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In vitro and *in vivo* studies of medicinal plants against hepatitis B and hepatitis C infections: A narrative review

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ABSTRACT

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections remain major global health problems. This review summarizes current evidence on medicinal plants with reported antiviral activity against HBV and HCV, focusing on experimental models and underlying molecular mechanisms. A narrative review approach was used to identify and present relevant studies from PubMed, Scopus, ScienceDirect, and Google Scholar using keywords related to hepatitis viruses and medicinal plants. Relevant studies were selected based on their relevance to the topic, particularly those reporting antiviral activity in *in vitro* and *in vivo* models. The findings were synthesized narratively by organizing the evidence according to plant species, extract types, viral targets, and mechanisms of antiviral action. Medicinal plants contained diverse bioactive compounds with antiviral potential, including flavonoids, alkaloids, chalcones, polysaccharides, and polyphenols. Evidence from *in vitro* and *in vivo* studies indicates that these compounds may inhibit viral attachment and entry, suppress polymerase activity, reduce hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) secretion, interfere with capsid assembly, and inhibit HCV non-structural proteins. Notable compounds such as epigallocatechin gallate (EGCG), silibinin, quercetin derivatives, and solanopubamine demonstrated reductions in viral nucleic acid levels and improvements in liver-related outcomes in experimental models. Medicinal plants are promising antiviral sources against HBV and HCV due to their multi-target bioactive compounds. However, variability in extracts and limited clinical evidence require further standardized and clinical studies to confirm their therapeutic use.

Implication for health policy/practice/research/medical education:
This narrative review highlights the potential of medicinal plants as multi-target antiviral agents against the hepatitis B and hepatitis C viruses. These findings may support the development of complementary or alternative therapeutic strategies, particularly in low-resource settings with limited access to conventional antiviral therapies. The study also provides a scientific basis for future pharmacological research by compiling evidence on medicinal plant species, their bioactive compounds, antiviral activity (including IC_{50} and CC_{50} values), experimental models, and underlying mechanisms, which may guide further investigation of plant-derived antiviral agents. Furthermore, this review contributes to medical education by enhancing understanding of plant-derived antiviral mechanisms and their potential integration into evidence-based clinical practice.

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Introduction

Chronic infection with the hepatitis B virus (HBV) and hepatitis C virus (HCV) accounts for most cases of cirrhosis and hepatocellular carcinoma worldwide, with substantial residual disease burden. Although current antiviral therapies have substantially improved clinical outcomes, important limitations remain. Nucleos(t)ide analogues effectively suppress HBV replication but rarely eliminate covalently closed circular DNA (cccDNA), the stable episomal form responsible for viral persistence and relapse after treatment discontinuation (1). Direct-acting antivirals (DAAs) achieve high cure rates in HCV infection; however, viral resistance, reinfection, unequal access in low-resource settings, and the absence of a preventive vaccine continue to hinder global disease control. These limitations highlight the need for complementary antiviral strategies targeting multiple stages of the viral life cycle (2).

Plants used in traditional hepatic medicine have been re-examined as sources of antiviral leads over the past decade, particularly as whole-extract or compound-level studies have begun to dissect mechanisms. Recent screening efforts have identified anti-HBV activity in the extracts of *Lindernia ruellioides* (3), *Euphorbia schimperi* (4), *Solanum schimperianum* (5), *Isatis indigotica* (6), and polyphenols from *Camellia sinensis* (7, 8) and anti-HCV activity in *Salix nigra* (2), *Azadirachta indica* (9), *Kleinhovia hospita* (10), and *Silybum marianum* (11). These antiviral activities are largely attributed to diverse classes of bioactive compounds, including flavonoids (e.g., quercetin, kaempferol, and epigallocatechin gallate [EGCG]), alkaloids (from *Isatis indigotica*), terpenoids, and lignans such as silibinin from *Silybum marianum*. These compounds exert their effects through multiple mechanisms, including inhibition of viral entry, suppression of viral replication enzymes, and modulation of host immune responses, highlighting their potential as sources of antiviral agents (12,13).

Recent studies have increasingly focused on elucidating the pharmacological mechanisms underlying these effects. However, previous reviews have not consistently integrated mechanistic data with the experimental models used for validation. Plant-derived compounds have been reported to interfere with viral attachment and entry (e.g., EGCG and theaflavins), inhibit polymerase-mediated genome replication (e.g., quercetin, kaempferol derivatives, and solanopubamine), modulate antigen secretion and hepatitis B virus X protein (HBx)-associated transcription, and activate host antiviral pathways such as Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling. This multi-target profile supports their potential role as adjuncts or lead compounds in antiviral drug development (4,5,12). Evaluation of these activities relies on complementary experimental platforms. *In vitro* systems, including HepG2.2.15, PLC/PRF/5, Huh7, and hepatocyte cultures, allow detailed mechanistic assessment of viral inhibition (13). *In vivo* models, such as HBV transgenic mice and human liver–chimeric mice, provide physiological validation and improve translational relevance. Integrating findings from these models is essential for assessing pharmacological significance (7,14).

