Plant-Derived Natural Products as Promising Candidates for Antiviral Drug Discovery: Mechanistic Insights, Preclinical Evidence, and Translational Opportunities

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Abstract
Viral infections continue to impose a substantial burden on global public health, contributing to millions of deaths annually and challenging healthcare systems worldwide. Despite advances in antiviral therapeutics, limitations such as drug resistance, narrow spectrum of activity, adverse effects, and high costs necessitate the exploration of alternative therapeutic strategies. Plant-derived natural products represent a rich reservoir of bioactive compounds with diverse structural scaffolds and pharmacological properties that have been utilized in traditional medicine systems for centuries. This review examines the current state of knowledge regarding the isolation, characterization, and development of plant-derived compounds as antiviral agents. Key themes include the systematic screening and selection of phytochemicals with antiviral activity, elucidation of their mechanisms of action targeting viral entry, replication, assembly, and release, as well as modulation of host immune responses. We analyze preclinical evidence from *in vitro* and *in vivo* studies demonstrating the efficacy of selected compounds against a range of viral pathogens, including influenza, herpes simplex virus, human immunodeficiency virus, hepatitis viruses, and emerging viruses such as severe acute respiratory syndrome coronavirus 2. Clinical evidence from human trials, structure–activity relationships, formulation strategies to enhance bioavailability, safety considerations including toxicity profiles and herb–drug interactions, and regulatory challenges are critically discussed. This comprehensive analysis provides insights into translational opportunities and future directions for integrating plant-based antiviral compounds into mainstream drug development pipelines, emphasizing the need for standardized methodologies, rigorous clinical evaluation, and collaborative interdisciplinary approaches.

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Introduction

The continuous emergence and re-emergence of viral pathogens pose significant threats to human health, economic stability, and social well-being across the globe. Viral infections ranging from seasonal influenza to pandemic-causing agents such as severe acute respiratory syndrome coronavirus 2 have demonstrated the vulnerability of human populations and the limitations of existing therapeutic arsenals [1]. The rapid evolution of viruses, coupled with their ability to develop resistance to conventional antiviral agents, underscores the urgent need for novel therapeutic approaches with diverse mechanisms of action and broad-spectrum antiviral activity [2]. Traditional antiviral drugs, while effective against specific viral targets, often face challenges including limited efficacy against emerging viral strains, significant adverse effects, high production costs, and accessibility issues in resource-limited settings [3]. Natural products have historically served as invaluable sources of therapeutic agents,

with approximately half of all clinically approved drugs being either natural products or derivatives thereof [4]. Plants, in particular, produce an extraordinary array of secondary metabolites evolved for defense against pathogens, including viruses, bacteria, and fungi [5]. These phytochemicals encompass diverse structural classes including alkaloids, flavonoids, terpenoids, phenolic compounds, saponins, and polysaccharides, each exhibiting unique pharmacological properties [6]. The structural complexity and chemical diversity of plant-derived compounds offer advantages over synthetic molecules, including the potential for multi-target interactions, synergistic effects when used in combination, and modulation of host defense mechanisms [7].

Ethnobotanical knowledge accumulated over millennia has identified numerous plant species with antiviral properties, many of which have been validated through modern scientific investigation [8]. The integration of traditional medicine practices with contemporary pharmacological research has facilitated the identification of promising lead compounds and provided insights into their therapeutic potential [9]. Recent advances in analytical techniques, including high-performance liquid chromatography, mass spectrometry, nuclear magnetic resonance spectroscopy, and bioactivity-guided fractionation, have enabled the precise isolation and characterization of bioactive constituents from complex plant matrices [10]. Furthermore, developments in computational chemistry, molecular docking studies, and systems biology approaches have enhanced our understanding of the molecular mechanisms underlying the antiviral activities of phytochemicals [11].

The objective of this comprehensive review is to critically examine the current landscape of plant-derived natural products as antiviral agents, with particular emphasis on mechanistic insights, preclinical evidence, clinical translation, and future prospects. We address the methodologies employed for screening and selecting antiviral compounds from plant sources, elucidate the diverse mechanisms by which these compounds interfere with viral life cycles and modulate host responses, and evaluate the evidence from preclinical and clinical studies. Additionally, we discuss formulation strategies designed to overcome pharmacokinetic limitations, safety and toxicity considerations, regulatory challenges, and the translational pathway from laboratory discovery to clinical application. By providing a holistic perspective on plant-based antiviral drug discovery, this review aims to stimulate further research and facilitate the development of effective, safe, and accessible antiviral therapeutics.

Global Burden of Viral Infections and Limitations of Conventional Antivirals

Viral infections represent one of the leading causes of morbidity and mortality worldwide, affecting billions of individuals annually and imposing enormous economic burdens on healthcare systems [12]. The World Health Organization estimates that respiratory viral infections alone account for millions of deaths each year, with influenza viruses causing seasonal epidemics that result in substantial hospitalizations and fatalities, particularly among vulnerable populations including the elderly, immunocompromised individuals, and those with underlying chronic conditions [13]. Chronic viral infections such as human immunodeficiency virus, hepatitis B virus, and hepatitis C virus affect hundreds of millions of people globally, leading to progressive disease, increased risk of malignancies, and significant reductions in quality of life [14]. The emergence of novel viral pathogens, exemplified by the severe acute respiratory syndrome coronavirus 2 pandemic, has highlighted the unpredictable nature of viral threats and the critical need for preparedness and rapid response capabilities [15].

Current antiviral therapeutic strategies primarily rely on small-molecule inhibitors that target specific viral enzymes or structural proteins essential for viral replication. Nucleoside analogs, protease inhibitors, neuraminidase inhibitors, and reverse transcriptase inhibitors constitute the mainstay of treatment for various viral infections [16]. While these agents have achieved considerable success in managing certain viral diseases, they are associated with several inherent limitations. The narrow spectrum of activity characteristic of most conventional antivirals restricts their applicability to single viral species or closely related strains, necessitating precise diagnostic identification before treatment initiation [17]. Moreover, the high mutation rates of RNA viruses facilitate the rapid emergence of drug-resistant variants, compromising therapeutic efficacy and limiting long-term treatment options [18].

Adverse effects associated with prolonged antiviral therapy represent another significant challenge, with toxicities ranging from mild gastrointestinal disturbances to severe hepatotoxicity, nephrotoxicity, and bone marrow suppression [19]. These side effects often lead to treatment discontinuation or dose modifications, potentially compromising viral suppression and clinical outcomes. The high costs of developing and manufacturing synthetic antiviral drugs also limit accessibility, particularly in low- and middle-income countries where the burden of viral diseases is often greatest [20]. Additionally, the lengthy timelines required for conventional drug development, from target identification through clinical trials to regulatory approval, impede rapid responses to emerging viral threats [21].

The limitations of conventional antivirals have catalyzed interest in alternative therapeutic approaches, including the exploration of natural products with antiviral properties. Plant-derived compounds offer several potential advantages, including diverse mechanisms of action that may circumvent resistance development, immunomodulatory effects that enhance host defense mechanisms, potential for combination therapies with synergistic effects, and relatively lower production costs in some instances [22]. Furthermore, the historical use of medicinal plants in traditional healing systems provides valuable leads for scientific investigation and drug development [23].

