ISSN: 3141-6071

Transformative Medival Biomedical Journal 2026; 1(1): 1– 6

TMBJ – 1 (1) – 1-6

MEDICINAL PLANTS AS TOOLS TO CURB ANTIVIRAL RESISTANCE: A NARRATIVE REVIEW

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DOI: https://doi.org/10.65760/tmbj.v1i1.1

Abstract

Antiviral resistance is a predictable consequence of viral replication under drug pressure, especially when treatment is prolonged, viral load is high, adherence is incomplete, or the antiviral target tolerates escape mutations. The problem is clinically visible across HIV, influenza, herpesviruses, hepatitis viruses, cytomegalovirus, and emerging viral infections. Medicinal plants are not replacements for validated antivirals, vaccines, diagnostics, or infection-control measures. Their more realistic value is as a source of chemically diverse leads, standardized botanical products, host-directed adjuncts, and combination partners that can widen antiviral target space and reduce reliance on single viral enzymes. Plant-derived polyphenols, flavonoids, terpenoids, alkaloids, lectins, and polysaccharides have shown preclinical activity at viral entry, fusion, polymerase/protease function, neuraminidase activity, virion release, and inflammatory host pathways. However, most data remain in vitro or in silico; pharmacokinetics, toxicity, reproducibility, and clinical efficacy are often insufficiently established. A Lancet-standard research agenda should therefore prioritize authenticated plant materials, orthogonal antiviral assays, resistance-passage experiments, pharmacokinetic/pharmacodynamic modelling, herb-drug interaction studies, and randomized trials of standardized preparations only when preclinical thresholds are met. Medicinal plants can help curb antiviral resistance only if developed under the same evidence, quality, stewardship, and safety standards applied to conventional medicines.

Search strategy and selection criteria

This narrative review was developed from searches of PubMed/MEDLINE, Google Scholar, WHO, CDC, FDA, EMA, and publisher databases for English-language articles and guidance published from Jan 1, 2000, to May 8, 2026. Search terms included “antiviral resistance”, “HIV drug resistance”, “influenza antiviral resistance”, “medicinal plants antiviral”, “plant-derived antiviral”, “phytochemicals antiviral”, “natural products drug discovery”, “host-directed antivirals”, “baicalin oseltamivir-resistant”, “sinecatechins HPV”, “banana lectin HIV influenza”, “herb-drug interaction antiretroviral”, and “herbal medicine quality control”. Priority was given to WHO/CDC/FDA/EMA sources, peer-reviewed reviews in high-impact biomedical journals, PubMed-indexed mechanistic and preclinical studies, and clinical trials or regulatory documents for standardized botanical products. In-silico-only studies were used sparingly and not treated as clinical evidence. The review is narrative rather than systematic; therefore, no formal risk-of-bias scoring or meta-analysis was performed.

ISSN: 3141-6071

Research in context

Evidence before this review: Antiviral resistance is documented across major viral infections, while medicinal plants and natural products have repeatedly yielded antiviral signals in preclinical research. However, clinical translation remains limited and uneven.
Added value of this review: This review reframes medicinal plants specifically as resistance-curbing tools: lead sources, adjuncts, entry inhibitors, host-directed agents, and standardized botanical products, rather than as general alternatives to antivirals.
Implications of all the available evidence: Future work should prioritize resistance endpoints, pharmacokinetic plausibility, herb-drug interaction testing, quality control, and stewardship-compatible indications before clinical claims are made.

Introduction

Antimicrobial resistance includes resistant viruses as well as bacteria, fungi, and parasites, and undermines the effectiveness of medicines used for treatment and prevention.[1] In antiviral therapy, resistance emerges when genetic variation, selective drug exposure, and adequate viral fitness coincide. It is most consequential in immunocompromised patients, chronic infections, and settings where drug exposure is subtherapeutic.[2] The result is not merely therapeutic failure; resistant strains can extend infectiousness, constrain future regimen choice, and increase the cost and complexity of care.

The contemporary resistance landscape illustrates why new tools are needed. WHO reports that HIV drug resistance can compromise all antiretroviral classes, including newer integrase inhibitors.[3] In 2024, WHO highlighted dolutegravir resistance above clinical-trial expectations among some people with unsuppressed viral load, with survey estimates of 3.9-8.6% and up to 19.6% in a treatment-experienced subgroup transitioned to dolutegravir while viraemic.[4] Influenza also demonstrates how rapidly a viral target can lose utility: WHO states that resistance to M2 inhibitors in currently circulating seasonal influenza A viruses is very high, exceeding 99%, and that these agents are not recommended for treatment.[5] CDC notes that neuraminidase changes such as H275Y can confer oseltamivir resistance in influenza A(H1N1)pdm09 viruses.[6] Laboratory resistance testing is therefore increasingly based on combined molecular and phenotypic approaches.[7]

This review asks a practical question: can medicinal plants become a tool to curb antiviral resistance? The answer is yes, but only in a defined sense. Medicinal plants may expand discovery space, yield resistance-sparing adjuncts, and support combination strategies. They should not be promoted as unverified substitutes for licensed antivirals.