Despite promising preclinical findings, variability in extract composition, limited pharmacokinetic characterization, and insufficient clinical validation remain important challenges. Addressing these limitations is necessary to support the potential use of plant-derived antivirals as adjunct or alternative therapeutic strategies for HBV and HCV management. This study aims to provide a narrative overview of medicinal plants with reported antiviral activity against HBV and HCV, focusing on experimental models and underlying molecular mechanisms.

Methods

This study was conducted as a narrative review to summarize and discuss current evidence on medicinal plants with antiviral activity against HBV and HCV. Relevant literature was identified through searches of electronic databases including PubMed, Scopus, ScienceDirect, and Google Scholar. The search strategy employed combinations of keywords such as "hepatitis B virus", "hepatitis C virus", "medicinal plants", "antiviral activity", "*in vitro*", and "*in vivo*".

The literature was considered based on its relevance to the topic, with particular attention to studies reporting antiviral activity of medicinal plants in experimental models and describing underlying molecular mechanisms. The selected literature was reviewed narratively, and the findings were presented according to plant species, type of extract, viral targets (HBV or HCV), and mechanisms of antiviral action. A descriptive approach was used to highlight recurring patterns, mechanistic insights, and consistencies across different experimental models.

Results

Virology and molecular characteristics of HBV and HCV

HBV is a small, enveloped virus of the *Hepadnaviridae* family with a genome consisting of a partially double-stranded DNA molecule of ~3.2 kb. Following entry, the genome is delivered to the hepatocyte nucleus and replicated into cccDNA, which serves as the transcriptional template for all viral RNAs. The viral polymerase (Pol/RT) then reverse-transcribes encapsidated pregenomic RNA (pgRNA) into relaxed circular DNA (rcDNA). A fraction of rcDNA is recycled back to the nucleus to replenish the cccDNA pool, while the remainder is packaged into progeny virions. Because cccDNA persists as a stable episome in the hepatocyte nucleus and is not targeted by current nucleos(t)ide analogues, sterilizing cure is essentially unattainable (1,15).

In contrast, HCV, belonging to the *Flaviviridae* family, is an enveloped virus that possesses a positive-sense single-stranded RNA genome (16). The replication cycle of HCV in Figure 1 is complex with distinct entry, replication, and assembly steps. The high mutation rate of HCV during replication is well documented, facilitating the virus's evasion of both humoral and cellular immune responses. The resulting antigenic diversity complicates vaccine development and helps HCV establish chronic infection (17,18).

Replication cycle and therapeutic targets

The replication cycle of HBV encompasses critical stages and potential therapeutic targets. Following infection, HBV infiltrates hepatocytes and subsequently releases its DNA genome, which undergoes conversion into cccDNA. The cccDNA functions as a template for the transcription of viral RNAs. Current therapeutic strategies target the HBV life cycle at several stages: nucleos(t)ide analogues inhibit Pol/RT, interferon-α enhances host antiviral responses, and emerging agents target host factors necessary for viral entry, capsid assembly, or HBsAg secretion. The HCV life cycle offers several druggable stages: entry, polyprotein processing, RNA replication, and assembly. Pan-genotypic DAA combinations targeting NS3/4A, NS5A, and NS5B now achieve sustained virological response rates above 95%, although resistance-associated substitutions and reinfection remain concerns in high-risk populations (17).

Research models used in HBV and HCV studies

The study of HBV and HCV necessitates the use of various *in vitro* and *in vivo* research models. Each model has its unique advantages and limitations, which can influence the outcomes of antiviral drug evaluation and understanding viral pathogenesis (19).

In vitro models

In vitro models are essential for preliminary screening of antiviral efficacy and for mechanistic studies that explore viral replication and host-pathogen interactions. The most commonly utilized *in vitro* systems include hepatocyte cell lines, primary hepatocytes, and bioengineered liver platforms (20).

a. Hepatoma cell lines

HBV and HCV infections have traditionally been studied using cell lines like HepG2 and Huh7. HepG2 cells have played a central role in HBV research, supporting viral antigen production and DNA replication following stable transfection of the HBV genome, which led to the development of derivative lines such as HepG2.2.15. However, these models exhibit deficiencies in specific *in vivo* characteristics, potentially limiting their capacity to accurately reflect the functions of actual hepatocytes. Huh7 cells have demonstrated the capability to support HCV replication, making them a valuable model for the screening of antiviral compounds. Despite their utility,

