INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Paper

From Traditional Remedy to Modern Application: A Critical Review of *Phyllanthus amarus* in the Management of Hepatitis B

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ARTICLE INFO

Published: 09 Apr 2026

Keywords:

Phyllanthus amarus, hepatitis B virus, traditional medicine, phytochemical Composition, hepatoprotective, antiviral activity, anti-inflammatory

DOI:

10.5281/zenodo.19480267

ABSTRACT

Phyllanthus amarus (P. amarus) is a hepatoprotective and antiviral herbaceous plant popular in traditional medicine systems in Asia, Africa, and South America, which has attracted considerable scientific interest. This review is a critical analysis of the ethnobotanical history, phytochemical composition, pharmacological mechanisms, and clinical evidence of P. amarus use in the treatment of hepatitis B virus (HBV) infection. This paper explores the transition of P. amarus from traditional medicine to become a modern therapeutic drug after undergoing preclinical and clinical research. The review also covers the issues of methodology, standardization, and the future directions of research that are required to incorporate this botanical medicine in the evidence-based regimens in the management of hepatitis B..

INTRODUCTION

Hepatitis B virus infection is one major global health challenge, as it is estimated that there are 296 million chronically infected individuals with HBV infection across the globe. Hepatitis B still takes the lives of about 820,000 every year because of its complications (such as cirrhosis and hepatocellular carcinoma). In spite of effective vaccines and antiviral therapies, hepatitis B remains a deadly virus. The existing treatment methods, which are mostly nucleos(t)ide analogs and interferons, have disadvantages such as viral clearance not being complete, resistance formation, high cost of treatment, and severe side effects, especially in the resource-constrained setting. In recent years, exploration of

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

complementary and alternative medicine has increased due to the necessity to have access to affordable and possibly synergistic forms of therapy. *Phyllanthus amarus* Schumach. & Thonn. (Euphorbiaceae), is one of the most promising botanical candidates in the management of hepatitis B. This is an ancient herb that has been used for centuries in Ayurvedic, Traditional Chinese Medicine, and other African traditional medicines to treat liver disorders, jaundice, and other hepatobiliary conditions.

The scientific study of *P. amarus* was accelerated after the 1980s reports indicated that the plant was effective in viral hepatitis. Since that time there have been many studies that have tried to explain its mechanisms of action, active constituents, and clinical effectiveness **[1]**. This review summarizes the existing information on *P. amarus* as an adjunct in treating hepatitis B, critically examining this evidence base and gap areas, which need to be filled to merge this option in the new treatment regimens.



Fig. 1: Phyllanthus amarus plant

Source: https://link.springer.com/article/10.1007/s13237-022-00409-z/figures/2

2. Ethnobotanical Background and Traditional Use

Phyllanthus amarus is a native of tropical and subtropical areas and has been formally identified in various systems of traditional medicine as a hepatoprotectant. The convergence of autonomous traditional applications in the varied cultures offers ethnopharmacological reasons for scientific research on *P. amarus* hepatoprotective and antiviral activities.

Table 1: Traditional uses of Phyllanthus amarus across different cultural medicine systems [2,3]

Traditional Medicine System	Local Name	Plant Parts Used	Traditional Indications	Preparation Method
Ayurvedic (India)	Bhumi amalaki	Whole plant	Liver diseases, jaundice, liver enlargement, diabetes, urinary disorders	Aqueous decoctions
Traditional Chinese Medicine	Various Phyllanthus spp.	Aerial parts	Heat clearing, liver inflammation, diuresis	Decoctions, infusions
African Traditional Medicine	Various local names	Whole plant/aerial parts	Liver complaints, malaria, digestive disorders	Aqueous infusions
Brazilian Folk Medicine	Quebra-pedra	Whole plant	Kidney stones, hepatic conditions	Decoctions, teas

3. Phytochemical Composition

The presence of a complex phytochemical composition of lignans, flavonoids, alkaloids, tannins, polyphenols, and triterpenoids has contributed to the therapeutic potential of *P. amarus*. According to phytochemical analyses, more than fifty bioactive compounds have been identified with a considerable variation in their geographic origin, harvest time, and method of extraction.