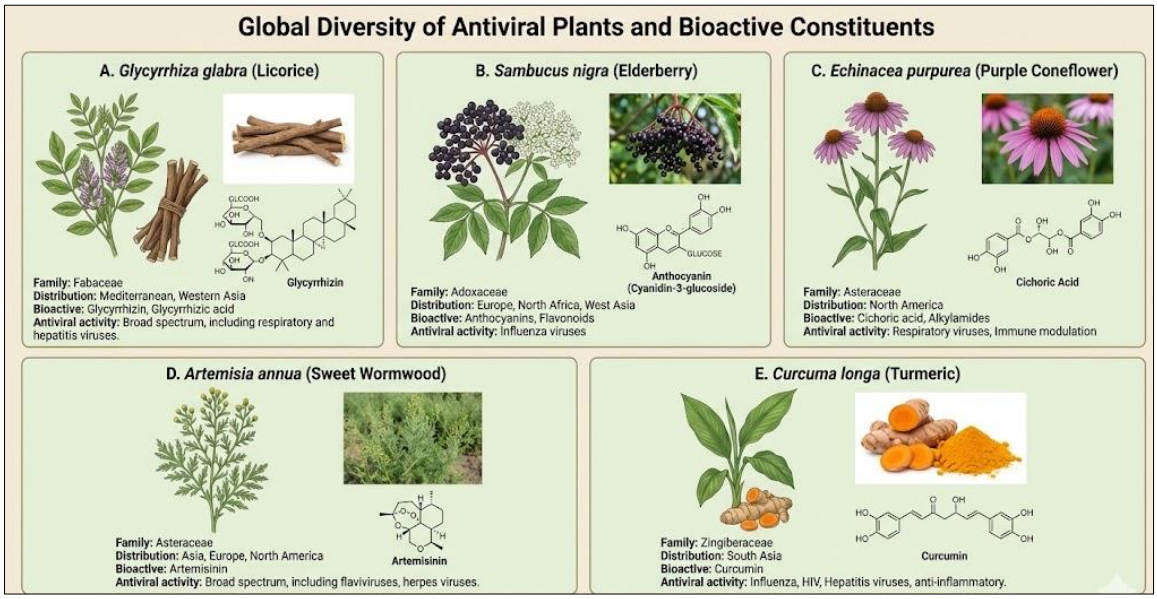

Fig 1: Representative plant species and extracts evaluated for antiviral activity

Screening and Selection of Plant-Derived Antiviral Compounds

The identification and isolation of bioactive compounds from plant sources require systematic approaches that integrate ethnobotanical knowledge, phytochemical analysis, and biological activity screening [24]. The initial selection of candidate plant species is often guided by traditional medicine practices, ethnopharmacological surveys, and historical documentation of plants used for treating infectious diseases [25]. Ethnobotanical studies conducted in diverse cultural contexts have revealed that numerous plant species have been employed traditionally for managing symptoms associated with viral infections, including fever, inflammation, respiratory distress, and skin lesions [26]. This traditional knowledge provides valuable starting points for scientific investigation, although rigorous validation through controlled experiments is essential to confirm antiviral activity and identify active constituents [27].

Comprehensive screening programs typically begin with the preparation of crude extracts using solvents of varying polarity, including water, ethanol, methanol, ethyl acetate, hexane, and dichloromethane, to extract compounds with different physicochemical properties [28]. Aqueous extracts often contain polar compounds such as polysaccharides, glycosides, and phenolic acids, whereas organic solvent extracts preferentially extract less polar constituents including terpenoids, alkaloids, and lipophilic flavonoids [29]. Sequential extraction procedures employing solvents of increasing polarity enable fractionation of crude extracts into enriched fractions, facilitating subsequent bioactivity-guided isolation of active compounds [30].

In vitro antiviral screening assays constitute the primary tool for evaluating the antiviral potential of plant extracts and isolated compounds. Cytopathic effect inhibition assays measure the ability of test compounds to prevent virus-induced morphological changes or cell death in cultured cells [31]. Plaque reduction assays quantify the reduction in viral plaques formed on monolayers of susceptible cells following treatment with test compounds, providing a measure of antiviral potency [32]. Viral yield reduction assays employ quantitative techniques such as quantitative polymerase chain reaction, enzyme-linked immunosorbent assay, or fluorescence-based methods to measure reductions in viral titers in culture supernatants [33]. Time-of-addition experiments help elucidate the stage of the viral life cycle targeted by test compounds, distinguishing between effects on viral entry, replication, or release [34].

Bioactivity-guided fractionation represents a systematic approach for isolating active constituents from complex plant extracts. Following initial screening of crude extracts, active fractions are subjected to chromatographic separation techniques including column chromatography, high-performance liquid chromatography, and thin-layer chromatography [35]. Each resulting fraction is tested for antiviral activity, and active fractions are further fractionated in iterative cycles until pure compounds are obtained [36]. Structural elucidation of isolated compounds is achieved through spectroscopic techniques including ultraviolet-visible spectroscopy, infrared spectroscopy, nuclear magnetic resonance spectroscopy, and mass spectrometry, often in combination with X-ray crystallography for definitive structure determination.

The selectivity of antiviral activity is assessed by determining the selectivity index, calculated as the ratio of the cytotoxic concentration affecting fifty percent of cells to the concentration inhibiting fifty percent of viral replication. Compounds with high selectivity indices exhibit preferential antiviral effects with minimal cytotoxicity, making them more promising candidates for further development. Structure-activity relationship studies involving chemical modifications of lead compounds help identify functional groups critical for antiviral activity and guide optimization efforts to enhance potency and selectivity.

Mechanistic Insights: Viral Targets and Molecular Pathways

Plant-derived antiviral compounds exert their effects through diverse mechanisms that interfere with multiple stages of viral life cycles, target viral structural and enzymatic proteins, and modulate host cellular processes essential for viral replication. Understanding these mechanisms is crucial for rational drug design, prediction of resistance development, and identification of combination therapy opportunities. The multi-target nature of many

phytochemicals distinguishes them from conventional antivirals and may contribute to reduced likelihood of resistance emergence.

Inhibition of viral entry represents a critical intervention point that prevents establishment of infection. Many plant-derived compounds interfere with viral attachment to host cell receptors by blocking viral surface glycoproteins or competing with viruses for binding sites on cellular receptors. Polysaccharides isolated from various plant species, including sulfated polysaccharides from algae and acidic polysaccharides from terrestrial plants, exhibit potent antiviral activity by electrostatically interacting with positively charged regions of viral envelope proteins, thereby preventing viral adsorption to negatively charged cell surface glycosaminoglycans. Lectins derived from plants recognize and bind to specific carbohydrate moieties on viral glycoproteins, preventing conformational changes required for membrane fusion or blocking receptor binding sites.

Following viral entry, membrane fusion between viral and cellular membranes is essential for releasing viral genetic material into the cytoplasm. Several phytochemicals inhibit this process by stabilizing viral envelope proteins in their pre-fusion conformation or by altering membrane properties that are necessary for fusion. Triterpene saponins and certain flavonoids have been shown to interfere with membrane fusion events, thereby blocking viral infectivity. Additionally, compounds that acidify endosomal compartments or interfere with endosomal maturation can prevent pH-dependent viral uncoating, a mechanism employed by many enveloped viruses.

Inhibition of viral nucleic acid replication constitutes another major mechanism of action for plant-derived antivirals. Numerous compounds target viral polymerases, including RNA-dependent RNA polymerases of RNA viruses and reverse transcriptases of retroviruses. Nucleoside analogs of plant origin can be incorporated into viral genomes during replication, leading to chain termination or introduction of mutations that compromise viral fitness. Non-nucleoside inhibitors bind to allosteric sites on viral polymerases, inducing conformational changes that reduce enzymatic activity. For example, glycyrrhizin and glycyrrhizic acid from licorice have been shown to inhibit viral replication through multiple mechanisms, including interference with viral gene expression and protein synthesis.

Protease inhibitors represent another important class of antiviral phytochemicals. Viral proteases are essential for processing polyproteins into functional viral proteins, and their inhibition prevents the production of infectious viral particles. Flavonoids such as quercetin, baicalein, and epigallocatechin gallate have demonstrated inhibitory activity against viral proteases from human immunodeficiency virus, hepatitis C virus, and severe acute respiratory syndrome coronavirus. These compounds typically bind to the active site of proteases through hydrogen bonding and hydrophobic interactions, competing with natural substrates.

