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Bioactive Constituents of *Phyllanthus amarus* Schumach. and Thonn. Mediate Hepatoprotection via Enhanced Antioxidant Defenses and Apoptosis Inhibition in APAP-Challenged LO_2 Cells

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Abstract

This study investigated the hepatoprotective potential of *Phyllanthus amarus* Schumach. & Thonn. ethanolic extract against acetaminophen (APAP)-induced toxicity in human LO2 hepatocytes. Phytochemical analysis revealed high phenolic (58.4 ± 3.2 mg GAE/g) and flavonoid (32.7 ± 2.1 mg QE/g) content, along with bioactive lignans. The extract exhibited excellent safety profile (IC50 >800 µg/mL) with >85% cell viability at 200 µg/mL. Pretreatment with 300 µg/mL extract significantly restored APAP-compromised cell viability to 82.5±4.1% (vs 48.3±3.8% in APAP-only), reduced LDH leakage by 62%, and normalized ALT/AST levels (55-60% reduction). Mechanistic studies demonstrated potent antioxidant activity, increasing SOD (2.3-fold) and CAT (2.4-fold) while elevating GSH (4.8±0.4 vs 1.5±0.2 µM/mg protein) and reducing lipid peroxidation (70% MDA decrease). Notably, the extract dramatically attenuated APAP-induced apoptosis from 45% to 12% ($p<0.001$), preserving nuclear morphology. These findings validate *P. amarus* as a multi-target hepatoprotective agent acting through membrane stabilization, oxidative stress mitigation, and apoptosis inhibition, suggesting its potential as a complementary therapy for drug-induced liver injury.

Keywords: *Phyllanthus amarus*; Acetaminophen toxicity; Hepatoprotection; Oxidative stress; Apoptosis; Herbal medicine

1. Introduction

Liver diseases remain a significant global health burden, with drug-induced liver injury (DILI) representing one of the most common causes of acute liver failure worldwide. Acetaminophen (APAP) overdose accounts for nearly 50% of all DILI cases in developed countries and is increasingly prevalent in developing nations [1]. Despite the availability of N-acetylcysteine (NAC) as the standard antidote, its narrow therapeutic window and potential side effects underscore the need for safer, more effective hepatoprotective agents [2]. This therapeutic gap has spurred growing interest in medicinal plants with hepatoprotective properties, particularly those with established ethnopharmacological use but requiring rigorous scientific validation.

Phyllanthus amarus, Schumach. & Thonn.a traditional medicinal plant in Ayurveda and other indigenous systems, has demonstrated promising hepatoprotective effects in preliminary studies [3]. Contemporary research has identified its bioactive constituents, including lignans (phyllanthin, hypophyllanthin), flavonoids, and phenolic acids, which exhibit antioxidant and anti-inflammatory properties [4]. However, most existing studies have focused on crude extracts without detailed mechanistic investigations, particularly regarding their effects on cellular apoptosis pathways and specific molecular targets in human hepatocytes [5]. Furthermore, the safety profile of *P. amarus* extracts at varying concentrations remains inadequately characterized, creating uncertainty about its therapeutic dosage range.

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The current study addresses these critical knowledge gaps through a comprehensive evaluation of *P. amarus* ethanolic extract's hepatoprotective mechanisms against APAP-induced toxicity in human hepatocytes. While previous works have examined antioxidant effects in animal models, our investigation provides novel insights at the cellular level, quantifying protection against membrane damage (through LDH, ALT, AST markers), oxidative stress (SOD, CAT, GSH, MDA), and apoptosis (AO/EB staining). This multilayered approach offers a more complete understanding of the plant's therapeutic potential compared to existing literature [6]. Additionally, our rigorous cytotoxicity assessment establishes crucial safety parameters for potential clinical translation, which previous studies have overlooked.

This research gains particular significance in the context of increasing global interest in plant-based hepatoprotective agents that can complement or potentially reduce reliance on NAC. With the World Health Organization reporting that 80% of developing countries' populations use traditional medicines for primary healthcare, scientifically validating plants like *P. amarus* becomes imperative [7]. Our study not only provides empirical support for its traditional use but also elucidates specific protective mechanisms, paving the way for standardized phytopharmaceutical development. The findings hold promise for addressing the unmet need for safer, more accessible hepatoprotective therapies, especially in resource-limited settings where APAP poisoning remains a major public health challenge.

2. Materials and Methods

2.1. Plant Material and Extraction

Fresh *Phyllanthus amarus* plants were collected from Thiruvananthapuram and authenticated in the Department of Botany, Mar Ivanios College (Autonomous), Thiruvananthapuram. The aerial parts were shade-dried at room temperature (25-28 °C) for 7 days and pulverized into fine powder using a mechanical grinder [8]. The powdered material (500 g) was subjected to Soxhlet extraction with 70% ethanol (2.5 L) for 48 hours at 60°C [9]. The ethanolic extract was concentrated using a rotary evaporator (Buchi R-210) at 40°C under reduced pressure, yielding a dark green semisolid residue (yield: 18.5% w/w), which was stored at 4 °C in airtight containers until further use [10].

2.2. Phytochemical Screening and Quantification

Preliminary phytochemical screening was performed using standard protocols [11]. Phenolic compounds were identified using the Folin-Ciocalteu reagent test, flavonoids via the aluminum chloride method, alkaloids with Mayer's and Wagner's reagents, tannins using ferric chloride, and saponins through the foam test [12]. For quantitative analysis, total phenolic content (TPC) was determined spectrophotometrically at 765 nm using the Folin-Ciocalteu method and expressed as gallic acid equivalents (GAE) per gram extract [13]. Total flavonoid content (TFC) was measured at 510 nm using the aluminum chloride method and calculated as quercetin equivalents (QE) [14].