Why medicinal plants are relevant to resistance

Modern antiviral pharmacology has been highly productive: by 2016, 90 antiviral drugs had been approved for nine human viral diseases.[8] Yet many agents remain narrow-spectrum and target a small set of viral proteins. Natural products offer a complementary discovery route because they occupy chemical space shaped by biological selection. Large drug-discovery analyses show that natural products and their derivatives have made major contributions to approved medicines, including anti-infectives.[9] Recent advances in metabolomics, dereplication, genome mining, and synthetic biology have made natural-product discovery less empirical and more mechanism-driven.[10,11]

Medicinal plants are especially relevant because they contain metabolite classes with plausible antiviral effects: flavonoids, tannins, lignans, alkaloids, terpenoids, saponins, coumarins, quinones, lectins, and polysaccharides. Reviews of plant-derived antivirals describe activity against RNA viruses at attachment, entry, replication, assembly, and release.[12] Metabolomics-focused reviews further show how plant secondary metabolites can be linked to antiviral phenotypes and biosynthetic pathways.[13] Regional ethnopharmacology reviews have catalogued dozens of plants and

ISSN: 3141-6071

bioactive metabolites with reported activity against SARS-CoV-2, HIV, and HBV targets, although much of this evidence remains preclinical.[14,15]

Three resistance-relevant features distinguish plant-derived candidates from many first-generation antivirals. First, crude extracts and purified phytochemicals may act at multiple stages of the viral life cycle. Second, some plant products are host-directed rather than purely virus-directed. Third, they can be deployed as adjuncts to reduce viral burden, shorten exposure, or restore activity against resistant variants. These attributes are promising but are not proof of clinical benefit.

Mechanisms with resistance-curbing potential

Direct inhibition of viral enzymes remains the clearest development path. Plant flavonoids and phenolics have been reported to inhibit viral polymerases, proteases, reverse transcriptase, neuraminidase, and integrase in experimental systems. From a resistance perspective, the most useful leads are not merely potent against wild-type virus but retain activity against variants resistant to standard agents or show low resistance selection during serial passage.

Entry blockade is another attractive mechanism because it can prevent infection before genome replication begins. Sinecatechins, a defined green-tea extract from Camellia sinensis, is a clinically approved topical botanical product for external genital and perianal warts; randomized controlled trial data support efficacy in anogenital wart clearance, although its exact clinical mechanism is not fully defined.[16] FDA labelling identifies sinecatechins as a partially purified fraction of green-tea leaf water extract and notes that the mode of action in wart clearance is unknown.[17] This example is important because it shows that a standardized botanical preparation can pass regulatory review, but it also shows the need to avoid mechanistic overclaiming.

Plant lectins illustrate a more mechanistically explicit entry strategy. Banana lectin inhibited HIV-1 infection by binding glycosylated viral envelope and blocking cellular entry in laboratory studies.[18] A molecularly engineered banana lectin later showed broad-spectrum anti-influenza activity and in-vivo efficacy in mice, with reduced mitogenicity relative to native lectin.[19] Such compounds are not ready for routine care, but they show how plant macromolecules can be engineered into more drug-like antiviral candidates.

Several plant metabolites also show activity against resistant influenza models. Sodium baicalin, derived from the Scutellaria baicalensis flavonoid baicalin, inhibited oseltamivir-resistant H1N1-H275Y influenza in cell and animal models via neuraminidase activity reduction.[20] Baicalein showed synergistic activity with ribavirin against influenza A(H1N1) in cell culture and mice.[21] These studies support the principle that plant-derived compounds can be tested against resistant phenotypes and as combination partners, rather than only against laboratory wild-type virus.

Host-directed activity may be the most resistance-sparing pathway. Host-directed antivirals target cellular pathways required for viral replication, theoretically lowering the probability that a virus can escape through a single target mutation.[22] NIAID-supported host-directed antiviral programmes emphasize this reduced probability of resistance while also acknowledging safety challenges.[23] Many medicinal plants have immunomodulatory or anti-inflammatory effects, but the therapeutic window is narrow: dampening harmful inflammation is not the same as improving viral clearance.

Evidence gaps and translational barriers

The main weakness of the field is not lack of antiviral signals; it is insufficient translation. Many studies report half-maximal inhibitory concentrations without selectivity indices, time-of-addition experiments, resistance-passage data, orthogonal confirmation, or pharmacokinetic plausibility. Extract studies often lack botanical authentication, voucher specimens, chemoprofiles, or batch reproducibility. In-silico docking is useful for prioritization but cannot establish antiviral efficacy.