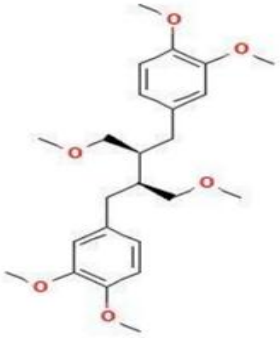


Fig. 2: Chemical structure of phyllanthin

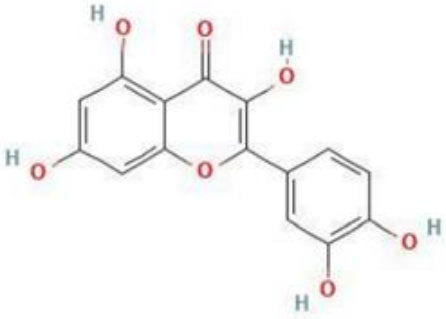


Fig. 3: Chemical structure of Quercetin

Table 2: Major phytochemical constituents of Phyllanthus amarus and their bioactivities [4]

Compound Class	Major Constituents	Primary Biological Activities	Clinical Relevance
Lignans	Phyllanthin, Hypophyllanthin, Niranthin	Hepatoprotective, Antiviral	Marker compounds for authentication; viral replication inhibition
Flavonoids	Quercetin, Rutin, Astragalin	Antioxidant, Anti-inflammatory	Oxidative stress reduction; hepatocyte protection
Ellagitannins	Geraniin, Corilagin	Antiviral, Immunomodulatory	Viral cycle interference; immune response modulation
Alkaloids	Securinine	Hepatoprotective	Liver damage prevention
Polyphenols	Various phenolic acids	Antioxidant, Anti-inflammatory	Free radical scavenging; inflammation reduction
Triterpenoids	Various compounds	Hepatoprotective, Anti-fibrotic	Stellate cell inhibition; cirrhosis prevention

The synergistic interaction among these diverse phytochemicals is probably the source of overall therapeutic effect on the overall therapeutic effect, which poses both opportunities and challenges for standardization and quality control in clinical applications.

4. Pharmacological Mechanisms in Hepatitis B Management

The therapeutic effects of *P. amarus* in hepatitis B management operate through multiple interconnected mechanisms, supported by in vitro and in vivo investigations.

Table 3: Pharmacological mechanisms of Phyllanthus amarus in hepatitis B management [5-9]

Mechanism Category	Specific Actions	Molecular Targets/Effects	Evidence Level
Antiviral Activity			
Direct viral inhibition	HBV DNA polymerase inhibition	Viral genome replication suppression	In vitro, Animal models
Antigen suppression	HBsAg and HBeAg secretion reduction	Decreased viral protein expression	Cell culture, Clinical
Viral assembly interference	HBsAg secretion pathway disruption	Prevention of viral particle formation	In vitro
Entry blockade	Hepatocyte viral entry inhibition	Prevention of naive cell infection	Preclinical
cccDNA reduction	Covalently closed circular DNA targeting	Addressing viral persistence	Experimental models
Hepatoprotective Effects			
Antioxidant activity	ROS neutralization	SOD, catalase, GSH-Px restoration	Animal studies, Clinical
Anti-inflammatory	Pro-inflammatory cytokine inhibition	TNF-α, IL-6 reduction	Preclinical, Clinical
Membrane stabilization	Hepatocyte integrity maintenance	Reduced ALT/AST leakage	Clinical studies
Anti-fibrotic	Stellate cell inhibition	Reduced collagen deposition	Animal models
Immunomodulatory Effects			
NK cell enhancement	Natural killer cell activation	Enhanced viral clearance	In vitro studies
T-cell stimulation	T-cell proliferation promotion	Improved cellular immunity	Immunological studies
Immune response optimization	Adaptive immunity enhancement	Breaking immune tolerance	Preliminary evidence

These processes have synergistic effects to deliver direct antiviral effects with indirect benefits of liver protection and immune system enhancement, although their exact molecular mechanisms are still to be clarified.