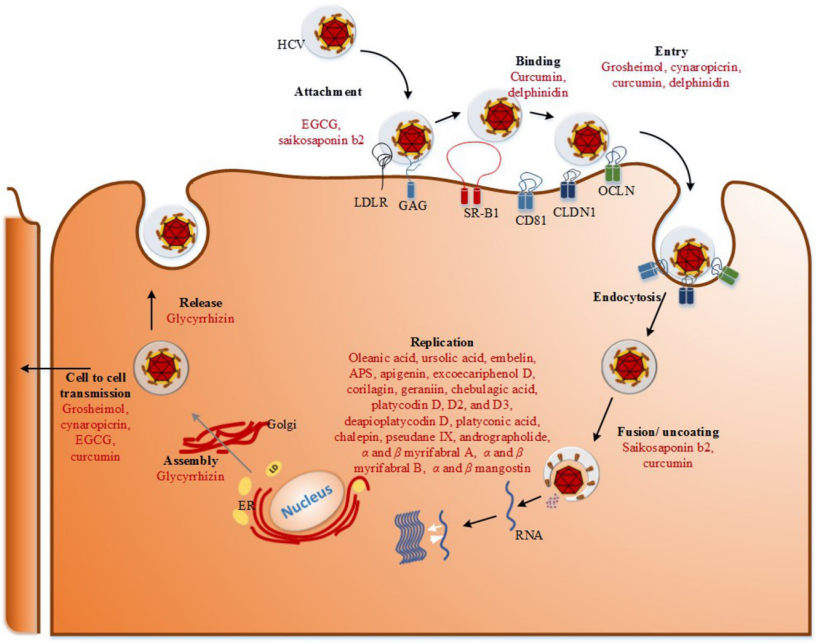

Figure 1. Schematic of the hepatitis C virus (HCV) life cycle, highlighting stages targeted by plant-derived natural compounds. HCV enters hepatocytes through sequential engagement of CD81, scavenger receptor class B type 1 (SR-B1), claudin-1 (CLDN1), and occludin (OCLN), followed by clathrin-mediated endocytosis and uncoating. The viral RNA genome is translated into a polyprotein that is processed into structural (Core, E1, E2, p7) and non-structural (NS2, NS3/4A, NS4B, NS5A, NS5B) proteins. Genome replication occurs within ER-derived membranous webs before new virions assemble on lipid droplets and egress via the secretory pathway. Plant-derived compounds evaluated in this review interfere with entry (theaflavins), translation/replication (silibinin, flavonoids), and/or NS3/NS5A function. Adapted from (16) with permission.

these lines frequently demonstrate dedifferentiation over time, resulting in diminished functionality (21,22).

b. Primary hepatocytes

Isolated primary human hepatocytes (PHHs) represent a more physiologically relevant model for the investigation of drug metabolism and viral infection. PHHs exhibit a range of *in vivo* characteristics, making them essential for investigating the metabolic pathways pertinent to drug testing. However, swift decline in hepatic function and dedifferentiation observed in cell culture could impede the feasibility of prolonged experimental studies (23).

c. Bioengineered liver models

Bioengineered liver-on-chip devices and three-dimensional spheroid cultures offer alternatives to monolayer systems. They maintain hepatocyte polarity and differentiated function for weeks, allowing longitudinal study of viral replication and drug-induced hepatotoxicity. Spheroid cultures demonstrate superior preservation of cell polarization and functionality in comparison to traditional two-dimensional cultures. This enhancement increases their applicability in drug response assays and investigations into the pathophysiology of liver disease (24).

d. Limitations of in vitro models

While *in vitro* models provide a convenient platform for rapid testing and mechanistic insights into HBV and HCV, they inherently lack complexity. They cannot fully replicate the interactions found in a whole organism, including immune responses and the presence of other liver cell types, which may influence disease progression and treatment responses (23).

In vivo models

In vivo models are critical for studying the complete biological context of HBV and HCV infections. The most commonly used *in vivo* systems include transgenic mice, tree shrews, and non-human primates (Table 1) (15).

a. Transgenic mice

Numerous transgenic mouse models have been established to investigate HBV. These mice show signs of chronic HBV infection and express HBV proteins or replication intermediates, allowing evaluation of possible vaccine candidates and treatment options. The main constraint of these models lies in their deviation from the complexities of human immune responses and manifestation of diseases (15).

b. Tree shrews and other animal models

The tree shrew (*Tupaia belangeri*) supports HCV replication after inoculation with patient-derived virus and has been proposed as a small-animal model because of its closer phylogenetic relationship to humans than rodents (27). However, the effectiveness of this approach may fluctuate, given the variable infection rates observed (28).

c. Non-human primates

Chimpanzees have traditionally been the primary model

Table 1. Cell culture models used for hepatitis B virus (HBV) and hepatitis C virus (HCV)

Cell model	Origin	Virus studied	Key characteristics	Main applications	Reference
HepG2	Human hepatoma cell line	HBV	Lacks endogenous NTCP; supports HBV replication after genome transfection	HBV genome transfection, antigen production, antiviral screening	(17)
HepG2.2.15	HepG2 cells stably transfected with the HBV genome	HBV	Constitutive production of HBsAg, HBeAg, and HBV DNA	HBV replication, antigen secretion, antiviral evaluation	
HepG2-NTCP	HepG2 cells engineered to express NTCP	HBV	Supports authentic HBV entry and early infection	HBV entry studies, infection inhibitors, early life-cycle analysis	
HepAD38	HepG2-derived inducible HBV cell line	HBV	Tetracycline-regulated HBV replication with high viral output	Controlled HBV replication, antiviral drug testing	
Huh7	Human hepatoma cell line	HCV	Highly permissive to HCV replication and infection	HCV replication, infection studies, and antiviral screening	(25)
Huh7-NTCP	Huh7 cells expressing NTCP	HBV	Permits entry and infection in Huh7 background	Comparative HBV–HCV studies, viral entry analysis	(17)
Huh7it/ Huh7it-1	Huh7 cells with an inducible HCV genome	HCV	Conditional HCV replication independent of viral entry	Mechanistic HCV replication studies, compound screening	(25)
HepaRG	Human hepatic progenitor cell line	HBV, HCV	Differentiated cells express NTCP and hepatocyte-like functions	Physiologically relevant HBV/HCV infection models	(17)
PHH	Human liver tissue–derived hepatocytes	HBV, HCV	Natural NTCP expression; supports complete viral life cycle	Most physiologically relevant for infection and translational studies	(26)
PBMCs	Human immune cells	HBV, HCV	Extrahepatic models for viral polymerase activity	Polymerase inhibition and immune-related antiviral studies	(15)

