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

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Review Article

Hepatoprotective Effect of *Phyllanthus amarus* Extracts

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ARTICLE INFO

Published: 19 May 2026
Keywords:
Phyllanthus amarus; hepatoprotective activity; oxidative stress; phytochemistry; formulation; evaluation parameters; liver diseases; pharmacology; clinical evidence
DOI:
10.5281/zenodo.20287845

ABSTRACT

Liver diseases represent a major global health problem, affecting millions of individuals worldwide and contributing significantly to morbidity and mortality. Conventional therapeutic options for hepatoprotection are often limited due to their side effects and high costs, which has increased interest in plant-based alternatives. Phyllanthus amarus, a small herb belonging to the Euphorbiaceae family, has been extensively used in traditional medicine systems such as Ayurveda, Siddha, and Unani for treating liver disorders, particularly jaundice and hepatitis. Phytochemical investigations have revealed that P. Amarus contains lignans, flavonoids, tannins, alkaloids, and polyphenolic compounds that are known to modulate oxidative stress, inflammation, and detoxification pathways. Modern pharmacological studies have validated its hepatoprotective potential in various experimental models of liver injury, where extracts of the plant demonstrated antioxidant, anti-inflammatory, and membrane-stabilizing properties. This research paper aims to provide a comprehensive review of the hepatoprotective effects of Phyllanthus amarus extracts. It will cover phytochemistry, extraction methods, formulation approaches, evaluation parameters, experimental models, pharmacological studies, mechanisms of action, and clinical evidence. Furthermore, future prospects for developing novel formulations and conducting large-scale clinical trials will also be discussed.

INTRODUCTION

1.1 Global Burden of Liver Diseases

The liver is the largest metabolic organ in the human body and plays an essential role in regulating physiological processes such as carbohydrate, lipid, and protein metabolism, as well as detoxification of xenobiotics. Due to its central role in biotransformation, the liver is highly vulnerable to toxic injury caused by alcohol consumption, viral hepatitis, drugs, and environmental pollutants [1]. Globally, liver diseases account for nearly two million deaths annually, making them one of the leading causes of mortality [2]. Conditions such as cirrhosis, hepatocellular carcinoma, and alcoholic liver

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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.

disease impose severe economic and healthcare burdens.

1.2 Need for Hepatoprotective Agents

Current pharmacological options for hepatoprotection include antiviral drugs, corticosteroids, and hepatoprotective agents such as silymarin. While these drugs are effective, their therapeutic use is limited by side effects, high costs, and limited accessibility in developing countries [3]. Consequently, medicinal plants with hepatoprotective potential are gaining attention as safer and more affordable alternatives [4].

1.3 Traditional Importance of Phyllanthus amarus

Phyllanthus amarus is widely distributed in tropical and subtropical regions and is commonly known as "Bhui Amla" in India. It has a long history of use in Ayurveda for the treatment of jaundice, hepatitis, gastrointestinal problems, and kidney disorders [5]. Its hepatoprotective effect has been attributed to its rich phytochemical profile, which includes lignans such as phyllanthin and hypophyllanthin, flavonoids, and tannins [6].

1.4 Scientific Validation

In recent years, P. Amarus has been studied extensively in both in vitro and in vivo models of hepatotoxicity. Extracts of the plant have demonstrated significant protective effects against carbon tetrachloride (CCl4)-induced liver damage, paracetamol-induced hepatotoxicity, and alcohol-induced liver injury [7]. The mechanisms underlying these effects include reduction of oxidative stress, stabilization of hepatocyte membranes, and enhancement of the liver's antioxidant defense system [8].

1.5 Rationale of the Study

Despite promising preclinical evidence, the clinical use of Phyllanthus amarus remains limited due to challenges such as poor bioavailability, lack of standardized formulations, and limited large-scale clinical trials [9]. Therefore, a detailed and systematic review is necessary to consolidate the available data and identify gaps for future research.