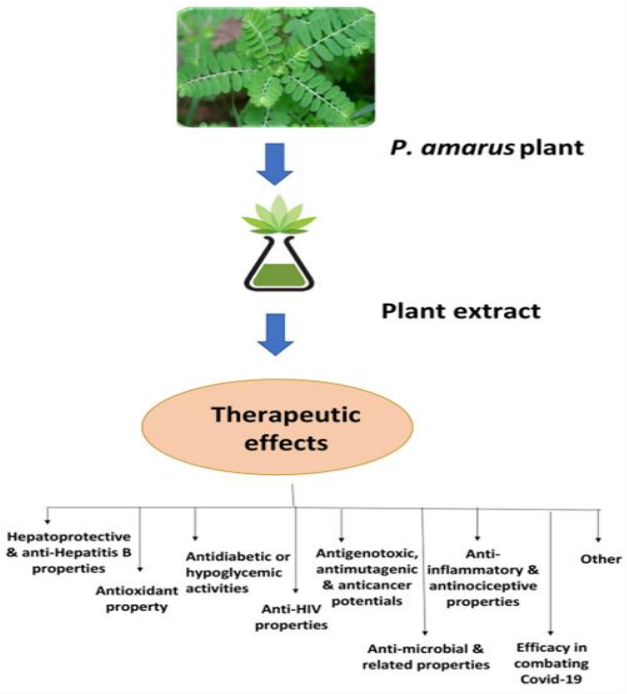


Fig. 4: Schematic representation of therapeutic potentials reported in P. amarus
Sources: https://link.springer.com/content/pdf/10.1007/s13237-022-00409-z.pdf

5. Preclinical Evidence

The hepatoprotective and anti-HBV effects of *P. amarus* have been significantly confirmed by animal experiments. Studies involving duck hepatitis B virus (DHBV) models, which are homologous to human HBV, have shown that it reduces viral load and clears HBsAg with the use of *P. amarus*. Research on transgenic mice who have been expressing the HBV genes has reported reduced viral antigen expression and improved liver **[10]**.

The toxicological analyses typically suggest excellent safety of *P. amarus* extracts at therapeutic dosages. Rodents for which acute and subchronic toxicity has been studied have shown no adverse effects that are significant at doses significantly higher than those suggested to be used therapeutically. Nevertheless, there is limited research on long-term toxicity and reproductive toxicity **[5]**.

Pharmacokinetics indicate difficulties of bioavailability of major substances. Most of the active constituents show low levels of oral absorption and high metabolism; therefore, examination of formulation mechanisms to promote bioavailability is required. The creation of standardized extracts with ideal pharmacokinetic properties is a significant research priority area.

6. Clinical Evidence

There have been conflicting yet overall promising clinical studies of *P. amarus* in the treatment of hepatitis B. There were initial uncontrolled trials that showed dramatic results of the virus clearance, which created a lot of enthusiasm. Nevertheless, later controlled studies have indicated less impressive results, which stress the effectiveness of study design **[11]**.

A landmark randomized controlled trial performed in India revealed tremendous decreases in the level of HBsAg and HBeAg of chronic hepatitis B patients who were under the *P. amarus* extract compared to placebo. Markers of liver functioning and quality of life scores also improved in patients.

Nonetheless, not all patients achieved full viral clearance, and those who stopped treatment had viral rebound.

Other clinical studies have shown inconsistent efficacy, presumably because the patient populations, stages of the disease, treatment period, and standardization of preparations were different. Certain trials have indicated that *P. amarus* can be more efficient in acute hepatitis B as compared to chronic infection, perhaps because of variations in immune status and viral integration **[12]**.Comparative studies comparing the use of *P. amarus* alone with the use of conventional antiviral treatment have largely indicated that the conventional treatments are more effective in the suppression of the virus. Nevertheless, synergistic strategies that combine *P. amarus* and conventional antiviral agents have proved to be effective and may be more effective and less toxic. The clinical trials have had an overall positive safety profile, where adverse effects were mild and infrequent, such as gastrointestinal discomfort and occasional allergic reactions. No severe adverse events that could be directly linked to *P. amarus* have been reported consistently in published trials.