NTCP: sodium taurocholate co-transporting polypeptide; HbsAg: hepatitis B surface antigen; HbeAg: hepatitis B e antigen; PHH: primary human hepatocytes; PBMCs: peripheral blood mononuclear cells.

organism in the study of HCV. Their role in supporting viral replication and demonstrating a progression similar to human infections underscores their significance in the investigation of HCV pathogenesis and therapeutic approaches. Ethical and cost barriers constrain their application in research (29).

d. Duck models for HBV

Ducks serve as a surrogate model for HBV research, owing to their natural susceptibility to duck hepatitis B virus (DHBV), an avian hepadnavirus whose replication cycle closely resembles that of HBV. Translating findings directly to human patients presents challenges, primarily due to the species-specific differences observed in disease expression and immune responses (30).

e. Advantages and limitations of in vivo models

In vivo models provide an environment for studying the complete pathology of the disease, immune responses, and drug metabolism. However, logistical challenges, ethical considerations, and high costs associated with animal modeling can hinder their application in extensive drug screening and mechanistic studies (15).

The studies reviewed here describe plant-derived compounds that interfere with HBV or HCV replication at one or more discrete stages of the viral life cycle. Due to the differing replication strategies of HBV (a DNA virus utilizing reverse transcription) and HCV (an RNA virus that replicates predominantly in the cytoplasm), natural substances demonstrate antiviral activity via separate mechanisms. The analyzed research reveals a consistent theme: numerous plant-derived compounds impede viral propagation by targeting conserved viral vulnerabilities, specifically entry mechanisms, polymerase-mediated genome replication, antigen synthesis, capsid assembly, and host immunological signaling. *In vitro* mechanisms are supported by *in vivo* evidence, enhancing the translational significance of these compounds (31).

Viral entry inhibition

Blocking entry prevents infection at its earliest step and is a well-validated antiviral strategy. The most definitive mechanistic data are derived from HCV investigations, namely theaflavins (TF1–TF3) sourced from *C. sinensis*. These polyphenols interact with the virion surface, modifying the envelope glycoprotein structures essential for binding to CD81, SR-B1, claudin-1, and occludin. The entry of HCV relies on consecutive receptor interactions and fusion; thus, minor structural alterations in the E1/E2 glycoproteins can substantially hinder infection (27). *In vitro* experiments in Table 2 demonstrate that theaflavins effectively suppress both free-virus infection and cell-to-cell transmission, with TF3 exhibiting pan-genotypic efficacy. This finding supports the recognized hypothesis that the rigidity of the virion membrane and the conformation of glycoproteins determine receptor tropism and infectivity. Despite these promising observations, current evidence remains largely confined to *in vitro* systems, and *in vivo* validation of entry inhibition is still limited. Furthermore, the molecular specificity of plant-derived compounds toward viral versus host membrane components remains to be established (8).

While HBV entry was not directly evaluated at the sodium taurocholate co-transporting polypeptide (NTCP) receptor level, marked decreases in hepatitis B surface antigen (HBsAg) secretion observed in multiple investigations indirectly indicate compromised virion maturation and entry capability. HBsAg is important for viral attachment and assembly; hence, extracts that diminish HBsAg expression ultimately limit the reservoir of infectious particles that can interact with hepatocyte receptors. This is consistent with HBV biology, in which reduced antigen availability correlates with decreased viral fitness and compromised early-stage proliferation. However, the absence of direct NTCP-binding or entry and fusion assays represents a notable methodological gap. Future studies incorporating receptor-level validation and mechanistic mapping would be essential to confirm whether the observed reductions in viral markers truly reflect entry inhibition or secondary downstream effects (3,12).

HBV reverse transcription mechanism

HBV polymerase (Pol/RT) facilitates the reverse transcription of pregenomic RNA into rcDNA. This enzyme possesses hydrophobic nucleotide-binding grooves that render it vulnerable to aromatic phytochemicals capable of establishing π–π stacking interactions. Flavonoids including quercetin-3-O-glucuronide (Q3G), quercetin-3-O-rhamnoside (Q3R), and kaempferol-3-O-glucuronide (K3G) derived from *E. schimperi* in Table 2 block Pol/RT by binding to the catalytic cleft, thereby obstructing nucleotide incorporation and diminishing HBV DNA levels *in vitro* (4). The structural-functional alignment supports these findings: the polymerase active site preferentially accommodates planar aromatic rings characteristic of flavonoids, demonstrating consistent binding affinity for the polymerase. Flavonoids from *H. rhamnoides* (quercetin, kaempferol, isorhamnetin) exhibit comparable polymerase inhibition, underscoring the evolutionary congruence between viral polymerase pockets and polyphenolic structures (12). Solanopubamine isolated from *S. schimperianum* inhibits both wild-type and lamivudine-resistant polymerase variants (39). Resistance mutations often alter steric configurations that reduce drug accessibility; however, solanopubamine appears to maintain binding through deeper hydrophobic interactions, providing a plausible explanation for its retained activity against resistant HBV strains. Despite these promising mechanistic insights, most evidence