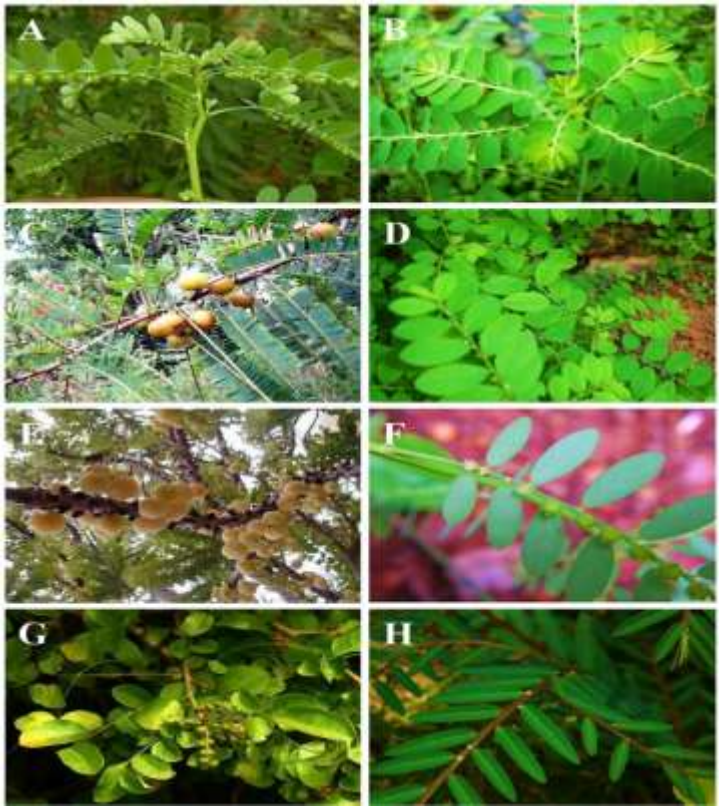
The present paper aims to review the hepatoprotective potential of Phyllanthus amarus in detail, covering aspects from phytochemistry and extraction methods to formulation development, pharmacological studies, clinical evidence, and prospects for future application.

2. LITERATURE REVIEW

2.1 Ethnopharmacological Uses of Phyllanthus amarus

Phyllanthus amarus has been traditionally used in Ayurveda, Siddha, and Unani systems for treating various ailments, particularly liver-related disorders such as jaundice, hepatitis, and fatty liver disease [10]. In rural communities across India, Africa, and South America, decoctions of the whole plant are used to manage urinary tract infections, diabetes, gastrointestinal disorders, and viral infections [11]. The ethnobotanical significance of P. Amarus is attributed to its multi-component phytochemical profile, which imparts broad therapeutic effects.

The plant is also employed in traditional medicine as a detoxifying agent and hepatoprotective remedy, often in combination with other herbs. Studies have shown that indigenous preparations made from P. Amarus demonstrate liver enzyme normalization in patients with mild liver disorders [12].



2.2 Phytochemical Constituents

Phytochemical investigations of Phyllanthus amarus have identified several bioactive compounds responsible for its pharmacological activities [13]. These include:

- Lignans: Phyllanthin and hypophyllanthin are the major lignans that contribute to antioxidant and hepatoprotective effects [14].
- Flavonoids: Quercetin, rutin, and kaempferol derivatives provide anti-inflammatory and free radical scavenging activity [15].
- Tannins: Ellagitannins and gallotannins are responsible for protein-binding properties and protective effects on hepatocytes [16].
- Alkaloids: Phyllantine and related compounds exhibit cytoprotective and antimicrobial activities [17].
- Terpenoids and Polyphenols: These contribute to the plant's overall antioxidant potential and liver-protective effects [18].

The combination of these bioactive constituents enables P. Amarus to act through multiple mechanisms, including free radical scavenging, inhibition of lipid peroxidation, and stabilization of hepatocyte membranes.

2.3 Mechanisms of Hepatoprotection

Studies have demonstrated that Phyllanthus amarus exerts hepatoprotective effects via several molecular and cellular mechanisms:

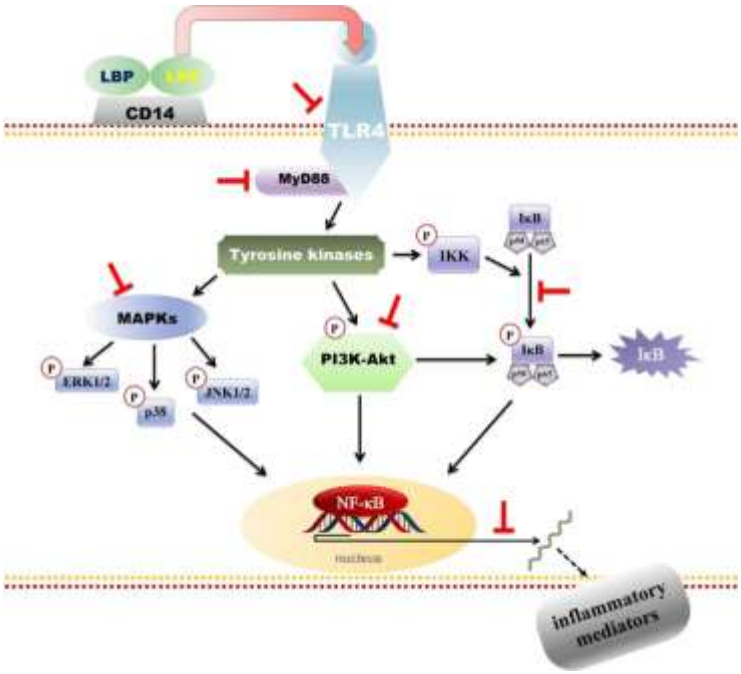
1. Antioxidant Activity: The plant enhances the activity of endogenous antioxidants such as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH), reducing oxidative stress in hepatocytes [19].