7. Critical Analysis and Limitations

Despite promising evidence, significant limitations constrain confident conclusions about *P. amarus* efficacy in hepatitis B management:

- **Methodological heterogeneity** across studies, including variations in patient selection criteria, treatment protocols, outcome measures, and follow-up duration, complicates comparative analysis and meta-analytical approaches.
- **Standardization of *P. amarus* preparations** represents a critical challenge. Phytochemical variability due to botanical source authentication, geographic origin, harvesting practices, and extraction methods results in preparations with potentially different therapeutic activities **[8,13]**.
- **Inadequate characterization of test materials** in many published studies limits reproducibility and clinical translation. Complete phytochemical profiles and validated biomarkers are often absent.
- **Small sample sizes** in many clinical trials reduce statistical power and generalizability of findings.
- **Publication bias** may favor positive results, potentially overestimating true efficacy. Negative and neutral results require equal publication consideration.
- **Absence of long-term studies** assessing sustained virological response and clinical outcomes such as cirrhosis progression and hepatocellular carcinoma development.
- **Incomplete mechanistic understanding** at the molecular level. While various mechanisms have been proposed, comprehensive studies employing modern molecular techniques are needed to identify specific molecular targets and pathways.
- **Quality control and regulatory issues** present practical barriers to clinical implementation. The absence of standardized pharmaceutical-grade preparations and validated biomarkers for quality assessment hampers clinical application and regulatory approval processes.
- **Limited pharmacokinetic data** on bioavailability and metabolism of key active compounds restricts optimization of dosing regimens **[14,15]**.
- **Unclear regulatory pathways** for botanical medicines in many jurisdictions create market access limitations and development uncertainties.

8. Future Perspectives and Research Directions

Advancing *P. amarus* from traditional remedy to evidence-based therapeutic option requires addressing several critical research priorities:

- **Standardization and quality control:** development of pharmaceutical-grade preparations with known phytochemical profiles by use of good agricultural and collection practices (GACP) and good manufacturing practices (GMP).
- **The rigorous clinical trials:** Adequately powered, well-designed, randomized controlled trials with long-term follow-up, use of standardized preparations, and clinically relevant endpoints such as prevention of disease progression, viral clearance, and quality of life outcomes.
- **Combination therapy trials:** The research of *P. amarus* as an adjunctive treatment to conventional antivirals could provide improved efficacy and reduced side effects.
- **Mechanistic elucidation:** Systems biology approaches such as genomics, proteomics, and metabolomics have been used to identify molecular targets, comprehend host-viral-botanical interactions, and develop predictive biomarkers for treatment response.
- **Pharmacokinetic optimization:** Novel delivery systems and formulation techniques to enhance bioavailability of active compounds. The studies conducted on structure-activity relationship may guide development of improved derivatives.
- **Comparative effectiveness and economic evaluation:** Real-world studies assessing *P. amarus* against standard care, with cost-effectiveness analyses particularly relevant for resource-limited settings where hepatitis B burden is highest.

CONCLUSION

Phyllanthus amarus is a promising botanical medicine in the management of hepatitis B with a long history of traditional use, plausible pharmacological mechanisms, and preliminary clinical evidence. Its hepatoprotective, antiviral, and immunomodulatory effects are potentially beneficial as an adjunctive therapy or where traditional treatment is scarce.Nevertheless, the evidence gaps are significant, which makes it impossible to draw any definite conclusions concerning clinical effectiveness. The change from the traditional remedy to the modern evidence-based health requires strict clinical validation, standardized pharmaceutical preparations, and extensive mechanistic knowledge.As global health initiatives increasingly recognize integrative approaches, *P. amarus* may find its place in comprehensive hepatitis B management strategies, especially in endemic countries where traditional health services are still culturally acceptable and affordable. This remarkable plant requires sustained multidisciplinary research to realize the therapeutic potential.

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HOW TO CITE: Sourav Maji, Kunal Mondal, Sayan Ghosh, Adrish Kumar Panja, Supriya Hazra, Deep Jyoti Shah, From Traditional Remedy to Modern Application: A Critical Review of Phyllanthus amarus in the Management of Hepatitis B, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 4, 1419-1426, https://doi.org/10.5281/zenodo.19480267