Table 1: Selected plant-derived compounds, viral targets, and *in vitro*/*in vivo* antiviral activity

Compound	Plant Source	Chemical Class	Viral Target	*In vitro* Activity	*In vivo* Activity	Proposed Mechanism
Glycyrrhizin	Glycyrrhiza glabra	Triterpene saponin	Influenza virus, HSV, HCV	IC50 range 0.1-50 micromolar	Reduced viral titers in mouse models	Inhibition of viral replication and membrane fusion
Quercetin	Multiple plant sources	Flavonoid	Influenza, dengue, HSV	IC50 range 5-100 micromolar	Decreased mortality in influenza-infected mice	Polymerase inhibition, antioxidant effects
Baicalin	Scutellaria baicalensis	Flavone glycoside	Influenza, HIV, HCV	IC50 range 1-40 micromolar	Reduced lung viral loads in animal models	Neuraminidase inhibition, immunomodulation
Curcumin	Curcuma longa	Diarylheptanoid	HIV, HSV, influenza, HCV	IC50 range 10-100 micromolar	Anti-inflammatory effects *in vivo*	Inhibition of viral entry and replication
Resveratrol	Vitis vinifera, Polygonum cuspidatum	Stilbene	Influenza, HSV, varicella-zoster	IC50 range 5-50 micromolar	Extended survival in viral infection models	NF-kappa B inhibition, antioxidant activity
Andrographolide	Andrographis paniculata	Diterpenoid lactone	Influenza, HIV, HSV	IC50 range 10-80 micromolar	Reduced viral replication in lungs	Immunostimulation, viral protein synthesis inhibition
Artemisinin	Artemisia annua	Sesquiterpene lactone	Cytomegalovirus, HCV, HIV	IC50 range 20-100 micromolar	Limited *in vivo* data available	Oxidative stress induction, protein modification
Emodin	Rheum palmatum, Polygonum spp	Anthraquinone	SARS-CoV, HSV, HBV	IC50 range 10-200 micromolar	Antiviral effects in animal infection models	Spike protein interaction, 3CL protease inhibition

Abbreviations: HSV, herpes simplex virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HBV, hepatitis B virus; SARS-CoV, severe acute respiratory syndrome coronavirus; IC50, half-maximal inhibitory concentration; NF-kappa B, nuclear factor kappa B; 3CL, 3-chymotrypsin-like protease.

Plant-derived compounds also modulate host immune responses, enhancing antiviral defenses while potentially mitigating excessive inflammatory responses that contribute to pathology. Polysaccharides from Echinacea, Astragalus, and other immunomodulatory plants stimulate innate immune cells, enhance cytokine production, and increase natural killer cell activity. Certain flavonoids and terpenoids activate pattern recognition receptors, triggering interferon production and establishment of antiviral states in cells. Conversely, anti-inflammatory phytochemicals such as curcumin and resveratrol suppress excessive production of pro-inflammatory cytokines, potentially preventing cytokine storm phenomena observed in severe viral infections.

Inhibition of viral assembly and release represents additional mechanisms employed by some plant-derived antivirals. Compounds that interfere with viral protein glycosylation,

lipid raft formation, or budding processes can prevent the formation of infectious viral particles. Neuraminidase inhibitors of plant origin prevent the release of influenza virions from infected cells by blocking cleavage of sialic acid residues. Furthermore, certain phytochemicals induce autophagy or apoptosis in infected cells, limiting viral spread while eliminating reservoirs of viral replication.

Preclinical Evaluation: *In vitro* and *In vivo* Studies

The preclinical evaluation of plant-derived antiviral compounds encompasses a spectrum of experimental approaches designed to assess efficacy, elucidate mechanisms, determine pharmacokinetic properties, and evaluate safety profiles prior to clinical translation. *In vitro* studies provide controlled environments for investigating direct antiviral effects, cytotoxicity, and preliminary mechanistic insights, while *in vivo* studies in animal models offer critical information regarding therapeutic efficacy in complex biological systems, pharmacokinetics, tissue distribution, and potential adverse effects.

Cell culture models represent the foundation of *in vitro* antiviral research, utilizing immortalized cell lines or primary cells susceptible to specific viral pathogens. Vero cells, derived from African green monkey kidney epithelial cells, are widely employed for culturing diverse viruses including influenza, herpes simplex virus, dengue virus, and coronaviruses. Human hepatoma cell lines such as Huh-7 and HepG2 are standard models for hepatitis C virus and hepatitis B virus research, while peripheral blood mononuclear cells and T-cell lines are utilized for human immunodeficiency virus studies. The selection of appropriate cell culture models is crucial, as antiviral activity can vary depending on cell type, viral strain, and multiplicity of infection.

Quantitative assessment of antiviral activity *in vitro* employs various methodological approaches. Plaque reduction assays, considered a gold standard for many viruses, provide direct visualization and quantification of infectious viral particles. Cytopathic effect-based assays utilize microscopic observation or colorimetric indicators to assess cell viability following viral infection in the presence of test compounds. Real-time quantitative polymerase chain reaction enables precise quantification of viral nucleic acids in infected cell cultures, offering high sensitivity and specificity. Flow cytometry-based methods allow detection of viral antigens or infected cells through fluorescently labeled antibodies, providing single-cell resolution and quantitative data. Reporter virus systems incorporating fluorescent or luminescent markers facilitate high-throughput screening and real-time monitoring of viral replication dynamics.

Time-of-addition studies provide valuable mechanistic information by determining the stage of viral infection affected by test compounds. Pre-treatment experiments assess prophylactic effects and ability to prevent viral entry, simultaneous treatment evaluates direct virucidal activity, and post-infection treatment examines effects on viral replication and spread. Viral entry assays employing pseudotyped viruses or temperature synchronization protocols enable specific evaluation of compounds targeting attachment, fusion, or uncoating processes. Viral replication assays measuring viral RNA or protein synthesis distinguish compounds affecting genome replication from those interfering with protein translation or post-translational modifications.