Table 2. *In vitro* studies of medicinal plants with anti-HBV and anti-HCV activity

Plant	Part of plant	Type of extract	Concentration	Bioactive compound	Study model	IC_{50}/ effective concentration	Main mechanism	Reference
Lindernia ruellioides (Colsm.) Pennell	Whole plant	Ethanolic	0.8–12.8 mg/L	Hydroxytyrosol	HepG2.2.15 cells	HBsAg: 4.02 mg/L; HBeAg: 5.19 mg/L	Inhibits HBsAg/HBeAg secretion by interacting via hydrogen bond interactions (binding energy −7.0 kcal/mol)	(3)
Euphorbia schimperi	Flower	Methanolic	6.25, 12.5, 25, 50, and 100 µg/mL	Quercetin-3-O-glucuronide	HepG2.2.15 cells	22.3–23.5 µM	Inhibits HBsAg/HBeAg secretion; HBV polymerase and core protein	(4)
				Quercetin-3-O-rhamnoside			Interferes with HBV core particle assembly	
				Kaempferol-3-O-glucuronide			Strong inhibition of HBV antigen secretion and replication	
Dracaena cinnabari	Resin	Methanolic	3.125, 6.25, 12.5, 25 µg/mL	2,4′-Dihydroxy-4-methoxydihydrochalcone	HepG2.2.15 cells	20.56 µg/mL	Suppresses HBsAg/HBeAg production and HBV replication	(32)
			6.25, 12.5, 25, 50, and 100 µg/mL	2,4′-Dihydroxy-4-methoxyhydrochalcone		6.36 µg/mL	Strong inhibition of HBV replication, comparable to lamivudine	
Hippophae rhamnoides	Aerial Parts	Ethanolic	10 µg/ml	Quercetin	HepG2.2.15 cells	–	Reduces HBsAg/HBeAg secretion via polymerase inhibition	(12)
			10 µg/ml	Kaempferol		–	Suppresses HBV antigen secretion	
			5, 10, and 20 µg/mL	Isorhamnetin		10 µg/mL	Weak inhibition of HBV antigens	
Isatis indigotica (Radix isatidis)	Roots	Polysaccharide (Ethanolic and Aqueous Extracts)	50, 100, and 200 µg/ml	Polysaccharide (RIP)	HepG2.2.15 cells	50–200 µg/mL	Inhibits HBV replication via JAK/STAT activation	(6)
Sophora moorcroftiana	Seeds	Ethanolic	0.0125–0.25 mM	Sophormodines A–C	HepG2.2.15 cells	0.046 mM (Sophormodine A)	Inhibits HBsAg and HBeAg secretion; reduces HBV DNA replication	(33)
Camellia sinensis	Leaves	Ethyl acetate	2.5 – 25 µg/mL	Theaflavin	Huh-7 cells	17.89 µM	Blocks early HCV entry	(8)
				Theaflavin-3′-monogallate		4.08 µM	Inhibits HCV entry	
				Theaflavin-3,3′-digallate		2.02 µM	Most potent HCV entry inhibitor	
Ruta angustifolia L.	Leaves	Ethanolic	100, 30, 10, 1, and 0.1 µg/mL	Ethanol extract	Huh7it-1 cells	2.9 µg/mL	Inhibits HCV replication (post-entry stage); decreases NS3 protein level	(34)
Artocarpus heterophyllus	Leaves	Dichloromethane	100, 50, 25, 12.5, 6.3 and 3.1 mg/mL	Sub-fraction FR3T3	Huh7it-1 cells	4.7 µg/mL	Inhibits post-entry stage; suppresses NS3 protein expression	(35)
Kleinhovia hospita L.	Leaves	Methanolic	0.01, 0.1, 1, 10, 50, 100 µg/mL	Methanol extract	Huh7it-1 cells	2.24 µg/mL	Inhibits HCV replication via host target modulation	(10)