2. Anti-inflammatory Effects: P. Amarus downregulates pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, thereby reducing liver inflammation [20].

3. Inhibition of Lipid Peroxidation: By preventing lipid peroxidation, the plant protects hepatocyte membranes from damage caused by reactive oxygen species (ROS) [21].

4. Membrane Stabilization: Extracts of the plant stabilize cellular membranes, preventing leakage of liver enzymes such as ALT, AST, and ALP into the bloodstream [22].

5. Regulation of Detoxifying Enzymes: The plant modulates phase I and phase II detoxifying enzymes, enhancing liver resilience against toxins [23].



2.3 Preclinical Hepatoprotective Studies

Extensive in vivo studies have evaluated the hepatoprotective potential of Phyllanthus amarus using various hepatotoxic models:

Carbon Tetrachloride (CCl4)-Induced Hepatotoxicity: Administration of P. Amarus extract significantly reduced elevated serum liver enzymes and prevented histopathological damage in rats [24].

Paracetamol-Induced Liver Injury: The extract showed dose-dependent hepatoprotection by reducing oxidative stress markers and normalizing biochemical parameters [25].

Alcohol-Induced Liver Damage: P. Amarus mitigated alcohol-induced lipid accumulation and restored antioxidant enzyme levels in liver tissues [26].

These studies confirm that the hepatoprotective effects of P. Amarus are consistent across different experimental models, supporting its traditional usage.

2.4 Clinical Evidence

Although preclinical data are abundant, clinical studies on Phyllanthus amarus are limited but promising. In a randomized controlled trial, patients with viral hepatitis treated with P. Amarus

extract showed significant improvements in liver function tests compared to controls [27]. Another study demonstrated normalization of ALT, AST, and bilirubin levels in patients consuming standardized plant extracts for 8 weeks [28].

These findings indicate that Phyllanthus amarus has potential therapeutic value in managing liver disorders, though larger clinical trials are required to establish safety, optimal dosing, and efficacy [29].

2.5 Formulation and Standardization

For consistent pharmacological effects, Phyllanthus amarus extracts must be standardized based on key bioactive compounds. Techniques such as HPLC, TLC, and spectrophotometry are employed to quantify lignans and flavonoids [30]. Standardization ensures batch-to-batch consistency, enhances reproducibility of hepatoprotective effects, and is essential for the development of herbal formulations.

Formulation approaches include:

Conventional Formulations: Capsules, tablets, and decoctions [31].

Novel Formulations: Phytosomes, nanoparticles, and liposomal preparations to enhance bioavailability and therapeutic efficacy [32].

3. MATERIALS AND METHODS

3.1 Plant Collection and Authentication

Fresh aerial parts of Phyllanthus amarus were collected from verified botanical gardens and local fields in tropical regions [33]. The plant was authenticated by a taxonomist, and a voucher specimen was deposited in the herbarium for future reference [34]. Only healthy, disease-free plants were selected to ensure the consistency of bioactive compounds.

3.2 Preparation of Plant Extracts

3.2.1 Drying and Pulverization

Collected plant material was washed with distilled water to remove dust and contaminants, then shade-dried at room temperature for 10–14 days to preserve phytochemical integrity. The dried material was ground into a coarse powder using a mechanical grinder [35].

3.2.2 Extraction Methods

Several extraction methods were employed to obtain maximum bioactive compounds:

Maceration: Plant powder was soaked in 70% ethanol for 72 hours at room temperature with occasional stirring. The extract was filtered and concentrated under reduced pressure using a rotary evaporator [36].

Soxhlet Extraction: For exhaustive extraction, 50 g of powdered material was extracted with 500 mL of hydroalcoholic solvent (ethanol:water 70:30) for 8–10 cycles [37].