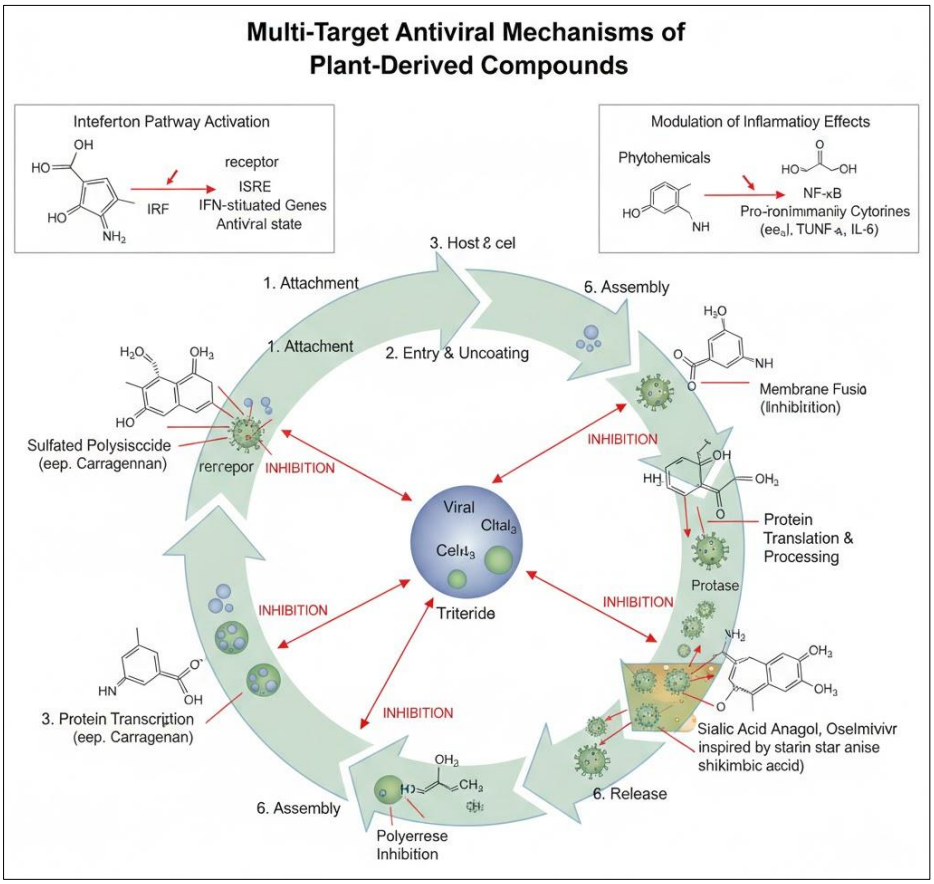

Fig 2: Mechanisms of action of selected phytochemicals against viral replication and entry

Animal models constitute an essential bridge between *in vitro* findings and clinical applications, providing complex biological contexts that recapitulate aspects of human viral infections. Mouse models are the most commonly employed due to their genetic tractability, well-characterized immunology, availability of reagents, and cost-effectiveness. Specific pathogen-free mice, transgenic mice expressing human receptors, and humanized mice with reconstituted human immune systems enable studies of viruses with restricted host ranges. Influenza virus infection models in mice have been extensively utilized to evaluate antiviral efficacy of plant-derived compounds, with readouts including survival rates, body weight changes, viral titers in respiratory tissues, lung pathology, and inflammatory markers.

Herpes simplex virus models employ cutaneous, ocular, or genital infection routes in mice or guinea pigs to assess therapeutic and prophylactic efficacy of antiviral compounds. Lesion severity scoring, viral shedding quantification, latency establishment, and reactivation frequencies provide comprehensive evaluation of antiviral effects. Hepatitis virus models have traditionally been challenging due to species specificity, but development of humanized mouse models and woodchuck hepatitis virus models in woodchucks have enabled preclinical evaluation of compounds targeting hepatitis B and C viruses. Human immunodeficiency virus research utilizes simian immunodeficiency virus infection in non-human primates, humanized mouse models, or ex vivo human tissue explant systems.

Pharmacokinetic studies in animal models provide critical information regarding absorption, distribution, metabolism, and excretion of plant-derived compounds. Oral bioavailability is often a major challenge for phytochemicals, particularly polar compounds such as glycosides and polysaccharides, which exhibit poor membrane permeability. Many flavonoids undergo extensive first-pass metabolism, resulting in low systemic exposure and necessitating formulation strategies to enhance bioavailability. Tissue distribution studies employing radiolabeled compounds or liquid chromatography-mass spectrometry methods reveal whether compounds achieve therapeutic concentrations in target organs such as lungs for respiratory viruses or liver for hepatitis viruses. Metabolism studies identify major metabolic pathways and active or inactive metabolites, informing dosing strategies and potential drug interactions.

Dose-response relationships established in animal models guide clinical dose selection and provide preliminary safety margins. Therapeutic index calculations comparing doses producing antiviral effects to those causing toxicity help identify compounds with favorable safety profiles. Combination therapy studies in animal models evaluate potential synergistic interactions between plant-derived compounds and conventional antivirals or between multiple phytochemicals. Such combinations may enable dose reduction, broaden antiviral spectrum, or delay resistance development.

Clinical Evidence and Human Trials

The translation of promising preclinical findings into clinical applications requires rigorous evaluation through well-designed human trials that assess safety, efficacy, optimal dosing, and patient populations most likely to benefit. Clinical evidence for plant-derived antivirals varies considerably in quality and extent, ranging from small observational studies and case reports to randomized controlled trials with hundreds of participants. Despite the widespread traditional use of medicinal plants for viral infections, high-quality clinical evidence remains limited for many compounds, highlighting the need for investment in rigorous clinical research.

Phase I clinical trials focus primarily on safety, tolerability, and pharmacokinetics in healthy volunteers or patients. These studies employ dose-escalation designs to identify maximum tolerated doses, characterize adverse event profiles, and establish pharmacokinetic parameters in human subjects. Several plant-derived compounds have progressed through Phase I evaluation, demonstrating acceptable safety profiles within defined dose ranges. For example, glycyrrhizin has been evaluated in clinical trials for chronic hepatitis, with dose-limiting toxicities including mineralocorticoid effects such as hypertension and hypokalemia at higher doses. Curcumin has been assessed in numerous Phase I trials for various indications, generally demonstrating good tolerability despite poor oral bioavailability.

Phase II trials evaluate preliminary efficacy in patients with viral infections while continuing to assess safety in larger cohorts. These proof-of-concept studies employ various endpoints depending on the viral infection, including viral load reductions, symptom severity scores, duration of illness, hospitalization rates, and biomarkers of infection or inflammation. Elderberry extracts standardized for anthocyanin content have been evaluated in randomized controlled trials for influenza, with some studies demonstrating significant reductions in symptom duration and severity compared to placebo. However, methodological limitations including small sample sizes, lack of standardization, and heterogeneity in extract composition have limited the strength of conclusions.

Echinacea preparations have been extensively studied for prevention and treatment of upper respiratory tract infections, predominantly of viral etiology. Meta-analyses of clinical trials have yielded mixed results, with some suggesting modest reductions in infection incidence and symptom duration, while others found no significant benefit. Variability in Echinacea species, plant parts utilized, extraction methods, and dosing regimens across studies complicate interpretation and underscore the importance of standardization. Recent trials employing well-characterized Echinacea purpurea extracts with defined phytochemical profiles have provided more consistent evidence of efficacy in reducing cold symptom severity and duration.

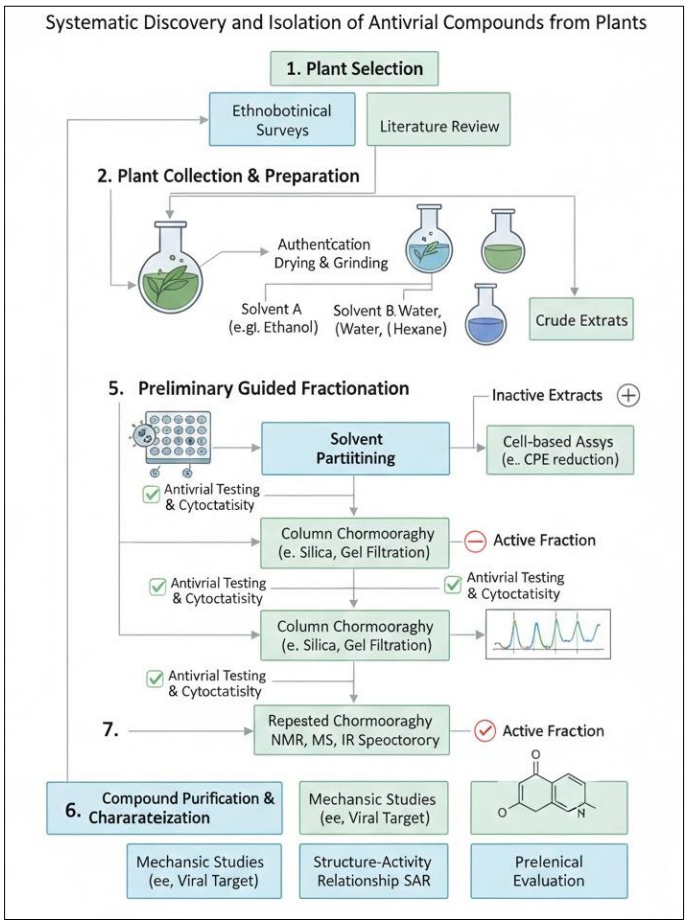

Fig 3: Workflow from plant extraction to isolation of bioactive antiviral compounds

Andrographis paniculata extracts and its major constituent andrographolide have demonstrated promise in clinical trials for respiratory viral infections. Systematic reviews and meta-analyses of randomized controlled trials have indicated that andrographis preparations significantly reduce symptom severity and duration in acute upper respiratory tract infections compared to placebo, with effect sizes comparable to conventional symptomatic treatments. Standardized extracts providing consistent andrographolide content appear more effective than unstandardized preparations, emphasizing the importance of quality control.