Table 2. Continued

Plant	Part of plant	Type of extract	Concentration	Bioactive compound	Study model	IC_{50}/ effective concentration	Main mechanism	Reference
Melicope latifolia	Fruit	Methanolic	100, 30, 10, 1, 0.1 and 0.01 µg/ml	O-methyloktadrenolon	Huh7it-1 cells	109 µg/mL	Inhibits HCV replication (suppresses NS3 protein expression)	(36)
				Alloevodionol		41.1 µg/mL	Inhibits HCV replication	
				Isopimpinellin		> 50 µg/mL	Inhibits HCV replication	
				Alloxanthoxyletin		21.72 µg/mL	Inhibits HCV replication	
				Methylevodionol		> 50 µg/mL	Inhibits HCV replication	
				N-methylflindersine		3.8 µg/mL	Strong inhibition of HCV replication	
Salix nigra	Leaves	Methanolic	10–50 µg/mL	Methanol extract	HepG2-NS3 cells	37 µg/mL	Suppresses HCV NS3 expression	(2)
		Aqueous		Water extract		42 µg/mL	Moderate inhibition of HCV replication	
		Ethyl acetate		Ethyl acetate extract		>100 µg/mL	Strong NS3 suppression at high dose	
		N-hexane		N-hexane extract		>100 µg/mL	Weak antiviral activity	
Herpetospermum caudigerum	Seeds	Ethanolic	12.5 – 200 µg/mL	Herpetin	HepG2.2.15 cells	HbsAg: 114.48 µg/mL HbeAg: 57.75 µg/mL	Inhibits HBsAg and HBeAg secretion; reduces HBV DNA replication	(37)
				Herpetone		HbsAg: 240.31 µg/mL HbeAg: 185.64 µg/mL		
				Herpetfluorenone		HbsAg: 176.99 µg/mL HbeAg: 134.53 µg/mL		
Onosma dichroanthum	Root	Hydroalcoholic	1–128 µg/mL	Hydroalcohol root extract	PLC/PRF/5 cells	63.78 µg/mL	Suppresses HBsAg transcription	(13)
Solanum schimperianum	Whole plant	–	7.5, 15, 30, and 60 µM	Solanopubamine	HepG2.2.15 cells	30 µM	Inhibits HBV antigens; active against resistant strains	(5)
Azadirachta indica	Seeds	Methanolic	100 – 1000 µg/mL	Methanol seed extract	HepG2-HCV cells	IC_{50}: 500 µg/mL; CC_{50}: 650 µg/mL	Suppresses HCV NS3/ NS5A expression	(9)
Ammi visnaga	Roots	Ethanolic	1–200 µg/mL	Ethanol root extract	Vero E6 cells	9.5 µg/mL	Inhibits HCV replication	(38)
Apium graveolens				Ethanol root extract		–	No significant anti-HCV activity	
Carapa procera				Tannins (procyanidins)	HCV-infected Huh-7 cells	0.71 µg/mL	Inhibits HCV replication and entry	
Pericopsis laxiflora				Tannins (procyanidins)		0.23 µg/mL	Blocks HCV replication and viral assembly	

* IC_{50} values measured at multiple time points (days 3–9).

HBV: hepatitis B virus; HCV: hepatitis C virus; NS3: non-structural protein 3; NS5A: non-structural protein 5A; IC_{50}: half maximal inhibitory concentration; CC_{50}: half maximal cytotoxic concentration; HbsAg: hepatitis B surface antigen; HbeAg: hepatitis B e antigen

remains limited to *in vitro* enzymatic or cell-based assays. Comparative potency against established nucleos(t)ide analogs and pharmacokinetic validation is still lacking. Moreover, the bioavailability and metabolic stability of flavonoids may restrict their clinical translation unless optimized through structural modification or formulation strategies (5).

Inhibition of viral antigen production (post-entry)

HBV antigen suppression

Chronic HBV infection is sustained by persistent secretion of HBsAg and hepatitis B e antigen (HBeAg), which contribute to T-cell exhaustion and immune tolerance. Therefore, the downregulation of these viral antigens represents a key antiviral objective. Several studies in Table 2 report that plant-derived compounds, including hydroxytyrosol from *L. ruellioides*, quercetin and kaempferol derivatives from *E. schimperi*, and chalcones from *D. cinnabari*, show dose-dependent inhibition of HBsAg and HBeAg secretion (40). The reduction in HBsAg transcripts induced by *O. dichroanthum* suggests possible interference with cccDNA transcription or its associated regulatory factors. As cccDNA is the transcriptional template that sustains HBV persistence, any compound that can destabilize it or silence its transcription would be therapeutically valuable. However, none of the studies reviewed here measured cccDNA copy number, half-life, or epigenetic state directly. Distinguishing whether these compounds suppress transcriptional activity, destabilize cccDNA, or exert downstream post-transcriptional effects has not been directly tested. Further investigations integrating molecular assays and long-term models of viral persistence are required to validate cccDNA-targeted activity (13).

HCV antigen suppression

In HCV infection, non-structural protein 3 (NS3) and non-structural protein 5A (NS5A) are essential for viral polyprotein processing and replication complex formation. *Salix nigra* has been reported to suppress NS3 transcription, while *A. indica* inhibits both NS3 and NS5A, resulting in impaired viral protein maturation and reduced replication efficiency (2,9). NS3 protease inhibition parallels the established clinical efficacy of DAAs, suggesting mechanistic convergence between certain plant-derived compounds and recognized antiviral drug classes (41).

Consistent with this framework, other phytochemicals evaluated in this review target post-entry replication events. The ethanol extract of *R. angustifolia* reduced NS3 protein expression and intracellular HCV RNA levels, indicating suppression during the replication phase (34). Similarly, the active sub-fraction FR3T3 from *A. heterophyllus* demonstrated marked anti-HCV activity (IC_{50} 4.7 ± 1.0 μg/mL) by inhibiting NS3 protein production and viral RNA replication, while exerting minimal effects on viral entry (35).