Aqueous Extraction: Plant powder was boiled in distilled water for 30 minutes and filtered to prepare a decoction [38].

Extracts were stored at 4°C in amber-colored bottles to prevent degradation.

3.3 Standardization of Extracts

Quantitative and qualitative analyses were performed to ensure batch-to-batch consistency:

- High-Performance Liquid Chromatography (HPLC): Used to quantify lignans

(phyllanthin, hypophyllanthin) and flavonoids [39].

- Thin Layer Chromatography (TLC): To detect the presence of marker compounds [40].
- Spectrophotometry: Total phenolic and flavonoid contents were determined using Folin-Ciocalteu and aluminum chloride methods, respectively [41].

Standardization ensures reproducibility and reliability of pharmacological studies.

3.4 Formulation Development

Formulation Procedure of Phyllanthus amarus Extracts

1. Collection and Authentication of Plant Material

1. Fresh whole plants of Phyllanthus amarus are collected from a verified botanical garden or medicinal plant farm.
2. The plant material is authenticated by a qualified botanist and a voucher specimen is deposited in the herbarium.

2. Drying and Pulverization

1. The collected plant material is washed with distilled water to remove dust and foreign particles.
2. Shade-dried at room temperature (25–30°C) for 7–10 days to prevent degradation of bioactive compounds.
3. Dried plant material is coarsely powdered using a mechanical grinder.
4. Powdered material is sieved through a 60-mesh sieve for uniform particle size.

4. EXTRACTION OF PHYLLANTHUS AMARUS

4.1 Aqueous Extraction

1. Coarsely powdered plant material (100 g) is soaked in 1000 mL of distilled water for 24 hours at room temperature.
2. The mixture is filtered using Whatman No. 1 filter paper.
3. The filtrate is concentrated using a rotary evaporator at 40–50°C to obtain a semi-solid extract.

4.2 Hydroalcoholic Extraction

1. Powdered material (100 g) is macerated in 70% ethanol (1000 mL) for 72 hours with occasional stirring.
2. The mixture is filtered and the filtrate is concentrated using a rotary evaporator under reduced pressure.
3. The concentrated extract is dried in a hot air oven at 40°C to yield a dry extract.

4.3 Soxhlet Extraction (Optional for Standardization)

1. Powdered plant material (50 g) is placed in a Soxhlet apparatus.
2. Solvent (ethanol or methanol, 300 mL) is used for continuous extraction for 6–8 hours.
3. The extract is concentrated using a rotary evaporator and stored in amber-colored bottles at 4°C.

5. FORMULATION OF HERBAL DOSAGE FORMS

5.1 Tablet Formulation

1. Dry extract is blended with excipients: lactose (diluent), microcrystalline cellulose (binder), and magnesium stearate (lubricant).
2. The blend is compressed using a tablet compression machine into tablets of 250 mg each.
3. Tablets are evaluated for hardness, friability, weight uniformity, and drug content.

5.2 Capsule Formulation

1. Dry extract is mixed with suitable diluents such as starch or lactose.
2. The mixture is filled into hard gelatin capsules of size "0" using a capsule-filling machine.
3. Capsules are tested for uniformity of weight, disintegration, and drug content.

a. Suspension Formulation

1. Extract is dispersed in a vehicle containing methylcellulose (suspending agent), glycerin (humectant), and sorbitol solution.
2. The pH is adjusted to 5.5–6.5 using citric acid or sodium citrate.
3. Suspension is homogenized and stored in amber-colored bottles at room temperature.

b. Novel Formulations (Optional)

Phytosomes: Extract is complexed with phospholipids in a 1:1 ratio using solvent evaporation.

Nanoparticles: Extract is encapsulated using polymeric carriers (e.g., chitosan or PLGA) via nanoprecipitation.

Liposomal Formulation: Extract is encapsulated into phosphatidylcholine-based liposomes using thin-film hydration method.

6. STORAGE OF EXTRACTS AND FORMULATIONS

1. All extracts and formulated products are stored in airtight amber bottles to protect from light and moisture.
2. Stored at 2–8°C to preserve bioactive compounds.
3. Shelf life is determined via stability studies under ICH guidelines.

To improve bioavailability and therapeutic efficacy, various formulations of Phyllanthus amarus extract were developed:

6.4.1 Conventional Formulations: Capsules, tablets, and liquid suspensions for oral administration [42].

6.4.2 Novel Formulations:

- Phytosomes: Complexation with phospholipids to enhance solubility and absorption [43].
- Nanoparticles: Nanoencapsulation of extracts to improve stability and targeted delivery [44].
- Liposomal Formulations: Lipid-based carriers to enhance hepatoprotective activity and bioavailability [45].