Glycyrrhizin has been investigated in clinical trials for chronic hepatitis B and C infections, administered intravenously in many studies to overcome bioavailability limitations. Some trials have reported improvements in liver function tests, reductions in hepatitis C virus RNA levels, and histological improvements in liver biopsies. However, results have been inconsistent across studies, and glycyrrhizin is not considered a standard treatment in current guidelines, though it may serve as adjunctive therapy in some contexts. Stronger glycyrrhizin derivatives have been developed and tested clinically with improved efficacy profiles.

Resveratrol has been evaluated in clinical trials for various viral infections, including human immunodeficiency virus and hepatitis C virus. While preclinical data suggested promising antiviral and anti-inflammatory effects, clinical trials have yielded modest results, potentially due to poor bioavailability and extensive metabolism. Novel formulations designed to enhance resveratrol bioavailability are under investigation and may improve clinical outcomes.

Artemisinin and its derivatives, primarily known as antimalarial agents, have shown *in vitro* antiviral activity against multiple viruses, but clinical evidence for antiviral applications remains limited. Small clinical studies have explored artemisinin derivatives for cytomegalovirus infections in immunocompromised patients and for hepatitis B and C infections, with mixed results requiring further investigation.

Table 2: Summary of clinical studies with plant-derived antivirals, including outcomes, formulation, and safety

Study	Plant Product	Viral Indication	Study Design	Sample Size	Formulation	Primary Outcome	Safety Profile
Zakay-Rones *et al*., 2004	Sambucus nigra extract	Influenza A and B	Randomized controlled trial	60	Standardized elderberry syrup, 15 mL four times daily	Significant reduction in symptom duration by 4 days	Well tolerated, no serious adverse events
Shah *et al*., 2007	Echinacea purpurea	Upper respiratory tract infections	Randomized controlled trial	282	Pressed juice tablets, 900 mg daily	Reduced infection duration and severity	Mild gastrointestinal effects in small percentage
Poolsup *et al*., 2004	Andrographis paniculata	Acute respiratory infections	Meta-analysis of RCTs	896 total participants	Various standardized extracts	Symptom score reduction and faster recovery	Generally well tolerated, rare allergic reactions
van Rossum *et al*., 1999	Glycyrrhizin	Chronic hepatitis C	Randomized controlled trial	46	Intravenous injection, 120 mg daily	Modest ALT normalization, mixed HCV RNA effects	Mineralocorticoid effects at higher doses
Cáceres *et al*., 1997	Andrographis paniculata	Upper respiratory tract infections	Randomized controlled trial	158	Dried leaf powder capsules, 1200 mg daily	Faster symptom resolution versus placebo	Mild adverse events, headache and fatigue
Jawad *et al*., 2012	Echinacea purpurea	Common cold prevention	Randomized controlled trial	755	Hydroethanolic extract, 2400 mg daily	Reduced cold episodes and cumulative cold days	Well tolerated, similar to placebo
Kong *et al*., 2009	Glycyrrhiza uralensis	Chronic hepatitis B	Randomized controlled trial	379	Modified glycyrrhizin injection	Improved liver histology in subset	Elevated blood pressure in some patients
Krawitz *et al*., 2011	Sambucus nigra	Influenza virus	*In vitro* followed by pilot study	64 pilot participants	Elderberry liquid extract standardized for flavonoids	Inhibition of viral neuraminidase and clinical improvement	No significant adverse effects reported

Abbreviations: RCT, randomized controlled trial; ALT, alanine aminotransferase; HCV, hepatitis C virus.

Phase III trials, which definitively establish efficacy and safety in large patient populations, are relatively uncommon for plant-derived antivirals due to the high costs and regulatory complexities involved. Most plant-based products are marketed as dietary supplements or traditional medicines rather than prescription pharmaceuticals, which reduces incentives for pharmaceutical companies to invest in expensive clinical trial programs. Nonetheless, several plant-derived compounds and standardized extracts have been evaluated in large-scale trials, particularly in countries with strong traditional medicine integration into healthcare systems.

The quality of clinical evidence is often compromised by methodological limitations including inadequate randomization, lack of blinding, small sample sizes, heterogeneous patient populations, variable product standardization, and publication bias favoring positive results. Many clinical trials of herbal medicines fail to adequately characterize the phytochemical composition of tested products, making replication difficult and limiting mechanistic insights. Future clinical research should prioritize rigorous study designs, standardized products with well-defined phytochemical profiles, appropriate sample sizes calculated through power analyses, validated endpoints aligned with regulatory requirements, and transparent reporting of all outcomes including negative results.

Formulation Strategies for Enhanced Efficacy and Bioavailability

The clinical translation of plant-derived antiviral compounds is frequently hindered by unfavorable pharmacokinetic properties including poor aqueous solubility, low membrane permeability, extensive first-pass metabolism, rapid clearance, and limited tissue distribution. These limitations necessitate the development of innovative formulation strategies designed to enhance bioavailability, improve stability, enable targeted delivery, and optimize therapeutic outcomes. Advances in pharmaceutical technology and nanotechnology have provided diverse approaches to overcome these challenges and unlock the full therapeutic potential of phytochemicals.

Enhancement of aqueous solubility represents a primary objective for many lipophilic phytochemicals. Cyclodextrin complexation involves encapsulation of poorly soluble compounds within the hydrophobic cavity of cyclic oligosaccharides, improving apparent solubility while protecting compounds from degradation. Various cyclodextrin derivatives including beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin, and sulfobutylether-beta-cyclodextrin have been employed to enhance the solubility and bioavailability of curcumin, quercetin, and resveratrol. Solid dispersion techniques, wherein compounds are dispersed at molecular levels within hydrophilic carrier matrices such as polyvinylpyrrolidone or polyethylene glycol, dramatically increase dissolution rates and absorption.

Lipid-based formulations exploit the lipophilic nature of many phytochemicals to enhance oral bioavailability. Self-emulsifying drug delivery systems spontaneously form fine emulsions upon contact with gastrointestinal fluids, facilitating absorption via lymphatic pathways and bypassing first-pass hepatic metabolism. Liposomes, spherical vesicles composed of phospholipid bilayers, encapsulate both hydrophilic and lipophilic compounds, protecting them from degradation while enabling controlled release and cellular uptake. Solid lipid nanoparticles and nanostructured lipid carriers combine advantages of liposomes with improved stability and scalability.

Polymeric nanoparticles fabricated from biocompatible and biodegradable polymers such as poly lactic-co-glycolic acid,

chitosan, or alginate provide versatile platforms for encapsulation and controlled release of antiviral phytochemicals. These nanoparticles can be surface-modified with targeting ligands to achieve tissue-specific or cell-specific delivery, potentially enhancing accumulation at sites of viral replication while minimizing systemic exposure and off-target effects. For respiratory viral infections, nanoparticles can be formulated for pulmonary delivery via inhalation, achieving high local concentrations in the lungs while reducing systemic absorption.