Although *M. latifolia* did not directly quantify NS3 protein levels, its isolated alkaloid and benzopyran derivatives reduced intracellular viral RNA in Huh7it-1 cells, suggesting interference with NS3-dependent replication complex functionality. Among these compounds, N-methylflindersine exhibited the strongest antiviral activity. Collectively, these findings indicate a recurrent mechanistic focus on post-entry replication inhibition, particularly targeting NS3-mediated processes and viral RNA amplification. Nevertheless, most data remain confined to cell-based systems, and comparative analyses with approved DAAs in terms of potency, resistance barriers, and pharmacokinetic properties are still lacking. Furthermore, given the high efficacy of current NS3-targeted therapies, the potential role of plant-derived compounds may be more realistic as adjunctive or resistance-modulating agents rather than standalone treatments. Rigorous *in vivo* validation and combination studies would therefore be essential to clarify their translational potential (36).

Disruption of HBV-related processes

The construction of the HBV capsid depends on precise dimerization and multimerization of hepatitis B core (HBc) proteins, while HBx regulates viral transcription through interactions with host factors such as damage-specific DNA binding protein 1 (DDB1). Evidence summarized in this review suggests that certain natural compounds may interfere with these processes. Alkaloids isolated from *S. moorcroftiana* (e.g., sophormodines A–C) have been shown to suppress HBsAg and HBeAg secretion and reduce HBV DNA levels in HepG2.2.15 cells, indicating an inhibitory effect on viral replication and protein expression (33). Similarly, lignan compounds isolated from *H. caudigerum* (e.g., herpetin and herpetfluorenone) also inhibit HBsAg and HBeAg secretion and reduce HBV DNA levels in the same cell model, further supporting their role in suppressing HBV replication (37). Collectively, these findings suggest that diverse classes of natural compounds, including alkaloids and lignans, may converge on common HBV-related processes, particularly viral antigen expression and genome replication. These mechanisms resemble those of antiviral agents currently under pharmaceutical development, highlighting conceptual therapeutic relevance (37). However, available data remain primarily based on in vitro studies, with limited validation in comprehensive replication or persistence models. Whether these compounds can achieve sufficient intracellular concentrations to modulate HBV-related processes in vivo remains uncertain. Further structural and pharmacodynamic investigations are necessary to determine their viability as clinically relevant antiviral agents (37).

Integration of in vitro and in vivo evidence

A notable strength of the included studies is the alignment between *in vitro* antiviral activity and *in vivo* validation. EGCG demonstrates inhibition of HBV antigen expression and replication markers *in vitro* and reduces HBV DNA levels by more than 100-fold in humanized mouse models (7). In the context of HCV, silibinin exhibits *in vitro* replication inhibition that is consistent with dose-dependent reductions in viral RNA in humanized mouse models in Table 3 (11). Conversely, the inability of EGCG to suppress HCV replication *in vivo* Table 3, despite strong *in vitro* activity, underscores a critical translational barrier: bioavailability. Compounds with favorable molecular affinity may fail to achieve therapeutic hepatic concentrations due to limited stability, rapid metabolism, or poor absorption. This highlights a fundamental challenge in natural antiviral development, where pharmacokinetic constraints often determine clinical feasibility. Nevertheless, even positive *in vivo* findings derived from transgenic or humanized mouse models should be interpreted cautiously, as these systems may not fully replicate the complexity of chronic human infection. Differences in immune responses, viral persistence mechanisms, and long-term safety profiles remain important considerations. Therefore, bridging studies and eventual clinical validation are essential to confirm therapeutic applicability (42).

Mechanistic synthesis and implications for antiviral development

Across the included studies, several mechanistic patterns recur that reflect the interplay between viral structure and the chemistry of plant-derived compounds (44,45). When synthesized across different stages of the viral life cycle, several recurring themes emerge. Aromatic polyphenols frequently interact with virion surface proteins and viral polymerases, reflecting structural complementarity between planar ring systems and the hydrophobic pockets of viral enzymes and glycoproteins. This may explain the consistent entry inhibition observed with theaflavins in HCV and the recurrent suppression of HBV polymerase activity by flavonoids. Many of these interactions appear to involve conserved viral regions, suggesting that certain polyphenolic scaffolds may preferentially target shared structural vulnerabilities in HBV and HCV (46).

In HBV, inhibition of viral antigen expression represents a particularly meaningful therapeutic target. Sustained secretion of HBsAg and HBeAg contributes to immune tolerance and T-cell exhaustion (47). The capacity of several plant extracts to reduce antigen transcription and secretion indicates potential interference with upstream regulatory pathways, including cccDNA transcription. The reduction in HBsAg observed with *O. dichroanthum* supports the hypothesis that modulation of cccDNA-associated transcriptional activity may represent a relevant strategy toward functional cure approaches. However, direct confirmation of cccDNA destabilization or epigenetic modulation remains limited and has not yet been measured (48).