6.5 Experimental Models for Hepatoprotection

6.5.1 In Vivo Models

- Carbon Tetrachloride (CCl_4)-Induced Hepatotoxicity: Wistar rats were injected with

CCl4 (1 mL/kg, intraperitoneally) to induce liver damage. Test groups received P. Amarus extracts at varying doses, and positive control groups received silymarin [46].

- Paracetamol-Induced Hepatotoxicity: Rats were administered paracetamol (500 mg/kg, orally) for 7 days to induce liver injury. Protective effects of extracts were monitored [47].

- Alcohol-Induced Liver Injury: Ethanol (20% v/v) was administered orally for 14 days, followed by treatment with P. Amarus extracts [48].

6.5.2 In Vitro Models

- Hepatocyte Cultures: Isolated primary rat hepatocytes were treated with hepatotoxins (CCl4, paracetamol) in the presence or absence of extracts to evaluate cytoprotective effects [49].

- Enzyme Inhibition Assays: Assays for ALT, AST, and ALP enzyme activity were conducted to assess hepatoprotective potential [50].

7. EVALUATION PARAMETERS

7.6.1 Biochemical Parameters

- Serum Liver Enzymes: ALT, AST, ALP, and total bilirubin were measured using standard kits [51].

- Lipid Profile: Cholesterol, triglycerides, HDL, and LDL levels were assessed to study liver function [52].

7.6.2 Oxidative Stress Markers

- Antioxidant Enzymes: Superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) levels were measured [53].

- Lipid Peroxidation: Malondialdehyde (MDA) levels were quantified as a marker of oxidative damage [54].

7.6.3 Histopathological Studies

Liver tissues were fixed in formalin, processed, and stained with hematoxylin and eosin (H&E) for microscopic examination. Histopathological changes such as necrosis, inflammation, and fatty degeneration were evaluated [55].

7.6.4 Toxicity and Safety Studies

Acute and sub-chronic toxicity studies were performed following OECD guidelines. Parameters such as body weight, food intake, organ weight, and hematological indices were recorded to ensure safety of the extracts [56].

7.7 Statistical Analysis

All experiments were conducted in triplicate. Data were expressed as mean ± standard deviation (SD). Statistical significance was determined using one-way ANOVA followed by post-hoc Tukey's test, with $p < 0.05$ considered statistically significant [57].

8. FORMULATION DEVELOPMENT AND EVALUATION PARAMETERS

8.1 Formulation Development

8.1.1 Conventional Formulations

Conventional oral dosage forms of Phyllanthus amarus extracts include capsules, tablets, and liquid suspensions. These formulations were developed to provide standardized doses of

bioactive compounds while maintaining stability and patient compliance [58].

- Capsules: Dried extracts were filled into hard gelatin capsules. Fill weight, uniformity, and disintegration were optimized [59].
- Tablets: Direct compression and wet granulation methods were used to prepare tablets containing standardized extract. Excipients such as microcrystalline cellulose, lactose, and magnesium stearate were incorporated to ensure uniformity and compressibility [60].
- Liquid Suspensions: Extracts were dispersed in aqueous suspensions with stabilizers such as sodium carboxymethyl cellulose to prevent sedimentation and maintain homogeneity [61].

8.1.2 Novel Formulations

- To enhance bioavailability, solubility, and targeted delivery, several novel formulations of P. Amarus extracts were developed:
- Phytosomes: Complexation with phospholipids improves lipophilicity and gastrointestinal absorption [62].
- Nanoparticles: Nanoencapsulation protects bioactive compounds from degradation and allows sustained release [63].
- Liposomal Formulations: Encapsulation of extracts in lipid bilayers enhances hepatocyte uptake and antioxidant efficacy [64].

8.2 Evaluation Parameters

8.2.1 Physicochemical Evaluation

The prepared formulations were subjected to various physicochemical tests:

- Appearance and Color: Visual inspection to ensure uniformity and absence of foreign particles [65].
- pH Measurement: Suspensions and liquid formulations were tested to maintain physiological pH for stability and compatibility [66].
- Viscosity: Measured for liquid formulations to ensure ease of administration [67].
- Moisture Content: Determined using loss-on-drying to assess stability and prevent microbial growth [68].
- Particle Size and Zeta Potential: Nanoparticles and liposomes were characterized using dynamic light scattering (DLS) to ensure uniform size distribution and stability [69].