Mucoadhesive formulations utilizing polymers such as chitosan, carbopol, or hyaluronic acid prolong residence time at mucosal surfaces, enhancing absorption of poorly permeable compounds and providing sustained local antiviral effects at viral entry sites. Chitosan, a cationic polysaccharide derived from chitin, exhibits intrinsic antimicrobial and antiviral properties in addition to its formulation advantages, making it particularly attractive for antiviral applications.

Prodrug strategies involve chemical modification of parent compounds to improve pharmacokinetic properties, with enzymatic or chemical conversion to active forms occurring *in vivo*. Esterification of phenolic groups, for example, increases lipophilicity and membrane permeability, with subsequent hydrolysis by esterases releasing active compounds. Glycosylation can improve solubility and stability while providing substrates for intestinal glycosidases or bacterial enzymes in the colon, enabling targeted delivery.

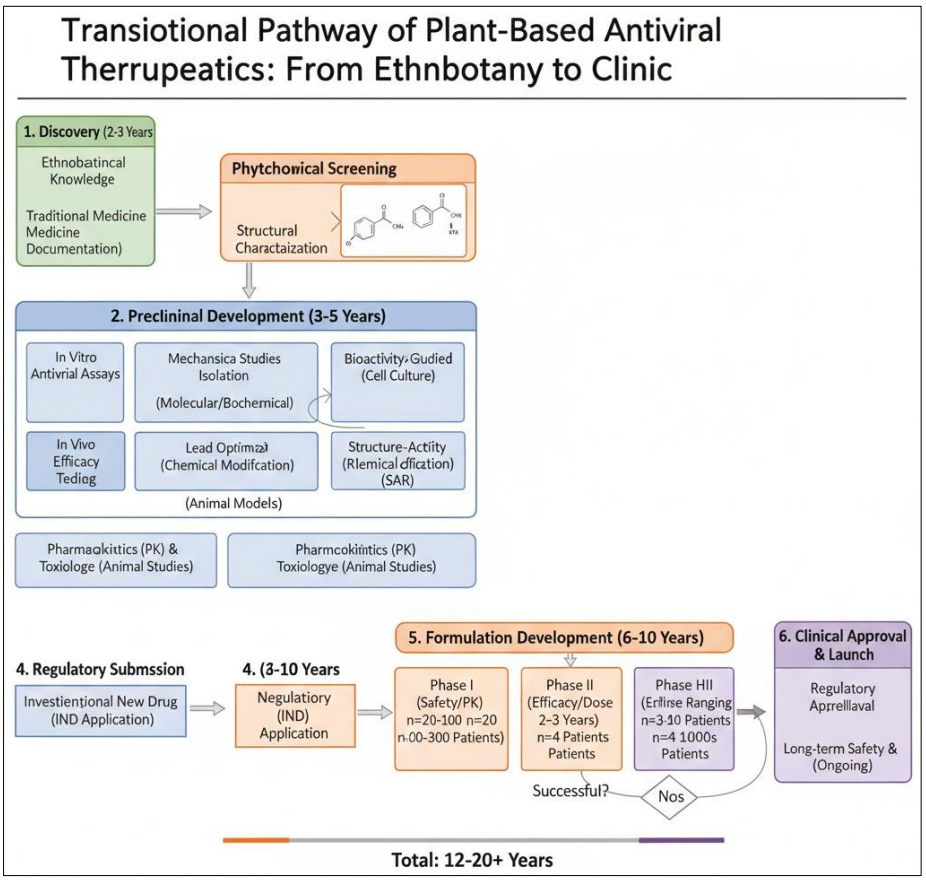

Fig 4: Translational pathway from preclinical studies to clinical evaluation of plant-derived antiviral

Microencapsulation and coating technologies protect sensitive phytochemicals from environmental degradation while enabling controlled release kinetics. Enteric coatings prevent premature dissolution in the acidic gastric environment, releasing compounds in the intestine where absorption is more favorable. Sustained-release formulations maintain therapeutic concentrations over extended periods, reducing dosing frequency and improving patient compliance.

Phytosome technology, involving complexation of phytochemicals with phospholipids, enhances membrane permeability and bioavailability. Phytosomes of flavonoids and other polyphenols have demonstrated significantly improved absorption and prolonged plasma residence times compared to unconjugated compounds. Commercial phytosome formulations of silymarin, curcumin, and green tea catechins have shown enhanced clinical efficacy. Combination formulations incorporating multiple plant-derived compounds or combining phytochemicals with conventional antivirals may provide synergistic benefits, broader antiviral spectrum, or reduced resistance development. Fixed-dose combinations simplify dosing regimens and improve adherence. However, potential interactions must be carefully evaluated to avoid antagonism or unexpected toxicities.

Safety, Toxicity, and Herb–Drug Interactions

Despite the common perception that natural products are inherently safe, plant-derived compounds can elicit adverse effects, exhibit organ toxicity, and interact with conventional medications, necessitating thorough safety evaluation. The therapeutic index of many phytochemicals may be narrower than anticipated, particularly with chronic use or in vulnerable populations such as pregnant women, children, elderly individuals, and those with hepatic or renal impairment. Comprehensive preclinical toxicology studies

and vigilant pharmacovigilance during clinical use are essential to ensure patient safety.

Acute toxicity studies in animal models establish lethal dose values and identify target organs of toxicity. Most plant-derived antiviral compounds exhibit relatively low acute toxicity, with lethal dose fifty percent values considerably higher than therapeutic doses. However, certain classes of compounds warrant caution. Pyrrolizidine alkaloids found in some medicinal plants can cause hepatotoxicity and hepatic veno-occlusive disease with both acute and chronic exposure. Aristolochic acids, present in Aristolochia species used traditionally in some cultures, are nephrotoxic and carcinogenic, leading to regulatory bans in many countries.

Chronic toxicity studies evaluate effects of prolonged exposure over weeks to months in animal models, revealing cumulative toxicities not apparent in acute studies. Glycyrrhizin, when administered chronically, inhibits 11-beta-hydroxysteroid dehydrogenase, leading to cortisol-mediated activation of mineralocorticoid receptors and subsequent hypertension, hypokalemia, and edema. These effects are dose-dependent and reversible upon discontinuation, but necessitate monitoring during prolonged use. Patients with cardiovascular disease, hypertension, or those taking medications affecting electrolyte balance require particular caution.

Hepatotoxicity represents a concern with certain plant-derived compounds and herbal products. While many phytochemicals exhibit hepatoprotective properties, others may cause liver injury, particularly with high doses or prolonged use. Kava, used traditionally in Pacific Island cultures, has been associated with cases of severe hepatotoxicity, leading to regulatory restrictions in several countries. Quality issues including contamination, adulteration, and improper processing have been implicated in some cases of herbal hepatotoxicity, highlighting the importance of quality assurance.

Genotoxicity and carcinogenicity assessments are critical for compounds intended for long-term use. While most plant-derived antivirals evaluated to date have not demonstrated significant genotoxic or carcinogenic potential in standard assays, comprehensive testing is warranted, particularly for compounds undergoing chemical modifications or novel derivatives. Some natural products contain promutagens that are activated to genotoxic metabolites by cytochrome P450 enzymes or gut microbiota.

Herb-drug interactions represent a significant clinical concern, occurring through pharmacokinetic or pharmacodynamic mechanisms. Pharmacokinetic interactions involve alterations in absorption, distribution, metabolism, or excretion of conventional drugs by phytochemicals. Many plant-derived compounds modulate cytochrome P450 enzymes responsible for drug metabolism. St. John's wort, widely used for depression, is a potent inducer of CYP3A4 and P-glycoprotein, significantly reducing plasma concentrations of numerous drugs including antivirals, immunosuppressants, oral contraceptives, and anticoagulants. Conversely, grapefruit juice and certain flavonoids inhibit CYP3A4, increasing drug concentrations and risk of toxicity.

