Can Draw from Traditional Wisdom

Contemporary pharmacology often relies on high-throughput screening of isolated compounds, yet traditional systems demonstrate alternative pathways for drug discovery and health maintenance. One crucial lesson is the value of polyherbal synergy. While modern medicine tends to prioritize single active ingredients, Ayurveda and TCM routinely prescribed complex formulations where multiple plants were combined to balance actions and reduce toxicity. For instance, Chinese epidemic prescriptions combining honeysuckle, forsythia and isatis aimed to clear heat, detoxify, and strengthen defenses simultaneously. This mirrors today's combination therapies for HIV and hepatitis, where multiple agents work together to suppress viral replication and prevent resistance.

Another important insight is the preventive orientation of traditional medicine. Ayurveda classified plants like Tulsi, Guduchi and Amla as *rasayana*-agents that enhanced resilience and prolonged life. These were consumed daily, not only in illness but also as tonics to prepare the body for future challenges. In TCM, tonic herbs such as ginseng and astragalus were prescribed to fortify *qi*, ensuring that pathogenic factors would have less opportunity to invade. Unani medicine similarly recommended seasonal regimens, diets, and herbal tonics to balance humors and ward off fevers. This preventive ethos is increasingly relevant as modern pharmacology shifts from reactive treatment to proactive health maintenance through immunomodulators, vaccines and functional foods.

Traditional medicine also teaches the integration of diet, lifestyle and environment into health management. Classical Chinese physicians blurred the line between food and medicine, prescribing dietary adjustments based on the patient's

constitution and season. Ayurvedic texts similarly emphasized that improper diet was a root cause of many fevers, while corrective foods could restore balance. Such integration anticipates today's interest in nutraceuticals and diet-based interventions for viral and metabolic diseases.

Finally, ethnomedicine underscores the importance of biocultural diversity as a source of pharmacological innovation. The persistence of local knowledge, often dismissed as superstition, has in fact guided the discovery of valuable molecules. Neem, Tulsi, Isatis and licorice are only a few among thousands of species catalogued in ancient pharmacopeias. Their continued study could yield antiviral, anti-inflammatory and immunomodulatory compounds at a time when viral pandemics pose global threats.

Equally important is the recognition of contextual healing-the role of belief, ritual, and community support in recovery. Placebo research today acknowledges that expectation and cultural meaning can modulate immune response. Ancient physicians integrated this psychosocial dimension into their practice, whether through Ayurvedic rituals, Taoist dietary rules, or Unani humoral regimens. Pharmacology can benefit from embracing this broader understanding of healing, moving beyond molecules to holistic well-being.

In summary, modern pharmacology can learn not only about specific plant compounds but also about systems-level approaches from traditional medicine. These include polyherbal synergy, preventive orientation, dietary integration, ecological diversity, and psychosocial context. Rather than dismissing ancient knowledge as outdated, contemporary science can view it as an evolving archive-one that continues to inspire innovative strategies against viral diseases.

Plant-Derived Bioactive Molecules with Antiviral Promise

Flavonoids

Flavonoids form one of the most widely distributed groups of secondary metabolites in plants, and their role in traditional medicine has been recognized for centuries. In Ayurveda, flavonoid-rich plants like *Ocimum sanctum* (Tulsi), *Tinospora cordifolia* (Guduchi) and *Phyllanthus emblica* (Amla) were praised as *rasayana*, substances that rejuvenate the body and protect against recurrent fevers. Tulsi in particular was brewed as an infusion to relieve cough, colds, and fevers, and its aromatic, bitter principles-now understood to contain flavonoids like apigenin and luteolin-were considered to "lighten kapha" and clear obstructions in respiration. Similarly, in TCM, honeysuckle (*Lonicera japonica*) and forsythia (*Forsythia suspensa*)-both rich in flavonoids-were central to epidemic formulas like *Yin Qiao San*, prescribed for fever, sore throat, and influenza-like outbreaks[19].

Modern pharmacological insights shed light on why these traditions emphasized flavonoids for epidemic disorders. Many flavonoids can interact directly with viral proteins, including enzymes responsible for replication. Quercetin, luteolin and baicalein, for example, have been shown to inhibit viral polymerases and proteases, thereby halting viral propagation. In addition, flavonoids often act at the host level: They stabilize cellular membranes, reduce oxidative stress through free radical scavenging and modulate signaling cascades like NF-κB and MAPK, which are central to inflammatory and antiviral responses. This dual activity-direct action on the virus and indirect support of host defenses-explains their broad efficacy across diverse viral syndromes.

Another noteworthy property is their ability to inhibit viral entry by blocking the binding of viral surface proteins to host cell receptors. This effect is relevant to both influenza and coronaviruses, where entry mechanisms are critical for infection. Thus, the empirical wisdom of using flavonoid-rich plants in epidemic fevers reflects a mechanism-based rationale that contemporary science continues to validate[20].

Terpenes

Terpenes are the largest class of plant secondary metabolites and are chiefly responsible for the aromatic qualities of medicinal herbs. Traditional systems often emphasized the inhalation or fumigation of terpene-rich plants during outbreaks,

suggesting an early recognition of their volatility and rapid action at respiratory surfaces. In Ayurveda, plants like Tulsi, camphor (*Cinnamomum camphora*), and eucalyptus-like species were commonly burned or brewed for inhalation to purify the air and relieve respiratory congestion. TCM made extensive use of *Artemisia* (qing hao) and aromatic barks like cinnamon (*Rou Gui*), where their terpene fractions contributed to dispersing external pathogens described as "wind-cold" or "wind-heat".

Pharmacologically, terpenes exert antiviral effects in multiple ways. Due to their lipophilic nature, they readily partition into viral envelopes, causing destabilization and preventing the virus from fusing with host membranes. Monoterpenes such as cineole, thymol, and menthol display these properties, disrupting viral integrity at the mucosal surface. Sesquiterpenes, on the other hand, often interfere with replication by inhibiting viral polymerases. Beyond direct virucidal action, terpenes influence host immunity. Some activate interferon signaling pathways, enhancing innate antiviral responses, while others modulate cytokine production to balance pro- and anti-inflammatory processes[21].

The traditional use of terpene-rich fumigants also aligns with their antimicrobial and antiviral volatility. Inhaling aromatic vapors could expose mucosal surfaces to active terpenes, creating an immediate protective environment. This may explain why practices like burning camphor or frankincense during epidemics were observed across multiple cultures, ranging from India to China and the Middle East. Thus, terpenes exemplify how traditional sensory cues-aroma, pungency-were linked to therapeutic value, anticipating their biochemical relevance to viral defense[22].

Tannins

Tannins, polyphenolic compounds responsible for the astringency of many barks, seeds, and fruits, were historically associated with purifying and contracting properties. In *Indian Materia Medica*, tannin-rich plants like *Terminalia chebula*, *Terminalia bellirica* and *Emblica officinalis*-the three constituents of the famed Ayurvedic formulation *Triphala*-were recommended not only for digestive regulation but also for chronic fevers, throat ailments and epidemic disorders. The astringency was interpreted as an ability to "tighten tissues" and reduce excessive discharges, including those seen in febrile states with diarrhea or respiratory secretions.

Chinese medicine also valued tannin-bearing materials, such as gallnuts and pomegranate rind, particularly in the treatment of dysenteric and febrile epidemics. These were prescribed to "clear heat" and "astringe leakage," concepts that align with tannins' protein-precipitating properties. Modern understanding suggests that tannins' ability to precipitate proteins may directly inactivate viral enzymes or coat viral surface proteins, preventing them from binding to host receptors. Some tannins form complexes with viral capsids, effectively neutralizing them before entry. Furthermore, tannins possess potent antioxidant properties, reducing oxidative damage caused by viral infections and they contribute to mucosal defense by strengthening epithelial barriers. This multifaceted activity-antiviral, antioxidant and barrier-protective-explains their widespread use across epidemic conditions.