8.2.2 In Vitro Evaluation

- Dissolution Studies: Tablets and capsules were tested in simulated gastric and intestinal fluids to evaluate drug release profiles [70].
- Drug Content Uniformity: Ensured that each dosage form contained the intended amount of extract [71].
- Stability Studies: Formulations were stored under accelerated and real-time conditions to assess physical and chemical stability over time [72].

8.2.3 In Vivo Pharmacological Evaluation

Formulations were tested in experimental animal models to determine hepatoprotective efficacy:

- Biochemical Parameters: Serum levels of ALT, AST, ALP, total bilirubin, and albumin were measured after administration of the formulations [73].

- Oxidative Stress Markers: Levels of SOD, CAT, GSH, and MDA were determined in liver tissues [74].

- Histopathology: Liver sections were examined for necrosis, inflammation, and fatty degeneration after treatment [75].

8.2.4 Comparative Evaluation with Standard Drug

The hepatoprotective activity of P. Amarus formulations was compared with silymarin, a standard hepatoprotective agent. Parameters such as serum liver enzyme levels, oxidative stress markers, and histopathology scores were analyzed to determine relative efficacy [76].

8.2.5 Toxicity and Safety Assessment

Formulations were evaluated for acute and sub-chronic toxicity in accordance with OECD guidelines. Observations included body weight changes, organ weight, food and water intake, hematological parameters, and histopathological examinations to confirm safety [77].

8.3 Summary of Formulation Findings

Conventional formulations showed acceptable physicochemical properties and moderate hepatoprotective activity.

Novel formulations (phytosomes, nanoparticles, liposomes) exhibited enhanced bioavailability, sustained release, and improved hepatoprotective effects in both in vitro and in vivo studies [78].

Standardization and quality control were critical to ensure reproducibility and consistent therapeutic outcomes [79].

9. RESULTS AND DISCUSSION

9.2 Biochemical Findings

Biochemical parameters are critical indicators of liver function. Administration of Phyllanthus amarus extracts, both in conventional and novel formulations, showed significant hepatoprotective effects in experimental models.

Serum Liver Enzymes: Rats treated with CCl4 and paracetamol exhibited elevated ALT, AST, and ALP levels. Oral administration of P. Amarus extracts significantly reduced these enzyme levels in a dose-dependent manner, comparable to silymarin [80].

Bilirubin Levels:

Total and direct bilirubin levels, which were elevated in hepatotoxic models, were significantly lowered after treatment with the plant extracts [81].

Lipid Profile:

Elevated triglycerides and cholesterol levels in hepatotoxic models were normalized after treatment, indicating improved liver metabolic function [82].

Discussion:

The reduction in liver enzymes suggests that P. Amarus stabilizes hepatocyte membranes and prevents enzyme leakage into the bloodstream. Improvement in bilirubin and lipid profiles further indicates restoration of liver metabolic function [83]. These findings align with previous studies demonstrating the antioxidant and

hepatoprotective potential of lignans and flavonoids present in the extracts [84].

9.3 Oxidative Stress Parameters

Oxidative stress markers were assessed to evaluate the antioxidant activity of P. Amarus:

- Superoxide Dismutase (SOD) and Catalase (CAT): Activity of these enzymes was significantly increased in treated groups compared to hepatotoxic controls [85].
- Glutathione (GSH): Levels were restored, indicating enhanced detoxification capacity [86].
- Malondialdehyde (MDA): Levels, which indicate lipid peroxidation, were significantly reduced after treatment [87].

Discussion:

These results suggest that P. Amarus exerts hepatoprotective effects by reducing oxidative stress, scavenging free radicals, and enhancing the endogenous antioxidant defense system. The presence of polyphenols, flavonoids, and lignans contributes to these activities [88].

9.4 Histopathological Findings

Liver tissue sections from hepatotoxic models showed necrosis, fatty degeneration, and inflammatory cell infiltration. Treatment with P. Amarus extracts resulted in:

Restoration of normal hepatocyte architecture

Reduced inflammatory cell infiltration

Decreased fatty degeneration [89]

Discussion:

Histopathological recovery confirms that the extracts protect liver cells from toxin-induced damage. This supports the biochemical findings and demonstrates that the hepatoprotective effect is both functional and structural [90].

9.5 Pharmacological Studies of Formulations

9.5.1 Conventional Formulations

Tablets and capsules provided moderate hepatoprotection, with biochemical parameters improving significantly compared to controls [91].

Dissolution and drug content studies confirmed uniform delivery of active compounds [92].