Quercetin, curcumin, and resveratrol have been shown to modulate various cytochrome P450 isoforms and drug transporters *in vitro*, though the clinical significance remains uncertain for many interactions. Glycyrrhizin may interfere with renal excretion of certain drugs and potentiate effects of corticosteroids. Careful consideration of potential interactions is essential when combining plant-derived antivirals with conventional medications, particularly those with narrow therapeutic indices such as anticoagulants, immunosuppressants, or antiarrhythmics.

Pharmacodynamic interactions occur when phytochemicals and conventional drugs exert additive, synergistic, or antagonistic effects on common biological targets. While synergistic antiviral effects may be therapeutically beneficial, additive toxicities require monitoring. For example, combining antiplatelet or anticoagulant medications with plant-derived compounds exhibiting similar effects may increase bleeding risk. Immunomodulatory phytochemicals might theoretically interfere with immunosuppressive therapies in transplant recipients, though clinical evidence is limited.

Pregnancy and lactation represent special considerations, as safety data for most plant-derived compounds in these populations are scarce. Many traditional medicines are contraindicated during pregnancy due to potential teratogenic effects, uterine stimulation, or hormonal influences. Animal reproductive toxicity studies and pregnancy registries provide some guidance, but cautious approaches are warranted.

Quality control and authentication of plant materials are paramount for ensuring safety and consistency. Misidentification of plant species, contamination with toxic plants, presence of heavy metals or pesticides, and adulteration with synthetic drugs have been documented in herbal products. Standardization based on marker compounds, fingerprinting techniques, and adherence to good manufacturing practices help ensure product quality and minimize safety risks.

Regulatory and Standardization Considerations

The regulatory landscape for plant-derived medicines varies considerably across countries, reflecting diverse cultural attitudes toward traditional medicine, differing regulatory frameworks, and varying standards for evidence and quality assurance. These regulatory differences create challenges for global development and marketing of plant-based antivirals while also influencing the types and quality of evidence required for approval. Understanding these regulatory pathways is essential for successful translation of promising compounds from laboratory to clinic.

In the United States, most plant-derived products are regulated as dietary supplements under the Dietary Supplement Health and Education Act, which does not require premarket approval by the Food and Drug Administration. Manufacturers may make structure-function claims but cannot claim to diagnose, treat, cure, or prevent diseases without undergoing the rigorous drug approval process. For a plant-derived compound to be approved as a pharmaceutical drug in the United States, sponsors must file an investigational new drug application prior to clinical trials, followed by a new drug application demonstrating safety and efficacy through adequate and well-controlled clinical trials. Botanical drug products, a specific regulatory category, allow for standardized botanical preparations to be approved as prescription drugs if they meet quality, safety, and efficacy requirements.

The European Medicines Agency employs several regulatory pathways for herbal medicines. The traditional use registration scheme allows marketing of herbal medicinal

products based on long-standing traditional use without requiring clinical efficacy data, provided safety is demonstrated and the product has been in medicinal use for at least 30 years, including 15 years within the European Union. Alternatively, herbal medicinal products can undergo the standard marketing authorization procedure requiring comprehensive preclinical and clinical data demonstrating quality, safety, and efficacy. Well-established use applications allow authorization based on scientific literature and expert opinions rather than requiring sponsors to conduct new clinical trials.

Many Asian countries with strong traditional medicine systems have developed specific regulatory frameworks integrating traditional knowledge with modern scientific standards. In China, traditional Chinese medicines are regulated separately from conventional drugs, with requirements for standardization, quality control, preclinical studies, and clinical trials adapted to the characteristics of herbal medicines. Japan's Kampo medicines, traditional formulations officially recognized in the national health insurance system, must meet pharmaceutical standards while preserving traditional compositions. India's Ayurvedic, Siddha, and Unani drugs are regulated under specific legislation requiring manufacturing standards and safety assurance, though clinical efficacy requirements may differ from conventional pharmaceuticals.

Standardization of plant-derived medicines presents unique challenges due to the inherent variability in phytochemical composition influenced by genetic factors, growing conditions, harvest timing, processing methods, and storage. Establishing specifications for marker compounds or groups of active constituents helps ensure batch-to-batch consistency, though the relationship between marker compounds and overall therapeutic activity may not always be straightforward. Fingerprinting approaches using chromatographic or spectroscopic techniques capture the complexity of multicomponent botanical preparations, enabling quality assessment that considers the totality of constituents rather than single compounds.

Good agricultural and collection practices provide guidelines for cultivation, harvesting, and primary processing of medicinal plants to ensure quality and sustainability. These practices address issues such as correct species identification, optimal harvest timing, appropriate drying and storage conditions, prevention of contamination, and environmental protection. Good manufacturing practices for botanical products encompass facility requirements, equipment maintenance, quality control testing, documentation, and personnel training to ensure consistent product quality.

Intellectual property considerations influence the development of plant-derived medicines. While naturally occurring compounds cannot be patented, novel formulations, dosage forms, uses, derivatives, or methods of isolation and purification may be patentable. Traditional knowledge protection mechanisms aim to prevent biopiracy and ensure equitable benefit sharing with indigenous communities and source countries, as outlined in the Convention on Biological Diversity and the Nagoya Protocol. Balancing intellectual property rights with access to medicines remains a contentious issue, particularly for antivirals needed in resource-limited settings.

Future Directions in Plant-Based Antiviral Drug Development

The field of plant-based antiviral drug discovery stands at an exciting juncture, with emerging technologies, evolving methodologies, and growing appreciation for natural product diversity creating unprecedented opportunities for therapeutic innovation. Future directions encompass multiple complementary approaches ranging from advanced screening technologies and computational methods to synthetic biology, systems pharmacology, and integration with modern medicine.

High-throughput screening platforms coupled with automated liquid handling, miniaturized assays, and advanced detection systems enable rapid evaluation of large botanical libraries against diverse viral targets [19 6]. Phenotypic screening using reporter viruses, high-content imaging, and artificial intelligence-driven image analysis can identify compounds affecting viral infection through any mechanism without requiring prior knowledge of molecular targets. Target-based screens employing purified viral enzymes, structural proteins, or reconstituted replication complexes enable focused identification of inhibitors for specific viral functions.

Computational approaches including virtual screening, molecular docking, and molecular dynamics simulations accelerate identification of promising compounds from virtual libraries of phytochemicals. Structure-based drug design utilizing crystallographic or cryo-electron microscopy structures of viral targets guides optimization of natural product leads and design of more potent analogs. Machine learning algorithms trained on existing structure-activity relationship data can predict antiviral activity of untested compounds, prioritizing experimental validation efforts. Network pharmacology and systems biology approaches elucidate complex mechanisms and identify synergistic combinations by modeling interactions between multiple compounds, targets, and biological pathways.

Synthetic biology and metabolic engineering offer innovative approaches to produce complex phytochemicals through microbial fermentation, potentially addressing supply chain limitations and sustainability concerns. Heterologous expression of plant biosynthetic pathways in yeast or bacteria enables scalable production of compounds difficult to extract from plants in sufficient quantities. Directed evolution and rational design of biosynthetic enzymes can generate novel analogs with improved properties. Semi-synthetic modifications of naturally derived scaffolds combine the structural complexity evolved in nature with medicinal chemistry optimization.

Emerging viral threats necessitate proactive antiviral drug discovery efforts. Broad-spectrum antivirals targeting conserved features of multiple viral families would provide valuable tools for responding to novel pathogens. Host-directed therapies targeting cellular processes essential for viral replication may be less prone to resistance development and could be effective against diverse viruses. Plant-derived immunomodulators that enhance antiviral immunity while limiting excessive inflammation represent promising host-directed strategies.