The longevity of tannin-rich remedies like *Triphala* also underscores their role in maintaining long-term resilience, suggesting a preventive as well as curative dimension. By improving gut health and immunity, tannin-based therapies may have indirectly bolstered resistance to viral illnesses[23].

Alkaloids

Alkaloids, nitrogen-containing compounds, are among the most potent natural molecules and were historically approached with caution due to their narrow therapeutic index. In Ayurveda, plants like *Datura* and *Rauwolfia* were known for their strong alkaloid content and prescribed sparingly for respiratory distress or fevers, always with careful dosing due to toxicity. In TCM, *Ephedra sinica* (Ma Huang) was a prominent alkaloid-bearing herb used to "release the exterior" in cases of cold and flu. Its

ephedrine alkaloids dilated bronchi and alleviated wheezing, making it indispensable for respiratory infections.

Pharmacologically, alkaloids interact with viral processes through several mechanisms. Some intercalate into viral nucleic acids, disrupting replication. Others inhibit viral polymerases or proteases, enzymes critical for viral propagation. A subset of alkaloids alters the acidic environment within endosomes, blocking viral uncoating and entry into host cells. These mechanisms highlight their potential as direct antivirals. At the same time, alkaloids often have systemic effects on neurotransmission and vascular tone, which can indirectly support immune resilience.

The dual-edged nature of alkaloids-potent activity but possible toxicity-explains their selective use in traditional medicine. Their effectiveness in acute situations like severe asthma or epidemic fevers justified their inclusion, but their administration was carefully supervised. For modern pharmacology, alkaloids remain important antiviral leads, though their safety profile demands refinement through isolation, derivatization, or controlled dosing[24].

Saponins

Saponins, glycosidic compounds characterized by their foaming action, occupy a special place in both Ayurvedic and Chinese traditions. In Ayurveda, *Sapindus* (soapnut) and licorice (*Glycyrrhiza glabra*) were recognized for their cleansing properties, both internally and externally. Soapnut extracts were used to wash and purify, while licorice was prescribed for sore throat, cough, and fever. In TCM, licorice (*Gan Cao*) became one of the most frequently used herbs, often included in formulations not only for its sweet harmonizing taste but also for its immunomodulatory and soothing properties.

At the biochemical level, saponins exert antiviral effects by disrupting lipid membranes. Viral envelopes, rich in cholesterol and phospholipids, are particularly susceptible. Saponins can insert into these membranes, destabilizing them and preventing viral fusion with host cells. Beyond direct virucidal activity, saponins are known for their capacity to stimulate immune responses. They enhance macrophage activation, cytokine release, and antibody production, properties that have led to their use as vaccine adjuvants in modern biomedical applications.

This dual action-directly targeting viral envelopes while boosting host immunity-makes saponins unique among phytochemicals. The long-standing use of licorice across both Indian and Chinese traditions for respiratory infections highlights how empirical knowledge anticipated these pharmacological properties. Moreover, their inclusion in complex formulations ensured that their activity was balanced by other plant constituents, reducing potential irritation while enhancing therapeutic benefit[25].

Synergistic Phytochemical Effects versus Single-Compound Activity

A defining characteristic of ethnomedicine is its reliance on synergy rather than singularity. Unlike modern pharmacology, which often isolates a single molecule for therapeutic use, traditional systems consistently employed multi-component formulations. This approach recognized that plants themselves contain a diversity of phytochemicals-flavonoids, terpenes, tannins, alkaloids and saponins-that work in concert.

For example, Tulsi contains flavonoids (antioxidant, antiviral), terpenes (aromatic, antimicrobial), and saponins (immune-stimulating). Licorice combines flavonoids, saponins, and triterpenes, making it both antiviral and anti-inflammatory. In practice, traditional physicians further combined multiple herbs. TCM's *Yin Qiao San*, uniting honeysuckle, forsythia, and licorice, exemplifies this philosophy. Ayurveda's *Triphala*, with tannin-rich fruits, synergizes digestive and immune benefits. These formulations often achieved effects greater than the sum of their parts, a phenomenon modern science refers to as "polypharmacology".

Synergy occurs because different classes of phytochemicals target different stages of the viral cycle. Flavonoids may inhibit viral entry, alkaloids block replication, saponins destabilize envelopes, while terpenes and tannins modulate host immunity

and oxidative stress. Together, they create a multi-pronged defense, making viral escape less likely. Moreover, supportive actions like reducing inflammation and strengthening mucosal barriers contribute to faster recovery.

The traditional emphasis on mixtures also minimized toxicity. For instance, the harshness of alkaloids could be softened by the soothing effects of mucilaginous or sweet herbs. This balancing principle ensured safety while preserving efficacy. Modern pharmacology increasingly recognizes the value of this strategy, with growing interest in multi-target therapeutics and combination therapies.

Thus, the ethnomedical approach to plant-derived bioactive molecules offers two lessons: that synergy enhances antiviral activity beyond what single compounds achieve and that a holistic balance of efficacy and safety is achievable when diverse phytochemicals act together.

Mechanistic Pathways of Herbal Antivirals

Blocking Viral Entry or Attachment[26,27]

The first and perhaps most critical point of viral infection is the interaction between viral surface proteins and host cell receptors. If this step is disrupted, the infection cascade cannot proceed. Many traditional remedies implicitly recognized this principle, even if they lacked the molecular vocabulary. In Ayurveda, fumigation with aromatic herbs such as camphor or Tulsi was a standard practice during outbreaks, reflecting an awareness that the initial "contact" between the pathogen and host could be hindered by plant volatiles. Similarly, in Chinese medicine, honeysuckle (*Jin Yin Hua*) and forsythia (*Lian Qiao*) were considered herbs that "expel external pathogens," a metaphor consistent with their ability to act at the early stages of viral invasion.

From a mechanistic perspective, plant-derived molecules interfere with viral entry in several ways. Polyphenolic compounds such as flavonoids and tannins can bind to viral glycoproteins, masking the ligands necessary for receptor recognition. This effect has been demonstrated with influenza hemagglutinin and HIV gp120, where plant polyphenols prevented the viral envelope from attaching to host cell receptors. Some alkaloids alter the electrostatic charge at the host cell membrane, disturbing viral docking. Saponins, by integrating into lipid bilayers, can increase membrane rigidity, reducing the likelihood of viral fusion. A classic example is glycyrrhizin from licorice (*Glycyrrhiza glabra*), which reduces the fluidity of viral envelopes and impairs their ability to merge with host cells.

Traditional use provides practical illustrations of these mechanisms. In *Indian Materia Medica*, neem (*Azadirachta indica*) leaves were chewed or applied in decoction to guard against fevers and "infectious air." Modern studies suggest that neem's polyphenols may block viral adhesion at mucosal surfaces. Similarly, garlic (*Allium sativum*) was consumed raw in folk medicine during influenza outbreaks; its organosulfur compounds are now known to interfere with viral entry proteins. These parallels highlight how ancient practices anticipated biochemical mechanisms that virology has since confirmed.

By blocking the earliest stages of infection, herbal antivirals create a preventive shield. This not only reduces viral load but also lowers the risk of systemic spread, demonstrating why so many traditional remedies were recommended for daily or seasonal use during epidemics.

Interference with Genome Replication or Protein Translation

Once inside the cell, a virus must replicate its genome and synthesize proteins to propagate. This intracellular phase provides another opportunity for herbal compounds to intervene. Traditional medicine often described these remedies as "cooling the fire" or "halting the spread" of illness, language that now corresponds with suppressing viral replication. In TCM, *Isatis root* (*Ban Lan Gen*) was prescribed for epidemic fevers; in Ayurveda, *Guduchi* (*Tinospora cordifolia*) was administered to reduce prolonged fever. Both plants contain alkaloids, flavonoids, and terpenes now known to act on molecular targets central to viral replication.