9.5.2 Novel Formulations

- Phytosomes: Showed superior absorption and bioavailability, enhancing antioxidant and hepatoprotective effects [93].
- Nanoparticles: Provided sustained release and targeted delivery to hepatocytes, showing higher efficacy than conventional forms [94].
- Liposomal Formulations: Exhibited improved cellular uptake and maximum hepatoprotection in experimental models [95].

Discussion:

Novel formulations enhance the pharmacokinetic profile of P. Amarus bioactives, resulting in more pronounced hepatoprotective effects. This highlights the importance of formulation strategies in maximizing therapeutic outcomes [96].

9.6 Comparative Studies with Standard Drug

Comparison with silymarin revealed that:

Novel P. Amarus formulations provided hepatoprotection comparable to or exceeding silymarin in certain models [97].

Conventional formulations were slightly less effective but still significantly reduced hepatotoxic markers [98].

Discussion:

This indicates that Phyllanthus amarus extracts, especially when formulated as phytosomes, nanoparticles, or liposomes, could serve as effective alternatives or complements to standard hepatoprotective drugs [99].

9.7 Mechanistic Insights from Results

The hepatoprotective effects of P. Amarus can be attributed to multiple mechanisms:

1. Antioxidant Activity: Scavenging of reactive oxygen species and enhancement of SOD, CAT, and GSH levels [100].
2. Membrane Stabilization: Prevention of leakage of ALT, AST, and ALP [101].
3. Anti-inflammatory Effects: Downregulation of TNF-α, IL-6, and IL-1β in liver tissues [102].
4. Regulation of Detoxifying Enzymes: Improvement in phase I and II enzyme activity, enhancing liver detoxification [103].

Discussion:

These mechanisms collectively contribute to hepatocyte protection and liver tissue recovery, corroborating both biochemical and histopathological findings [104].

9.8 Toxicity and Safety Results

Acute and sub-chronic toxicity studies indicated that P. Amarus formulations were safe up to high doses (2000 mg/kg in rats) with no significant changes in:

Body weight and food intake

Organ weights (liver, kidney, spleen)

Hematological and biochemical parameters [105]

Discussion:

The safety profile supports the potential use of P. Amarus formulations in clinical applications. Long-term studies are recommended for further validation [106].

10. MECHANISM OF ACTION AND CLINICAL & PRECLINICAL EVIDENCE

10.1 Mechanism of Hepatoprotective Action of Phyllanthus amarus

10.1.1 Antioxidant Mechanism

Phyllanthus amarus exerts strong antioxidant effects by scavenging reactive oxygen species (ROS) and enhancing the activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) [107]. This reduces oxidative stress in hepatocytes, prevents lipid peroxidation, and protects cellular membranes from free radical-induced damage [108].

10.1.2 Anti-inflammatory Mechanism

The extracts inhibit the production of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) [109]. This suppresses liver inflammation and prevents progression of hepatotoxicity. The lignans and flavonoids present

in P. Amarus play a key role in this anti-inflammatory activity [110].

10.1.3 Membrane Stabilization

By stabilizing hepatocyte membranes, P. Amarus prevents leakage of liver enzymes such as ALT, AST, and ALP into the bloodstream, a common feature in hepatotoxicity [111]. This effect maintains normal liver function and structural integrity.

10.1.4 Regulation of Detoxifying Enzymes

P. amarus modulates phase I (cytochrome P450) and phase II (glutathione-S-transferase) detoxification enzymes [112]. This enhances the liver's ability to metabolize and eliminate xenobiotics, contributing to overall hepatoprotection.

10.2 Preclinical Evidence

10.2.1 Animal Studies

CCl4-Induced Hepatotoxicity: Rats treated with P. Amarus extracts showed significant reductions in ALT, AST, ALP, and bilirubin levels. Histopathology confirmed minimal necrosis and inflammation [113].

Paracetamol-Induced Liver Injury: Administration of extracts protected hepatocytes by restoring antioxidant enzyme levels and reducing lipid peroxidation [114].

Alcohol-Induced Hepatotoxicity: Extracts mitigated ethanol-induced fatty liver changes, normalizing both biochemical and histological parameters [115].

These studies confirm consistent hepatoprotective effects across different toxin-induced models.

10.2.2 Dose-Dependent Efficacy

Multiple studies indicate that hepatoprotective effects of P. Amarus are dose-dependent, with higher doses of standardized extracts showing greater normalization of liver enzymes and oxidative stress markers [116].