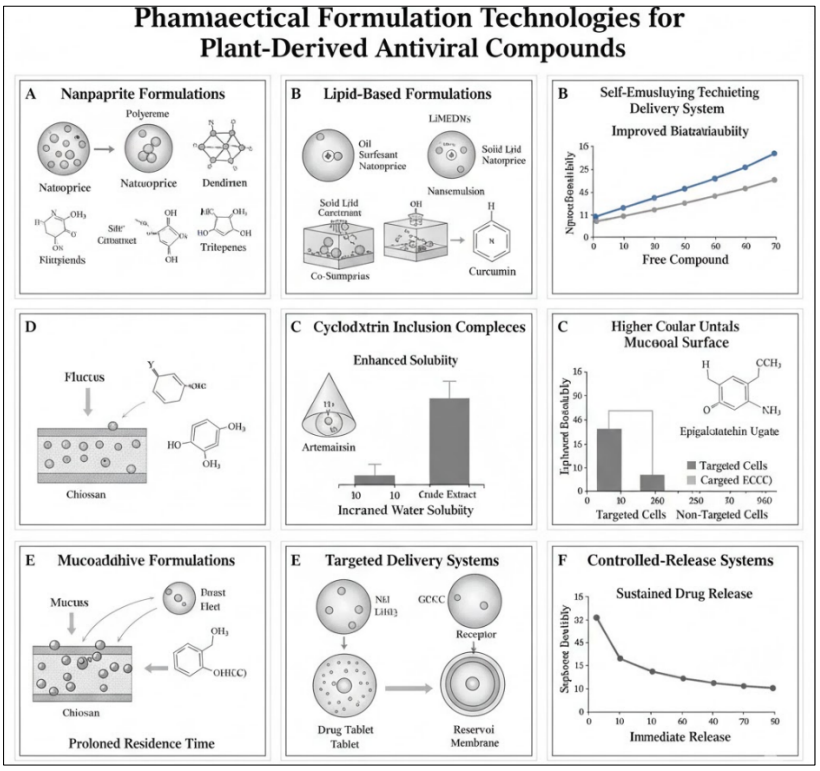

Fig 5: Formulation strategies for improving stability, bioavailability, and targeted delivery of antiviral phytochemicals

Integration of plant-derived antivirals with conventional therapies through rational combination regimens may enhance efficacy while reducing resistance development. Synergy studies employing checkerboard assays, isobologram analysis, or high-throughput combination screening identify optimal pairings. Mechanistic complementarity, such as combining inhibitors of viral entry with those targeting replication, provides rationale for combination strategies. Phytochemicals that reverse resistance to conventional antivirals through efflux pump inhibition or other mechanisms warrant investigation.

Personalized medicine approaches considering individual genetic variations in drug metabolism, viral strain characteristics, and immunological status may optimize therapeutic outcomes. Pharmacogenomic markers predicting response to plant-derived antivirals or susceptibility to adverse effects could guide treatment selection. Viral sequencing to identify resistance mutations or predict drug susceptibility enables precision antiviral therapy.

Sustainable sourcing and conservation of medicinal plants must be addressed to ensure long-term availability while protecting biodiversity. Overharvesting of wild populations threatens numerous valuable medicinal plant species. Cultivation programs, sustainable wildcrafting practices, and development of renewable sources through biotechnology contribute to conservation efforts. Equitable benefit sharing with indigenous communities and source countries acknowledges traditional knowledge contributions and provides economic incentives for conservation.

Interdisciplinary collaboration among ethnobotanists, phytochemists, virologists, pharmacologists, clinicians, and regulatory experts is essential for successful translation of plant-based antivirals. Academic-industry partnerships can accelerate development by combining academic expertise in natural product chemistry and virology with industry capabilities in formulation, large-scale manufacturing, and clinical development. Public-private partnerships and funding from governmental and philanthropic organizations support research addressing global health priorities.

Enhanced understanding of the gut microbiome's role in metabolizing phytochemicals and modulating their bioactivity opens new avenues for optimizing plant-based antivirals. Prebiotics and probiotics might be combined with phytochemicals to enhance beneficial microbial transformations or synergize immunomodulatory effects. Individual variations in gut microbiome composition could contribute to variability in response to plant-derived medicines.

Advances in delivery technologies including inhalable formulations for respiratory viruses, transdermal patches for sustained delivery, and mucoadhesive films for oral or genital viral infections expand therapeutic possibilities. Stimuli-responsive drug delivery systems that release antivirals in response to viral infection markers or inflammatory signals could provide targeted therapy with reduced off-target effects.

Conclusion

Plant-derived natural products represent a rich and largely untapped resource for antiviral drug discovery, offering diverse chemical scaffolds, multiple mechanisms of action, and centuries of traditional use as foundations for modern therapeutic development. This comprehensive review has examined the multifaceted landscape of plant-based antivirals, from initial screening and isolation through mechanistic elucidation, preclinical evaluation, clinical translation, and formulation optimization. The evidence demonstrates that numerous phytochemicals exhibit significant antiviral activity against diverse viral pathogens through mechanisms including inhibition of viral entry, replication, assembly, and release, as well as modulation of host immune responses.

Preclinical studies have established proof-of-concept for many plant-derived compounds, revealing potent antiviral effects in cell culture systems and animal models of viral infection. However, the translation of these promising findings to clinical applications has been hampered by pharmacokinetic limitations, insufficient standardization, inadequate clinical evidence, and regulatory complexities. The development of innovative formulation strategies employing nanotechnology, lipid-based carriers, and targeted delivery systems offers solutions to bioavailability challenges and represents a critical enabling technology for advancing plant-based antivirals.

Clinical evidence, while growing, remains heterogeneous in quality and limited in scope for most plant-derived antivirals. Rigorous, well-designed randomized controlled trials employing standardized products with defined phytochemical composition are essential to definitively establish efficacy and safety. The integration of modern analytical techniques, systems biology approaches, and computational methods with traditional knowledge creates unprecedented opportunities for rational design and optimization of plant-based antiviral therapeutics.

Safety considerations, including potential toxicities and herb-drug interactions, must be thoroughly evaluated and transparently communicated. The perception of natural products as inherently safe can lead to complacency regarding proper preclinical toxicology studies and pharmacovigilance. Quality assurance through standardization, authentication, and adherence to good manufacturing practices is paramount to ensure consistent therapeutic outcomes and patient safety.

The regulatory landscape presents both challenges and opportunities, with diverse pathways across jurisdictions reflecting different philosophical approaches to natural product medicines. Harmonization of regulatory standards, clear guidelines for botanical drug development, and mechanisms to leverage traditional use evidence while maintaining scientific rigor would facilitate global development and access to plant-based antivirals.

Looking forward, the convergence of traditional knowledge with cutting-edge technologies in genomics, synthetic biology, nanotechnology, and artificial intelligence promises to accelerate the discovery and development of plant-derived antivirals. Broad-spectrum antivirals, host-directed therapies, and rational combinations addressing the growing challenges of viral resistance and emerging pathogens are areas of particular promise. Sustainable sourcing practices, equitable benefit sharing, and interdisciplinary collaboration will be essential to realize the full potential of plant-based antiviral drug discovery while preserving biodiversity and respecting traditional knowledge.

In conclusion, plant-derived natural products offer significant promise as sources of novel antiviral therapeutics that could complement and potentially overcome limitations of conventional antivirals. The path forward requires sustained investment in rigorous scientific research, development of enabling formulation technologies, conduct of high-quality clinical trials, establishment of clear regulatory pathways, and commitment to quality assurance and safety evaluation. By integrating the wisdom of traditional medicine with the tools of modern science, the global community can harness the therapeutic potential of plant-based antivirals to address current and future viral health threats.

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