Mechanistically, flavonoids can directly inhibit viral RNA- and DNA-dependent polymerases by

occupying the catalytic site, effectively stalling genome duplication. Quercetin and luteolin, for example, demonstrate inhibition of viral polymerases in influenza and hepatitis viruses. Terpenes may intercalate into nucleic acids or disturb the replication complexes anchored to host membranes. Alkaloids such as berberine are reported to suppress reverse transcriptase activity, blocking retroviral replication. Beyond genome synthesis, herbal compounds also interfere with viral protein translation. Certain alkaloids inhibit ribosomal function or disrupt viral proteases, preventing the proper processing of viral polyproteins.

Saponins add another layer by affecting the membrane platforms where many viruses assemble their replication machinery. By disturbing lipid rafts, saponins hinder the formation of replication complexes. This is particularly important for enveloped viruses that rely on host membranes for budding and assembly.

Historically, the practical use of such plants reflected these properties. *Andrographis paniculata* (Kalmegh) was used in Ayurveda for fevers associated with epidemics. Modern research attributes this to diterpenoids that inhibit transcriptional activation pathways, effectively suppressing viral RNA production. In TCM, *Ma Huang* (Ephedra) was administered for influenza-like illness, with its alkaloids indirectly improving host clearance while also affecting viral replication environments.

Thus, interference with genome replication and protein synthesis exemplifies how herbal antivirals do not merely act at the cell surface but penetrate into the molecular heart of viral life cycles. This broad-spectrum mechanism is one reason many herbal compounds are active against multiple viral families.

Immunomodulatory and Anti-Inflammatory Roles

A distinguishing strength of herbal antivirals is their ability to modulate the host immune system rather than focusing solely on the pathogen. Ancient physicians in Ayurveda and TCM emphasized resilience (*ojas* in Sanskrit, *zheng qi* in Chinese) as the foundation for withstanding epidemics. Herbs like Tulsi, Amla, and Astragalus were valued not just for treating acute illness but for strengthening the "vital force" in advance.

Immunomodulation can take two complementary forms: enhancement of antiviral defenses and suppression of damaging inflammation. Many plant polysaccharides stimulate innate immunity by activating macrophages, natural killer cells, and dendritic cells. For example, polysaccharides from *Astragalus membranaceus* upregulate interferon production, priming cells to resist viral replication. Saponins from licorice and ginseng act as immune adjuvants, enhancing antibody production and adaptive immunity.

At the same time, unchecked inflammation can cause severe pathology, as seen in "cytokine storm" syndromes during viral infections like influenza or coronaviruses. Herbal compounds provide a balancing role here as well. Flavonoids such as baicalin and curcumin suppress NF-κB activation, reducing excessive pro-inflammatory cytokines like IL-6 and TNF-α. Glycyrrhizin from licorice reduces the recruitment of neutrophils and limits tissue damage in the lungs, a property long reflected in its traditional use for soothing coughs and sore throats.

Ayurvedic rasayana herbs such as Guduchi and Amla were recommended for convalescence after fevers, a recognition that immune restoration is as important as viral clearance. TCM similarly prescribed tonic formulas during recovery to rebuild *qi*. These practices mirror modern understanding of immunonutrition and recovery-phase immunomodulation.

Therefore, the immunomodulatory and anti-inflammatory actions of herbal antivirals demonstrate their systemic value: they not only suppress the virus but also restore the immune equilibrium, ensuring that the body's own defense does not become a source of damage. This two-way regulation may explain why herbal remedies often show fewer adverse effects than synthetic immunostimulants.

Antioxidant Effects Supporting Antiviral Defense

Oxidative stress is a universal feature of viral infections, arising from both viral manipulation of host metabolism and the host's immune response. Excessive reactive oxygen species (ROS) promote viral replication, induce cellular apoptosis and worsen tissue injury. Traditional systems may not have spoken in terms of "oxidative stress," but they recognized the need for herbs that "cool heat," "detoxify" and restore balance after febrile illness. Plants like Amla, rich in vitamin C and polyphenols, were central to such treatments in Ayurveda, while green tea and honeysuckle served similar roles in East Asia.

Flavonoids, tannins and phenolic acids act as potent free radical scavengers. By neutralizing ROS, they preserve the structural and functional integrity of host cells. This preservation is critical because viral replication often exploits oxidative environments. For example, hepatitis viruses induce oxidative stress in hepatocytes, promoting viral persistence; antioxidants from Guduchi and licorice counter this effect, limiting liver damage.

Antioxidant activity also complements immunomodulation. By reducing oxidative burden, these phytochemicals prevent excessive activation of inflammatory pathways. Quercetin and catechins, widely distributed in medicinal plants, downregulate ROS-dependent signaling cascades that lead to cytokine overproduction. This synergy ensures viral clearance while minimizing collateral damage to tissues.

Cultural practices reflected this principle through dietary integration. In India, Amla was incorporated into daily diet as *Chyawanprash* to build resistance, while in China, teas infused with chrysanthemum and honeysuckle were consumed to "clear heat" and prevent fevers. These preventive traditions align with modern recognition that antioxidants maintain immune homeostasis and prepare the body against infection.

Thus, antioxidant effects represent a supportive but essential mechanism of herbal antivirals. They buffer the host environment, reduce the likelihood of viral exploitation of oxidative stress, and ensure that recovery occurs with minimal tissue injury.

Respiratory Viruses (Influenza, RSV, Coronaviruses including SARS-CoV-2)

Respiratory viruses constitute some of the most serious global health concerns due to their ease of transmission and their potential for seasonal or pandemic outbreaks. Among these, influenza viruses, respiratory syncytial virus (RSV), and coronaviruses-including SARS-CoV-2-have been the subject of intense research into both synthetic and natural antivirals. Historically, influenza marked one of the first successes in antiviral therapy with the discovery of amantadine, which blocks the M2 ion channel of influenza A. This discovery stimulated interest in identifying plant-based compounds with similar inhibitory effects. Flavonoids such as quercetin, kaempferol, and catechins have since been found to suppress influenza replication by inhibiting hemagglutinin-mediated viral entry as well as neuraminidase activity, thus reducing the release of new virions from infected cells. Traditional remedies like elderberry extracts (*Sambucus nigra*), rich in anthocyanins, have long been used to treat influenza-like illnesses, and modern studies now validate their ability to shorten symptom duration and reduce viral titers[28].

RSV, a major cause of infant and elderly respiratory disease, has also been explored in the context of herbal medicine. Natural tannins and saponins disrupt the viral envelope, while compounds from licorice (*Glycyrrhiza glabra*) show both antiviral and anti-inflammatory activity, decreasing viral replication and mitigating airway inflammation. Polysaccharides from herbs such as *Astragalus membranaceus* can enhance interferon pathways, strengthening host defenses against RSV.

The coronavirus family, long recognized in veterinary medicine but thrust into prominence with SARS (2003), MERS (2012), and COVID-19 (2019), has also drawn attention to phytomedicine. Extracts from *Houttuynia cordata*-a staple in Chinese medicine-display direct inhibitory effects on coronavirus proteases and enhance cellular

immunity. Flavonoids such as luteolin and baicalein inhibit the main protease (Mpro) of SARS-CoV-2, while catechins from green tea block viral entry by interfering with spike protein–ACE2 receptor binding. Resveratrol and related stilbenes modulate host signaling, reducing the inflammatory cascades that exacerbate coronavirus pathology. The traditional reliance on "heat-clearing" and "detoxifying" herbs in Chinese medicine for epidemic respiratory illnesses now finds a clear mechanistic rationale.

Taken together, these findings illustrate that phytochemicals act at multiple levels-blocking entry, reducing replication, modulating immunity, and controlling inflammation-making them versatile agents against respiratory viruses. Their long use in traditional systems as preventive tonics or symptomatic relievers is increasingly validated by molecular virology, positioning them as valuable adjuncts in managing respiratory epidemics[29].

Herpesviridae (HSV, VZV)

The herpesvirus family, including herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) and varicella-zoster virus (VZV), exemplifies persistent human pathogens. Unlike acute respiratory viruses, herpesviruses establish latency, making complete eradication difficult. Early antiviral drug discovery revolved around HSV; idoxuridine, approved in the 1960s, was the first antiviral agent used clinically and acyclovir later revolutionized therapy by selectively targeting viral DNA polymerase. Yet natural products have paralleled these synthetic advances by offering structurally novel inhibitors.