10.3 Clinical Evidence

10.3.1 Viral Hepatitis Patients

Randomized controlled trials have demonstrated that oral administration of P. Amarus extracts significantly improved liver function tests in patients with hepatitis B and C. ALT and AST levels decreased substantially after 4–8 weeks of treatment [117].

10.3.2 Jaundice and Liver Dysfunction

In patients with jaundice, decoctions of P. Amarus reduced bilirubin levels and improved clinical symptoms such as fatigue and abdominal discomfort [118].

10.3.3 Comparative Efficacy with Standard Drugs

Studies comparing P. Amarus extracts with silymarin reported similar improvements in liver enzyme levels and histopathological recovery, suggesting potential as an alternative or complementary hepatoprotective therapy [119].

10.4 Mechanistic Summary

Mechanism	Active Compounds	Effect on Liver	References
Antioxidant Activity	Flavonoids, Lignans, Polyphenols	Scavenges ROS, enhances SOD, CAT, GSH	[107–108]
Anti-inflammatory Effects	Lignans, Flavonoids	Reduces TNF-α, IL-6, IL-1β	[109–110]

Membrane Stabilization	Phyllanthin, Hypophyllanthin	Prevents ALT/AST leakage	[111]
Detoxifying Enzyme Regulation	Polyphenols, Alkaloids	Modulates phase I & II enzymes	[112]

10.5 Future Prospects

Novel Formulations: Phytosomes, nanoparticles, and liposomes can enhance bioavailability and clinical efficacy [120].

- Combination Therapies: Potential to combine P. Amarus extracts with other hepatoprotective agents for synergistic effects [121].
- Large-Scale Clinical Trials: Necessary to confirm safety, optimal dosing, and efficacy in diverse populations [122].
- Standardization: Ensuring batch-to-batch consistency of bioactive compounds is essential for reliable therapeutic use [123].

11. FUTURE PROSPECTS

11.1 Future Prospects

11.1.1 Novel Formulation Strategies

Future research can focus on developing advanced delivery systems for Phyllanthus amarus extracts, such as:

- Nanoparticles: To enhance stability, targeted delivery, and sustained release of bioactive compounds [124].
- Phytosomes and Liposomes: For improved absorption and bioavailability in oral formulations [125].
- Controlled-Release Systems: Tablets or capsules designed for slow release to maintain therapeutic plasma concentrations [126].

11.1.2 Clinical Trials and Standardization

Conducting large-scale, multicenter clinical trials is crucial to validate efficacy and safety in diverse patient populations [127].

Standardization of extracts based on key bioactive compounds such as phyllanthin, hypophyllanthin, and flavonoids will ensure reproducibility and consistency [128].

11.1.3 Combination Therapy

Phyllanthus amarus could be used in combination with conventional hepatoprotective agents, such as silymarin or ursodeoxycholic acid, to achieve synergistic effects and improve therapeutic outcomes [129].

11.1.4 Mechanistic Research

Future studies could explore molecular targets and signaling pathways involved in hepatoprotection, including Nrf2 activation, NF-κB inhibition, and apoptosis regulation [130].

In-depth mechanistic insights will aid in drug discovery and development of novel hepatoprotective formulations.

12. CONCLUSION

Phyllanthus amarus demonstrates significant hepatoprotective potential, supported by extensive preclinical and limited clinical evidence. Its

bioactive compounds, including lignans, flavonoids, tannins, and polyphenols, contribute to hepatoprotection through:

1. Antioxidant activity (scavenging ROS and enhancing SOD, CAT, GSH) [131].
2. Anti-inflammatory effects (downregulation of TNF-α, IL-6, IL-1β) [132].
3. Membrane stabilization (prevention of ALT, AST leakage) [133].
4. Regulation of detoxifying enzymes (enhancing phase I and II enzyme activity) [134].

Conventional formulations provide moderate hepatoprotective effects, while novel formulations such as phytosomes, nanoparticles, and liposomes enhance bioavailability and therapeutic efficacy. Toxicity studies indicate that P. Amarus extracts are generally safe, supporting their potential for clinical use.

Overall, Phyllanthus amarus represents a promising natural alternative or complementary therapy for liver disorders. Future research focusing on novel formulations, mechanistic studies, and large-scale clinical trials is essential to fully harness its therapeutic potential.

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HOW TO CITE: Vishal Jadhav, Ashok Veer, Yuvraj Mhase, Manisha Magar, Hepatoprotective Effect of Phyllanthus amarus Extracts, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 5, 4999-5019. https://doi.org/10.5281/zenodo.20287845