ISSN: 3141-6071

Clinical evidence is even thinner. Sinecatechins is the strongest example of a standardized plant-derived antiviral product in routine clinical use, but its indication is local HPV-associated warts rather than systemic resistant viral disease. For influenza, HIV, HBV, HCV, SARS-CoV-2, dengue, and herpesviruses, most medicinal-plant evidence remains preclinical. This does not invalidate the field; it defines the development threshold. A candidate intended to curb resistance should demonstrate activity against resistant clinical isolates, synergy or additivity with standard antivirals, acceptable cytotoxicity, low resistance selection, plausible exposure at the site of infection, and a manufacturable quality specification.

There is also a conceptual barrier. Multi-component extracts may be appealing because they act on several targets, but their complexity complicates dosing, interaction assessment, and regulatory approval. Conversely, purified compounds are easier to regulate but may lose the network pharmacology that made the original extract active. The most credible strategy is staged development: authenticate the plant, standardize the extract, identify active fractions, define mechanism, test resistance selection, optimize formulation, and then decide whether the final product should be a purified molecule, enriched fraction, or standardized botanical drug.

Safety, stewardship, and quality control

Medicinal plants can increase resistance risk if used poorly. The best-known cautionary example is Hypericum perforatum (St John's wort), which reduced indinavir exposure in healthy volunteers; the Lancet pharmacokinetic study reported a 57% mean reduction in indinavir area under the curve and warned that subtherapeutic antiretroviral concentrations could cause treatment failure and resistance.[24] Similar concerns apply whenever herbal products induce or inhibit CYP enzymes, transporters, or renal clearance pathways for antivirals.

Quality control is therefore not optional. WHO guidance on herbal medicines stresses that safety and efficacy depend substantially on quality and that contaminants, residues, and adulterants must be controlled.[25] EMA good agricultural and collection practice guidance similarly emphasizes identification of critical production steps to ensure quality and reduce contamination of herbal substances.[26] For antiviral-resistance applications, quality requirements should include species authentication, plant part, harvest conditions, extraction method, marker compounds, impurity limits, microbial testing, stability, and batch-to-batch antiviral potency.

Stewardship principles should also apply. A plant-derived product should not be used as monotherapy for HIV, HBV, HCV, influenza in high-risk patients, or severe viral disease unless supported by rigorous clinical trial evidence. Its place is more likely as an adjunct, topical agent, prophylactic barrier product, or lead compound for medicinal chemistry. WHO's traditional medicine strategy supports evidence generation, regulation, safety, and appropriate integration, not uncritical adoption.[27]

A development framework for resistance-focused plant antivirals

A resistance-focused pipeline should start with the intended use case. For acute respiratory viruses, the target product profile may be a short-course oral or inhaled adjunct that lowers viral load early, retains activity against resistant variants, and has minimal interaction with neuraminidase inhibitors, polymerase inhibitors, or nirmatrelvir-ritonavir. For sexually transmitted viruses, the target could be a topical entry inhibitor or immunomodulatory treatment with low systemic absorption. For chronic infections, the bar should be higher because long exposure magnifies toxicity and interaction risk.

Preclinical packages should include resistant and wild-type isolate panels, serial-passage resistance selection, combination matrices with approved antivirals, cytotoxicity in relevant human cells, organoid or animal models where available, and exposure-response modelling. Clinical packages should move from phase 1 safety and interaction studies to virological proof-of-mechanism trials before patient-centred outcomes are claimed. Resistance endpoints should be prespecified: viral load decay, emergence of genotypic mutations, phenotypic susceptibility shifts, and post-

ISSN: 3141-6071

treatment rebound. Public-health use should be linked to surveillance platforms capable of detecting resistance signals, as illustrated by harmonized influenza susceptibility-monitoring approaches.[28]

Equity is a final consideration. Medicinal plants are often sourced from regions with rich biodiversity and traditional knowledge. Development should include benefit-sharing, protection of Indigenous and local knowledge, biodiversity conservation, and affordable access. A product that extracts value from traditional knowledge without returning health, economic, or scientific benefit would fail modern ethical standards.

Conclusion

Medicinal plants can contribute to curbing antiviral resistance, but not through indiscriminate herbal substitution. Their most credible roles are as sources of novel antiviral scaffolds, standardized topical products, entry inhibitors, host-directed adjuncts, and combination partners that broaden target coverage and reduce dependence on single viral enzymes. The field should now move from cataloguing antiviral plants to testing resistance-relevant hypotheses: activity against resistant isolates, barriers to escape, pharmacological attainability, interaction safety, and reproducible manufacturing. The clinical message is conservative: plant-derived antivirals should be developed with the same evidentiary discipline as conventional drugs. When that standard is met, medicinal plants can become part of antiviral stewardship rather than a threat to it.

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