Phenolic compounds, particularly flavonoids, tannins, and phenolic acids, have demonstrated inhibitory effects against HSV DNA polymerase and immediate early proteins. Green tea catechins, propolis-derived flavonoids and resveratrol derivatives reduce viral replication in vitro. Lemon balm (*Melissa officinalis*), a European folk remedy for cold sores, has shown clinical benefits by interfering with HSV entry and replication. Licorice root, long valued in both Ayurveda and TCM, contains glycyrrhizin, which exhibits anti-HSV activity while also alleviating inflammation at lesion sites.

Varicella-zoster virus, the cause of chickenpox and shingles, has fewer therapeutic options, and resistance to acyclovir has been documented in immunocompromised patients. Here, essential oils and triterpenes provide alternative routes. Compounds from aloe vera not only soothe lesions but also show modest antiviral action. In Ayurveda, neem (*Azadirachta indica*) leaves and bark extracts were applied for eruptive fevers, possibly reflecting empirical benefits against varicella-like diseases.

One striking feature of herbal antivirals against herpesviruses is their combined antiviral and symptom-relieving effects. By modulating inflammation and supporting wound healing, plants like aloe and licorice not only reduce viral titers but also promote lesion resolution and patient comfort. This dual action reinforces their role as complementary approaches alongside synthetic antivirals[30].

Hepatitis Viruses (HBV, HCV)

Hepatitis B virus (HBV) and hepatitis C virus (HCV) remain major global health challenges, affecting hundreds of millions worldwide. Antiviral research into these viruses has been extensive, leading to the development of nucleos(t)ide analogs for HBV and direct-acting antivirals for HCV. Ribavirin, discovered in 1972, was one of the first broad-spectrum agents used against viral hepatitis. Yet even with modern therapies, herbal compounds retain a significant place, especially in hepatoprotective support and regions with limited drug access.

In Ayurveda, *Phyllanthus species* (notably *Phyllanthus amarus*) were long used for jaundice and liver complaints. Modern research has demonstrated their ability to suppress HBV DNA polymerase, inhibit viral antigen expression, and reduce viral replication. Glycyrrhizin, used clinically in Japan for chronic hepatitis, not only reduces HBV titers but also prevents liver fibrosis by controlling inflammatory responses. Similarly, extracts of *Picrorhiza kurroa*, another Ayurvedic

liver tonic, protect hepatocytes while displaying inhibitory activity against viral replication[31].

For HCV, silymarin-a flavonolignan complex from *Silybum marianum* (milk thistle)-has been one of the most studied herbal agents. Beyond hepatoprotection, silymarin directly interferes with HCV NS5B RNA polymerase, suppresses oxidative stress, and improves liver enzyme profiles. Polyphenols such as catechins and curcumin further reduce viral replication and enhance host interferon pathways, making them synergistic with conventional antivirals.

The dual antiviral and hepatoprotective properties of these herbs reflect traditional wisdom: maintaining liver function was considered central to managing fevers and chronic illness. By limiting both viral burden and liver injury, these plants provide holistic management strategies, validated by contemporary molecular studies[32].

Retroviruses (HIV)

Retroviruses, especially HIV, represent a landmark in antiviral research due to the scale of the epidemic and the sophistication of drug development that followed. Since the 1980s, more than two dozen agents targeting reverse transcriptase, protease, and integrase have transformed HIV from a fatal disease to a chronic condition. However, herbal sources remain important both as potential leads and supportive agents.

Michellamine B, an alkaloid from *Ancistrocladus korupensis*, exhibits potent inhibition of HIV reverse transcriptase, marking it as one of the most promising natural scaffolds. Flavonoids such as rutin and apigenin demonstrate inhibitory effects on HIV protease, while triterpenes and coumarins from other medicinal plants block viral replication pathways. Propolis extracts, widely used in folk medicine, have shown synergistic inhibition of HIV enzymes *in vitro*[33].

In African and Asian ethnomedicine, plants like *Hypoxis hemerocallidea* (African potato) and *Momordica charantia* (bitter melon) were employed to strengthen immunity and manage wasting syndromes. Later biochemical studies revealed immunostimulatory polysaccharides and proteins with anti-HIV potential. *Uncaria tomentosa* (cat's claw) has been investigated for immunomodulatory effects, complementing antiretroviral therapy by reducing inflammation and oxidative stress.

While no herbal therapy can replace combination antiretroviral therapy, the structural novelty of plant-derived molecules continues to inspire drug discovery. Additionally, herbal immunomodulators offer supportive care, improving quality of life and countering drug-associated side effects. This dual role ensures their ongoing relevance in HIV management and pharmacological innovation[34].

Emerging and Neglected Viruses (Dengue, Chikungunya, Zika)

Emerging arboviruses such as dengue, chikungunya, and Zika virus pose unique challenges, as no widely approved antivirals exist for these infections. This has led to renewed focus on phytochemicals as possible interventions. Dengue fever, long endemic in tropical regions, has been managed traditionally with plants like papaya (*Carica papaya*) leaves, neem, and *Andrographis paniculata*. Contemporary studies confirm that papaya leaf extract improves platelet counts in dengue patients, while neem flavonoids inhibit dengue virus proteases. Quercetin and related flavonoids suppress replication of dengue NS5 RNA polymerase, while terpenes destabilize viral envelopes.

Chikungunya, another mosquito-borne infection, is characterized by fever and severe joint pain. In Ayurveda and local traditions, bitter herbs such as *Andrographis* and neem were used during outbreaks. Laboratory investigations have shown that diterpenes and alkaloids from these plants reduce chikungunya viral replication and moderate inflammatory joint pathology. Similarly, essential oils from lemongrass and clove have demonstrated virucidal activity against chikungunya virus[35].

Zika virus, an emerging threat linked to neurological complications and congenital abnormalities, has also been targeted with plant-derived molecules. Flavonoids such as quercetin, luteolin, and curcumin inhibit viral entry and replication, while antioxidant-rich extracts reduce

oxidative stress in infected tissues. Traditional use of fever-relieving and detoxifying herbs in endemic regions may have provided empirical relief for Zika-like illnesses even before the virus was scientifically identified.

These examples underscore the adaptability of phytochemicals to novel viral threats. Their broad-spectrum mechanisms-ranging from enzyme inhibition to immunomodulation-make them valuable as first-line interventions when no synthetic drugs are available. By aligning traditional ethnomedicine with modern pharmacological validation, herbal antivirals stand as a promising resource for managing both endemic and emerging viral infections[36].

From Crude Extracts to Advanced Formulations

Decoctions, Tinctures, and Essential Oils

The earliest phase of herbal therapy relied on relatively simple yet effective methods of extraction-decoctions, tinctures and essential oils-which continue to hold relevance today. A decoction involves boiling coarse plant material, such as roots, bark, or seeds, in water for a defined period. This process allows heat to rupture cell walls and release polar constituents such as flavonoids, glycosides, saponins, and alkaloids. In Ayurveda, decoctions (kwathas) were often prescribed for fevers, respiratory disorders, and digestive ailments, and their preparation was codified in ancient texts with detailed specifications regarding plant ratios, boiling times, and dosage. Similarly, in Traditional Chinese Medicine (TCM), decoctions formed the backbone of prescriptions, combining multiple herbs to harmonize therapeutic effects. The advantage of decoctions lies in their accessibility and ability to deliver multi-component extracts; however, they are limited by poor stability, batch variability, and the inconvenience of daily preparation[37].

Tinctures represented an advance in herbal formulation by utilizing alcohol or hydroalcoholic mixtures as solvents. Alcohol extraction captures not only water-soluble molecules but also less polar constituents such as essential oils, resins, and certain alkaloids. The preservative nature of alcohol extends the shelf life of tinctures significantly compared to aqueous decoctions. In Western herbalism, tinctures became prominent as portable and stable preparations. For instance, tinctures of Echinacea, valerian and belladonna were widely prescribed for infections, insomnia, and spasmodic disorders, respectively. The enhanced bioavailability of certain lipophilic compounds in tinctures offered a pharmacological edge, yet the variability in ethanol content and the unsuitability for children or patients avoiding alcohol posed practical challenges[38].