Functional cure, defined as sustained HBsAg loss after treatment withdrawal, is now the principal endpoint in HBV drug development, since integrated HBV DNA and long-lived cccDNA make a sterilizing cure essentially unattainable. Plant-derived compounds that suppress HBsAg production, therefore align conceptually with this therapeutic paradigm and merit evaluation within that framework rather than against the more demanding goal of viral elimination. Compounds that disrupt capsid assembly or HBx/HBc interactions also provide an additional mechanistic parallel with emerging antiviral strategies. As capsid assembly modulators constitute an important class of investigational HBV therapeutics, the interaction of certain phytochemicals with protein dimerization interfaces suggests conceptual alignment

Table 3. *In vivo* studies of medicinal plants with anti-HBV and anti-HCV activity

Plant	Bioactive compound	Study model	Dose	Main outcome/mechanism	Reference
Curcuma longa (turmeric)	Curcumin	HBx-transgenic mice (HBV-related HCC model)	50 mg/kg/day	Reduced liver damage, dysplasia, and tumor formation; suppressed HBx expression and enhanced liver regeneration	(43)
Silybum marianum	Silibinin	Chimeric mice with humanized livers	469, 246, and 61.5 mg/kg	Induced dose-dependent decline of serum and intracellular HCV RNA; anti-inflammatory gene modulation	(11)
Camellia sinensis (green tea)	EGCG	Hu-FRG human liver chimeric mice	50 mg/kg, twice daily (5 days)	Reduced serum HBV DNA (>100-fold) and hepatic HBsAg expression (~70%)	(7)
Camellia sinensis (green tea)	EGCG	SCID/uPA humanized liver mouse model	100 mg/kg, twice daily	Showed additive inhibition of HCV infection with anti-HCV antibody (clone AR4A); limited efficacy as monotherapy due to low bioavailability	(42)

HBV: hepatitis B virus; HCV: hepatitis C virus; HBx: hepatitis B virus X protein; HCC: hepatocellular carcinoma; EGCG: epigallocatechin gallate; Hu-FRG: human-Fah$^{-/-}$/Rag2$^{-/-}$/Il2rg$^{-/-}$ (humanized liver chimeric mice); HbsAg: hepatitis B surface antigen; SCID/uPA: severe combined immunodeficiency/urokinase-type plasminogen activator

with this therapeutic direction. Nevertheless, validation in advanced replication and persistence models is necessary before clinical relevance can be inferred (49).

Integration of *in vitro* and *in vivo* findings highlights a central principle in antiviral drug development: mechanistic potency alone does not guarantee translational success. While EGCG and other polyphenols demonstrate notable *in vitro* antiviral activity, inconsistent *in vivo* outcomes underscore the impact of pharmacokinetic limitations, particularly bioavailability. In contrast, compounds such as silibinin exhibit more consistent translational performance, likely attributable to more favorable pharmacokinetic properties (50). These observations emphasize that effective natural antiviral development requires simultaneous consideration of molecular activity and hepatic tissue exposure. Overall, the collective evidence indicates that medicinal plants exert antiviral effects through multisite molecular modulation and, in some cases, immunoregulatory activity. Rather than serving as direct replacements for established antiviral agents, phytochemicals may hold greater potential as adjunctive or complementary therapies that target conserved viral dependencies while addressing mechanisms of immune evasion. Continued mechanistic refinement, pharmacokinetic optimization, and controlled *in vivo* validation will be essential to clarify their role in future therapeutic strategies against hepatitis B and C (51).

Conclusion

This review highlights evidence regarding medicinal plants with anti-HBV and anti-HCV activity, with particular emphasis on their validated mechanisms of action and phytochemical characteristics in both *in vitro* and *in vivo* models. A variety of plant-derived compounds, including flavonoids, alkaloids, chalcones, tannins, and polysaccharides, have demonstrated the ability to inhibit key stages of the viral life cycle, including viral entry, genome replication, antigen expression, and protein-mediated regulatory processes. In addition, several compounds exhibit immunomodulatory and hepatoprotective effects in experimental settings. These findings support the pharmacological potential of medicinal plants as multi-target antiviral agents. However, this review has several limitations. The included studies show considerable variability in experimental models, extract composition, and reported antiviral activity (including IC_{50} and CC_{50} values), which limits direct comparison across studies. In addition, most of the available evidence is derived from *in vitro* and *in vivo* models, with limited clinical validation. Therefore, future studies should focus on improving the consistency of experimental models, providing more standardized reporting of antiviral activity, and expanding clinical validation to strengthen the translational relevance of plant-derived antiviral agents for hepatitis B and hepatitis C management.

Authors' contribution

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Conflict of interests

The authors declare no conflict of interest.

Declaration of AI-assisted Tools in the Writing Procedure

Artificial intelligence (AI)-assisted tools (Grammarly, Claude by Anthropic) were used for language editing, grammar correction, and structural suggestions to improve the clarity and readability of the manuscript. No AI tools were used for literature search, data collection, data analysis, or interpretation of findings. All content was reviewed and approved by the authors.

Ethical considerations

This article is a review and does not involve human or animal subjects. The manuscript complies with ethical publishing standards and is free from plagiarism, as verified through comprehensive checks. All information is derived from a fair synthesis of published literature, with strict adherence to academic integrity.

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