Essential oils occupy a distinct category within crude preparations. These volatile, aromatic fractions are typically obtained by steam distillation or cold pressing. Chemically, essential oils are rich in terpenoids, phenolics and small lipophilic molecules that exert broad antimicrobial and antiviral activity. For example, thymol and carvacrol from thyme and oregano demonstrate direct virucidal effects by disrupting viral envelopes, while eucalyptol from eucalyptus acts as both a decongestant and mild antiviral. Historically, essential oils were used in fumigation rituals and topical salves, serving both therapeutic and preservative functions. Their high volatility facilitates absorption through the respiratory tract and skin, making them especially useful for respiratory infections and dermatological conditions.

Despite their effectiveness, these crude preparations share inherent shortcomings: inconsistent concentrations of active molecules, rapid degradation during storage, and inter-batch variability due to geographical, seasonal, or processing differences. As demand grew for more reliable, reproducible medicines, these limitations stimulated the development of standardized extracts**,** bridging traditional methods and modern pharmaceutical rigor.

Standardized Extracts

The evolution from crude preparations to standardized extracts marks a crucial turning point in herbal medicine, aligning traditional practices with scientific and regulatory requirements.

Standardization involves identifying and quantifying one or more marker compounds within a plant extract to guarantee consistent potency and therapeutic efficacy. This step was vital because decoctions and tinctures often showed wide variability in phytoconstituent levels, influenced by climate, soil composition, harvest timing, and processing conditions. Inconsistent phytochemistry translated into inconsistent clinical outcomes, hampering integration into evidence-based medicine.

In modern practice, standardized extracts ensure reproducibility by fixing the concentration of bioactive molecules or chemical markers. For instance, extracts of *Ginkgo biloba* are standardized to contain 24% flavone glycosides and 6% terpene lactones, guaranteeing predictable pharmacological effects on cognition and circulation. Similarly, milk thistle extracts are standardized for silymarin content, which has hepatoprotective and antiviral properties, while ginseng preparations are normalized to specific ginsenoside levels. Such practices have transformed herbal products into reliable therapeutic agents that can be rigorously evaluated in clinical trials and accepted in pharmacopeias across Europe, Asia, and North America.

Standardized extracts not only enhance reproducibility but also enable detailed pharmacokinetic and pharmacodynamic studies. Researchers can correlate plasma levels of marker compounds with clinical outcomes, building mechanistic insight into herbal actions. Moreover, standardized extracts improve global trade and regulation, as manufacturers and healthcare providers can trust that a given product meets predetermined specifications. For example, European phytopharmaceutical guidelines demand specific ranges of marker compounds for marketed extracts, ensuring both safety and efficacy.

However, one of the ongoing debates is whether standardization should focus solely on single molecules or consider the entire phytochemical matrix. Herbal medicines often derive their effectiveness from synergistic interactions among multiple constituents, not just one isolated marker. Overemphasis on a single compound risks oversimplifying complex plant pharmacology. For this reason, some experts argue for "broad-spectrum standardization," in which multiple markers are quantified to capture a fuller phytochemical profile.

The rise of standardized extracts also laid the foundation for advanced delivery systems. Once active molecules were well-characterized, scientists could investigate why many of them still showed poor bioavailability or stability *in vivo*. This recognition paved the way for applying nanotechnology-particularly liposomes, niosomes and phytosomes-to overcome pharmacokinetic barriers and maximize therapeutic potential[39].

Integration with Nanotechnology: Liposomes, Niosomes, and Phytosomes

While standardized extracts significantly improved reproducibility, many phytochemicals still face pharmacokinetic challenges, including low aqueous solubility, poor permeability, rapid metabolism, and instability in the gastrointestinal tract. Nanotechnology-based delivery systems have emerged as powerful solutions, enabling herbal actives to reach therapeutic concentrations in systemic circulation. Among the most studied platforms are liposomes, niosomes and phytosomes, each offering unique advantages in delivering plant-derived molecules.

Liposomes are spherical vesicles composed of phospholipid bilayers capable of encapsulating both hydrophilic and lipophilic compounds. They shield sensitive phytoconstituents from enzymatic degradation, prolong circulation times, and improve tissue targeting. For example, curcumin-loaded liposomes demonstrate enhanced anti-inflammatory and antiviral activity compared to free curcumin, while quercetin liposomes show superior bioavailability and antioxidant capacity. Liposomes have also been employed in nasal and pulmonary delivery of herbal antivirals, maximizing their efficacy in respiratory infections.

Niosomes, composed of non-ionic surfactants, are structurally similar to liposomes but are more stable and cost-effective. Their amphiphilic nature allows

them to encapsulate diverse phytochemicals, improving solubility and absorption. Niosomal formulations of herbal compounds like resveratrol, glycyrrhizin, and berberine have shown significant improvement in oral bioavailability and therapeutic outcomes. Niosomes also provide controlled release, reducing dosing frequency and minimizing side effects-an advantage particularly relevant for chronic viral infections.

Phytosomes represent an innovative delivery system specifically tailored for herbal actives. Unlike liposomes and niosomes, phytosomes form molecular complexes between phytoconstituents and phospholipids, typically phosphatidylcholine. This design improves the compatibility of plant molecules with lipid membranes, dramatically enhancing absorption across the gastrointestinal tract. Classic examples include silymarin phytosomes, which achieve several-fold higher plasma levels than conventional extracts, and curcumin phytosomes, which significantly improve systemic exposure and therapeutic activity. Phytosomes are particularly useful for polyphenols and flavonoids, whose oral bioavailability is otherwise limited.

Integration with nanotechnology extends beyond these three systems. Polymeric nanoparticles, solid lipid nanoparticles, dendrimers and nanoemulsions are increasingly used to optimize herbal formulations. For example, nanoemulsified essential oils of clove and eucalyptus exhibit enhanced antiviral and antibacterial activity compared to their crude forms. These advanced systems enable site-specific delivery (e.g., hepatic targeting for hepatitis antivirals), controlled release and synergistic combinations of multiple phytochemicals.

Ultimately, nanotechnology transforms herbal medicine from empirically effective but pharmacologically inconsistent remedies into predictable, potent and clinically translatable therapies. By merging centuries-old botanical wisdom with cutting-edge drug delivery strategies, modern science ensures that traditional remedies remain relevant in addressing 21st-century health challenges.

Safety, quality and standardization concerns[40-42]

Variability in Phytochemical Content across Regions and Harvest Seasons

A persistent obstacle in the standardization of herbal medicines is the pronounced variability in phytochemical content. Unlike synthetic pharmaceuticals, which are produced under strictly controlled conditions to yield consistent molecular structures, medicinal plants are subject to a multitude of environmental, genetic, and handling factors that significantly alter their chemical profiles. This complexity is well documented in the WHO Monographs on Selected Medicinal Plants, which note that the chemical quality of a plant is determined not only by its species identity but also by geographical location, soil composition, climate, and the timing of harvest.

The degree of variation is often striking. For instance, essential oil content in aromatic plants such as mint or lavender can differ substantially depending on whether they are harvested in early or late flowering stages. Plants exposed to high levels of stress, such as drought or excessive sunlight, may accumulate greater quantities of flavonoids or alkaloids as protective mechanisms, while those cultivated in nutrient-rich, temperate environments may present lower concentrations. This phenomenon leads to the development of different "chemotypes"-plants of the same species but producing distinct sets of dominant compounds. Such chemical diversity, although biologically fascinating, creates significant problems for ensuring uniformity in medicinal use.

Mukherjee and Houghton emphasize this issue in Evaluation of Herbal Medicinal Products, where they stress that dosage reliability is nearly impossible to guarantee without accounting for natural variability. When the same herbal preparation may contain different concentrations of bioactive compounds depending on origin and season, patients may experience inconsistent therapeutic effects. In clinical research, this variability introduces confounding factors, making it difficult to reproduce outcomes and establish reliable evidence for efficacy.

Moreover, variability is not limited to cultivation conditions but extends into post-harvest handling and storage. Improper drying can lead to enzymatic degradation of active compounds, while exposure to excessive humidity may encourage microbial contamination or chemical breakdown. WHO guidelines on Good Agricultural and Collection Practices (GACP) specifically address these issues, outlining procedures for cultivation, harvesting and storage aimed at reducing inconsistencies. Adherence to GACP, coupled with stringent quality control during processing, is a cornerstone of producing standardized herbal medicines.

The issue of variability also extends to the global trade of herbal raw materials. *New Look to Phytomedicine* notes that the same species exported from two different countries often shows different pharmacological activity, due not only to environmental factors but also to differences in harvesting traditions and post-harvest technologies. Such discrepancies complicate regulatory oversight and international commerce, as importing countries must establish standards that account for a broad range of chemical profiles.

Addressing this problem requires a multi-pronged strategy. Firstly, genetic selection and controlled cultivation of medicinal plants can reduce variability. Cultivating identified chemotypes under standardized conditions ensures greater consistency. Secondly, chemical fingerprinting methods such as HPLC and LC-MS can be employed to establish a reference profile for raw materials, making it possible to detect and quantify variations between batches. Thirdly, harmonization of international standards is critical, as inconsistency in national regulatory approaches undermines efforts at global quality assurance.

In conclusion, phytochemical variability is a natural but manageable challenge. By integrating agricultural practices, advanced analytical methods, and international cooperation, it becomes possible to reduce variability to acceptable levels, thereby ensuring that patients receive safe and effective herbal medicines with predictable therapeutic outcomes.

Potential Herb–Drug Interactions

While variability in plant chemistry complicates standardization, another equally serious concern is the potential for interactions between herbal remedies and conventional medicines. This issue is underscored in all three of your sources, each of which stresses that herbal products are pharmacologically active substances and therefore capable of altering drug pharmacokinetics and pharmacodynamics.

Herb–drug interactions occur through several mechanisms. The most well-documented pathway involves the cytochrome P450 enzyme system in the liver, which metabolizes a majority of prescription drugs. As described in *Evaluation of Herbal Medicinal Products*, herbs such as St. John's Wort act as inducers of CYP3A4, leading to accelerated metabolism and reduced plasma levels of drugs including oral contraceptives, immunosuppressants and antiretrovirals. Conversely, herbs such as grapefruit and goldenseal inhibit cytochrome activity, slowing metabolism and risking toxic accumulation of medications like statins and anticoagulants.

Another mechanism involves the modulation of drug transporters. P-glycoprotein, for example, regulates drug absorption and distribution. Certain herbal flavonoids can inhibit or induce this transporter, thereby altering bioavailability. *New Look to Phytomedicine* provides examples of this phenomenon, citing how ginseng and garlic supplements may interfere with cardiovascular medications, potentially leading to increased bleeding risks or reduced drug efficacy.

Herbs may also exert direct pharmacodynamic interactions by producing additive or opposing effects alongside pharmaceuticals. For example, valerian and kava have sedative properties, which may intensify the central nervous system depression caused by benzodiazepines or alcohol. Similarly, ginkgo biloba, known for its antiplatelet activity, may synergize with aspirin or clopidogrel, heightening the risk of hemorrhage. WHO monographs caution that while many of these interactions are biologically plausible, they remain

underreported due to the lack of systematic pharmacovigilance.

The implications for public health are significant. Patients frequently self-administer herbal products without informing their healthcare providers, assuming them to be "natural and safe." This perception masks the reality that herb-drug interactions can have severe consequences, particularly for patients on polypharmacy regimens, such as the elderly or those with chronic illnesses. Furthermore, the underreporting of adverse effects hinders the development of reliable safety databases.

Mitigating these risks requires a multi-level approach. Clinicians should routinely inquire about herbal use during consultations, while regulatory bodies must mandate clearer labeling on herbal products regarding known interaction risks. On the research side, both in vitro mechanistic studies and well-designed clinical trials are necessary to provide definitive evidence on the nature and extent of these interactions. Patient education campaigns also play a vital role in encouraging transparency and caution when combining herbal and conventional medicines.

In conclusion, herb–drug interactions represent a critical safety concern in the modern use of phytomedicines. Recognizing and addressing these interactions is essential for integrating herbal remedies safely into evidence-based healthcare, and it requires collaboration between researchers, healthcare professionals, regulators and the public.

Need for Validated Analytical and Pharmacological Methods

Perhaps the most important unifying theme across all three sources is the call for validated analytical and pharmacological methods to underpin the safe and effective use of herbal medicines. The WHO monographs stress that identity tests, purity requirements and validated assays are the foundation of quality assur ance. Similarly, Mukherjee and Houghton argue that without rigorous authentication and validated quality control methods, herbal medicine cannot advance beyond anecdotal use into the realm of evidence-based therapy.

Analytical validation begins with confirming the authenticity of the plant material. Traditional identification methods, while valuable, are prone to error, especially given the prevalence of adulteration and substitution in herbal markets. Modern molecular techniques such as DNA barcoding offer precise species-level identification, reducing the risk of mislabeling. Once identity is established, chemical fingerprinting methods such as HPLC, LC-MS, GC-MS and NMR spectroscopy allow for quantification of major and minor constituents, providing a reproducible "signature" for each herbal preparation. *New Look to Phytomedicine* highlights how such techniques are increasingly used to define chemical markers, enabling standardization of complex mixtures.

Pharmacological validation, meanwhile, requires demonstrating biological activity and safety through standardized assays. In vitro studies are used to identify potential mechanisms of action, while in vivo models test efficacy and safety under biological conditions. Toxicological evaluation, including acute, sub-chronic, and chronic studies, is crucial for identifying potential risks. WHO guidelines stress that traditional use alone is not sufficient evidence of safety; systematic evaluation is necessary.

One of the major challenges lies in the complexity of herbal preparations, which often contain multiple active constituents acting synergistically. This makes it difficult to attribute activity to a single compound or to establish a direct dose-response relationship. Mukherjee and Houghton note that polyvalence-the interaction of multiple compounds within an extract-is both a strength and a weakness of herbal medicines. While it may enhance efficacy, it complicates validation and standardization.

Validated analytical and pharmacological methods also form the basis for regulatory frameworks. Without them, regulatory authorities cannot enforce quality standards or protect consumers from substandard or adulterated products. Furthermore, validated methods facilitate international trade by

harmonizing requirements across countries, ensuring that exported and imported products meet agreed-upon safety and efficacy criteria.

In summary, the development and implementation of validated methods are indispensable for the future of herbal medicine. They provide the tools to guarantee quality, confirm safety, establish efficacy, and build the scientific credibility necessary for herbal products to stand alongside conventional pharmaceuticals. This integration requires significant investment in research, regulatory collaboration and industry compliance, but it is the only path to ensuring that traditional remedies evolve into reliable, evidence-based therapies.

Current Research Gaps and Translational Opportunities[43-45]

Lack of Robust Clinical Trials

Although traditional knowledge and laboratory evidence point to the antiviral potential of many plants, the clinical research supporting these claims is still very limited. Most human studies that have been conducted are small in scale, often single-center and rarely reach the level of rigor required for strong evidence. A common pattern is the use of open-label or pilot studies that lack proper randomization and blinding, which introduces bias and reduces the reliability of results. Even when trials report positive outcomes, the absence of replication under standardized conditions prevents their findings from being generalized to wider populations.

Another weakness is the inconsistency in the herbal preparations tested. Researchers frequently use crude extracts described only by the plant's common name or origin, without full chemical profiling. Because the phytochemical composition of a plant can vary significantly by region, season, and processing method, results obtained from one trial may not apply elsewhere. This lack of standardization undermines both efficacy assessments and safety monitoring. Without chemical fingerprinting, it is difficult to attribute therapeutic or adverse effects to specific compounds, making reproducibility nearly impossible.

Clinical trial endpoints also vary greatly, ranging from self-reported symptom improvement to nonspecific measures of "general well-being." Few studies incorporate hard clinical outcomes, such as viral load reduction, hospitalization time, or survival, which are essential for establishing true antiviral efficacy. Biomarkers of immune function and inflammation, which could shed light on mechanisms of action, are rarely included. As a result, the clinical data that do exist often remain too fragmented to inform treatment guidelines or regulatory approval.

To close these gaps, future research must adopt modern clinical trial methodologies. Adaptive trial designs allow multiple herbal candidates to be evaluated simultaneously, with ineffective treatments discontinued early. This design not only conserves resources but also generates high-quality evidence more efficiently. Trials should include robust endpoints such as virological measures, standardized symptom scoring, and validated biomarkers. Importantly, the herbal interventions must be produced under controlled manufacturing conditions, with detailed chemical profiles included in the study protocol. This ensures that results can be reproduced and compared across different centers.

A stronger evidence base will also require collaboration between academic researchers, clinicians, and industry stakeholders. Large, multicenter trials coordinated across regions can help establish whether promising herbal antivirals hold consistent efficacy across diverse populations. Only through such systematic efforts can herbal antiviral research progress beyond anecdotal or preliminary findings and achieve credibility alongside conventional drug development.

Limited Regulatory Approval Pathways

The path from promising laboratory discovery to approved therapeutic is particularly complex for herbal antivirals. Regulatory agencies in different parts of the world classify plant-based products in very different ways: as dietary supplements, traditional medicines, or botanical drugs. Each classification carries different requirements for

quality, safety, and efficacy. This patchwork of regulations creates uncertainty for developers and contributes to the slow progress of herbal antivirals into mainstream healthcare.

One of the most difficult requirements is the need for precise definition of the product. Regulatory authorities demand specifications for identity, purity, stability, and potency, which is straightforward for a single synthetic molecule but extremely challenging for complex plant extracts. Herbal preparations often contain dozens or even hundreds of bioactive compounds, many of which may act in synergy. Defining the "active ingredient" in such mixtures is not always possible. This complexity often stalls regulatory submissions, as authorities cannot evaluate safety and efficacy without consistent, reproducible definitions of the product.

In many jurisdictions, simplified regulatory pathways exist for herbal products with a history of traditional use. These pathways often emphasize safety and historical evidence rather than clinical efficacy. While this allows products to reach consumers more easily, it also means that many herbal antivirals enter the market without robust proof of effectiveness. On the other end of the spectrum, pursuing full drug approval requires meeting the same standards as synthetic pharmaceuticals, which demands costly large-scale trials, validated quality control methods, and well-defined manufacturing processes. Very few herbal antivirals have been able to satisfy these requirements.

A promising solution is the development of regulatory dossiers around standardized fractions or enriched groups of phytochemicals rather than crude, uncharacterized extracts. By narrowing the focus to chemically defined subsets that retain pharmacological activity, researchers can create products that meet quality and reproducibility requirements while preserving therapeutic synergy. This modular approach also makes it easier to monitor safety and efficacy, as regulators can evaluate well-characterized components rather than heterogeneous mixtures.

International harmonization is also critical. Currently, a product considered a medicine in one country may only be marketed as a supplement in another. Establishing consistent global standards for herbal antivirals would reduce regulatory fragmentation and encourage investment in high-quality development. Such frameworks should balance the need for rigorous evidence with the recognition that complex plant products require tailored evaluation methods, rather than forcing them into models designed solely for single molecules.

In summary, regulatory barriers are one of the main reasons why promising herbal antivirals remain stuck at the experimental stage. By developing modular dossiers, emphasizing standardization, and harmonizing global pathways, these obstacles can be reduced, opening new opportunities for translation into clinical practice.

Possibility of Combining Herbal Antivirals with Conventional Therapies

Combination therapy is already a cornerstone in the treatment of many viral diseases. Using multiple agents with different mechanisms of action reduces the chance of viral resistance and often enhances therapeutic outcomes. Herbal antivirals offer potential value in this strategy because they frequently target host factors, entry pathways, or inflammatory processes that complement the direct-acting effects of conventional drugs.

For example, certain flavonoids and saponins have been shown to block viral entry by interfering with cell surface receptors, while standard antivirals such as protease inhibitors act at later stages of replication. Combining the two could, in theory, create a layered defense that prevents both infection and proliferation. Other plant-derived compounds exhibit strong immunomodulatory or anti-inflammatory properties, which could be used to reduce tissue damage caused by viral-induced cytokine storms. In this sense, herbal antivirals may not only contribute direct antiviral activity but also play a role in managing host responses to infection.

However, combining therapies introduces its own challenges. Many herbal compounds influence the

same metabolic enzymes and transporters that process pharmaceutical drugs. This means that co-administration could lead to altered absorption, distribution, metabolism, or elimination of conventional antivirals. In some cases, this could reduce drug efficacy; in others, it could increase toxicity. Systematic studies are needed to characterize these interactions before combinations can be recommended clinically.

Early-phase combination trials should therefore incorporate intensive pharmacokinetic and pharmacodynamic monitoring, using probe drugs and biomarkers to detect interactions. Preclinical assays, such as checkerboard and time-of-addition studies, can also help identify synergy or antagonism before human trials begin. The goal is to ensure that combinations are not only more effective but also safe and predictable.

If these challenges are addressed, the integration of herbal antivirals into combination regimens could become a major translational opportunity. Rather than competing with synthetic drugs, herbal compounds could serve as adjunct therapies, enhancing efficacy, reducing side effects and broadening the arsenal against viral diseases. This approach is especially valuable in settings where access to expensive pharmaceuticals is limited, as affordable plant-based adjuncts could extend the effectiveness of standard treatments.

AI and Bioinformatics in Predicting Plant–Virus Interactions

The complexity of plant-derived products poses challenges for traditional drug discovery, but advances in computational science are opening new avenues for translation. Artificial intelligence (AI) and bioinformatics are increasingly being used to predict interactions between plant compounds and viral targets, accelerating the identification of promising candidates.

Machine learning models trained on existing antiviral compound libraries can analyze structural features and predict which plant-derived molecules are most likely to exhibit activity. This allows researchers to focus laboratory testing on a smaller pool of high-value compounds, reducing time and cost. Network pharmacology approaches go a step further by mapping entire sets of plant metabolites onto host-virus interaction networks, helping to explain how complex mixtures may act on multiple targets simultaneously.

Bioinformatics also plays a key role in linking plant genomics and metabolomics. By sequencing the genomes of medicinal plants and identifying biosynthetic gene clusters, researchers can predict which metabolites are likely to be produced. These predictions can then be matched with metabolomic data to confirm the presence of antiviral compounds. This approach not only speeds up discovery but also facilitates semi-synthetic optimization, where natural scaffolds are modified to improve potency and pharmacokinetics.

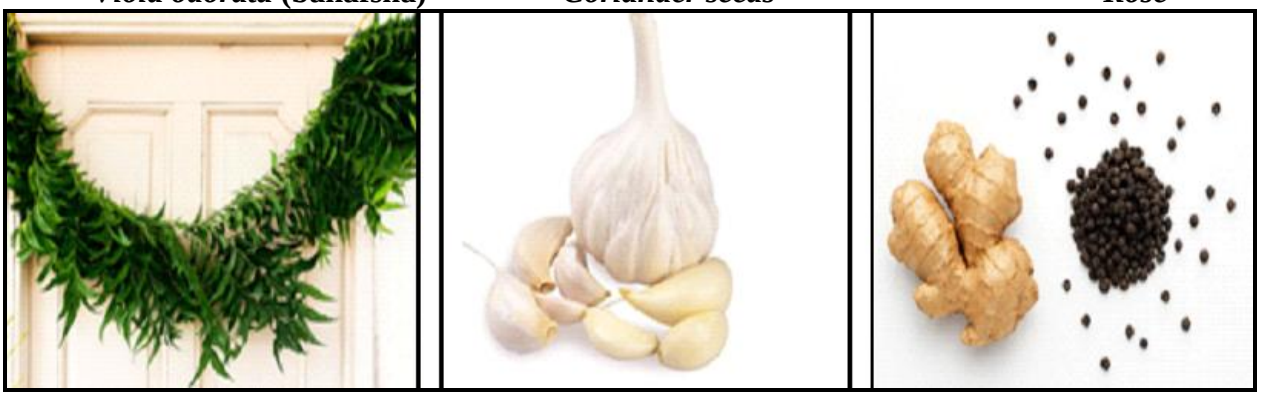
Despite these advances, challenges remain. AI predictions are only as reliable as the data they are built on and plant research is often limited by incomplete or inconsistent datasets. Variability in chemical composition and differences in assay protocols further reduce the accuracy of models. To improve reliability, researchers must invest in creating curated databases that include validated chemical structures, standardized bioassay results and reproducible pharmacological data.

Looking forward, AI and bioinformatics are likely to play a central role in bridging traditional plant knowledge with modern antiviral therapy. By integrating computational predictions with experimental validation, these tools can transform the discovery process from trial-and-error screening into a targeted, hypothesis-driven approach. This not only accelerates the identification of promising herbal antivirals but also provides mechanistic insights that support regulatory approval and clinical application.

***Tulsi* (*Ocimum sanctum*)** ***Guduchi* (*Tinospora cordifolia*)** ***Neem* (*Azadirachta indica*)**

***Isatis root* (*Ban Lan Gen*)** ***Honeysuckle* (*Jin Yin Hua*)** ***Forsythia* (*Lian Qiao*)**

Viola odorata* (banafsha)** ***Coriander seeds ***Rose***



Neem leaves at doorways **Garlic** **Ginger and black pepper**

Tulsi (*Ocimum sanctum*)

Guduchi (*Tinospora cordifolia*)

Isatis root

Licorice root

Garlic

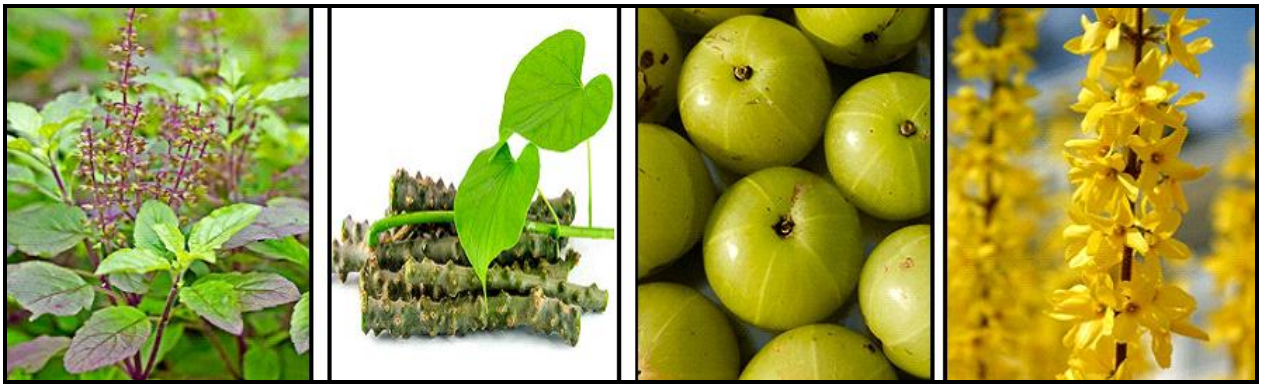
Neem

Honeysuckle

Ginger

Black Pepper

Forsynthia



Tulsi | ***Tinospora cordifolia*** | ***Phyllanthus emblica*** | ***Forsythia***

Cinnamomum camphora | ***Artemisia*** | **eucalyptus** | **Cinnamon**

Terminalia bellirica | ***Amla*** | ***Terminalia chebula***

Datura | ***Vinca*** | ***Rauwolfia***

Sapindus ***Saponaria*** ***Licorice***

Joint-pine **Andrographis paniculata**

Astragalus **Guduchi**

CONCLUSION

The exploration of medicinal plants as antiviral agents stands at a critical intersection between tradition and modern science. On one hand, centuries of ethnobotanical knowledge provide an invaluable catalogue of species long employed against fever, respiratory infections, and epidemic outbreaks. On the other, contemporary pharmacological research has begun to confirm the biological plausibility of many of these remedies, revealing compounds that can inhibit viral entry, modulate immune pathways, or attenuate inflammatory cascades. This dual heritage underscores the immense promise of plant-based antivirals: they are culturally grounded, widely accessible and chemically diverse. Yet, promise alone does not guarantee therapeutic impact and the limitations must be acknowledged with equal clarity.

Key among the constraints is the unevenness of scientific evidence. Much of the available data is preclinical, derived from *in vitro* assays or small animal models, which while valuable, cannot substitute for large-scale clinical trials. Standardization remains another critical hurdle: differences in harvesting time, cultivation methods,

and processing techniques often produce variability in phytochemical content, making reproducibility and regulatory assessment difficult. Moreover, the potential for herb-drug interactions complicates the integration of these products into established therapeutic regimens, especially in patients already receiving multiple medications for chronic conditions. Without systematic toxicological evaluations and pharmacokinetic profiling, the safety margins of many herbal antivirals remain uncertain.

Despite these challenges, the current global health landscape reveals why this field cannot be overlooked. The COVID-19 pandemic highlighted both the vulnerabilities of relying solely on synthetic antivirals and the urgent need for accessible, diverse therapeutic options. In regions with limited access to high-cost pharmaceuticals, locally available medicinal plants continue to serve as a first line of care. This reality calls not for a dismissal of traditional remedies, but for structured pathways to rigorously evaluate, refine, and where appropriate, integrate them into official healthcare systems. Recent health policy documents have emphasized this point, noting that responsible use of herbal medicines in infectious disease management can complement biomedical approaches when guided by quality, safety and efficacy standards.

To bridge these divides, collaboration is essential. Ethnobotanists contribute contextual knowledge, ensuring that plant selection reflects genuine traditional use rather than arbitrary screening. Virologists bring the expertise to test hypotheses against modern viral biology, clarifying mechanisms of action and identifying molecular targets. Pharmaceutical scientists add the tools of formulation, standardization, and clinical trial design, transforming crude remedies into reproducible therapeutic candidates. Such multidisciplinary networks not only expand scientific rigor but also safeguard cultural heritage, ensuring that indigenous knowledge systems are respected and translated responsibly.

Beyond the laboratory and clinic, policy frameworks and research infrastructure will shape the trajectory of herbal antiviral development. Capacity building in analytical chemistry, pharmacovigilance and clinical trial management is urgently needed in regions where medicinal plants are most widely used. Investments in training and infrastructure will empower local researchers to move beyond descriptive ethnobotanical surveys toward generating evidence that meets international standards. Equally important is the establishment of benefit-sharing mechanisms, ensuring that communities who have safeguarded traditional knowledge are included as partners in the commercialization process rather than left on the margins.

Global health agencies increasingly recognize that innovation must be inclusive, sustainable, and respectful of biodiversity. Encouraging multidisciplinary consortia, creating funding streams dedicated to plant-based antiviral discovery, and aligning regulatory guidance with the realities of complex natural products are practical steps that can accelerate translation. If pursued with balance and foresight, these efforts could elevate herbal antivirals from promising leads to reliable tools in the fight against infectious diseases.

In conclusion, herbal antivirals embody both opportunity and complexity. Their vast chemical repertoires and deep cultural roots make them attractive candidates in the ongoing search for new therapeutics. However, without stronger evidence, harmonized regulations and systematic collaboration across disciplines, their potential will remain only partially realized. The way forward lies in balance: respecting tradition while embracing innovation, recognizing limitations while investing in possibilities and above all, fostering partnerships that unite ethnobotany, virology and pharmaceutical science in the shared goal of advancing global health.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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