2.3. Cell Culture and Cytotoxicity Assessment

The human normal hepatocyte LO2 cell line (ATCC® CRL-1548™) was cultured in DMEM supplemented with 10% FBS, 100 U/mL penicillin, and 100 µg/mL streptomycin at 37 °C in a humidified 5% CO_2 incubator [15]. For cytotoxicity assessment, cells (1×10^4 cells/well) were seeded in 96-well plates and treated with P. amarus extract (50-1000 µg/mL) for 24 hours [16]. MTT solution (0.5 mg/mL) was added and incubated for 4 hours, followed by DMSO addition to dissolve formazan crystals. Absorbance was measured at 570 nm using a microplate reader (BioTek Synergy HT) [17]. Cell viability was calculated as percentage relative to untreated controls.

Evaluation of Hepatoprotective Activity

LO2 cells were pretreated with *P. amarus* extract (100, 200, and 300 µg/mL) for 2 hours before exposure to 20 mM acetaminophen (APAP) for 24 hours [18]. Cell viability was assessed using MTT assay as described above. LDH leakage was measured using a commercial kit (Cayman Chemical) according to the manufacturer's protocol [19]. ALT and AST activities in culture supernatant were determined using kinetic methods with commercial kits (Randox Laboratories) [20]. Results were expressed as percentage reduction compared to APAP-treated controls.

2.4. Measurement of Antioxidant Enzyme Activity

After treatments, cells were lysed and centrifuged at 10,000×g for 15 minutes at 4°C to obtain the supernatant for enzyme assays [21]. Superoxide dismutase (SOD) activity was measured by monitoring inhibition of nitroblue tetrazolium reduction at 560 nm [22]. Catalase (CAT) activity was determined by measuring H_2O_2 decomposition at 240 nm [23]. Reduced glutathione (GSH) content was assayed using Ellman's reagent (5,5'-dithiobis-2-nitrobenzoic acid) at

412 nm [24]. Lipid peroxidation was evaluated by measuring malondialdehyde (MDA) levels through reaction with thiobarbituric acid at 532 nm [25].

2.5. Analysis of Anti-Apoptotic Effects

Cells grown on coverslips were treated as described, then stained with acridine orange (100 µg/mL) and ethidium bromide (100 µg/mL) for 5 minutes [26]. After washing with PBS, cells were visualized under a fluorescence microscope (Nikon Eclipse Ti2) at 400× magnification. Viable cells (green nuclei), early apoptotic cells (green nuclei with condensed chromatin), late apoptotic cells (orange nuclei with condensed chromatin), and necrotic cells (orange nuclei with normal chromatin) were counted in five random fields per treatment. The apoptotic index was calculated as percentage of apoptotic cells relative to total cells counted.

3. Results

3.1. Phytochemical Composition of *Phyllanthus amarus* Ethanolic Extract

Phytochemical screening of the ethanolic extract revealed the presence of phenolics, flavonoids, alkaloids, tannins, and saponins. Quantitative analysis demonstrated high levels of total phenolic (58.4 ± 3.2 mg GAE/g) and flavonoid (32.7 ± 2.1 mg QE/g) content.

Table 1 Phytochemical Profile of *P. amarus* Ethanolic Extract

Phytochemical	Result
Total Phenolic Content	58.4 ± 3.2 mg GAE/g
Total Flavonoid Content	32.7 ± 2.1 mg QE/g
Alkaloids	Present
Tannins	Present
Saponins	Present

3.2. Cytotoxicity Evaluation on Human Hepatocytes

The MTT assay demonstrated that *P. amarus* extract exhibited low cytotoxicity on normal human hepatocytes (LO2 cell line), with cell viability remaining above 85% at concentrations up to 200 µg/mL. The IC_{50} value exceeded 800 µg/mL, indicating a high safety margin for therapeutic applications.

3.3. Hepatoprotective activity against acetaminophen-induced toxicity

Pretreatment with *P. amarus* extract (100–300 µg/mL) significantly attenuated acetaminophen (APAP)-induced hepatocyte damage. At 300 µg/mL, the extract restored cell viability to 82.5 ± 4.1%, compared to 48.3 ± 3.8% in the APAP-only group ($p < 0.01$). Additionally, LDH leakage was reduced by 62%, and ALT/AST levels decreased by 55–60%, confirming membrane stabilization and hepatoprotection.

Table 2 Effect of *P. amarus* Extract on Liver Function Markers

Parameter	APAP-only	APAP + 300 µg/mL Extract	Normal Control
LDH Release (U/L)	320 ± 25	122 ± 0.18*	95 ± 0.12
ALT (U/L)	180 ± 20	72 ± 1.10*	45 ± 0.8
AST (U/L)	165 ± 18	68 ± 0.9*	40 ± 0.6

*p < 0.01 vs. APAP group

3.4. Restoration of Antioxidant Defense Mechanisms

The extract significantly enhanced intracellular antioxidant enzyme activity in APAP-exposed hepatocytes. SOD and CAT levels increased by 2.3-fold and 2.4-fold, respectively, while GSH content rose from 1.5 ± 0.2 µM/mg protein to 4.8 ± 0.4

μM/mg protein ($p < 0.01$). Concurrently, lipid peroxidation (MDA levels) decreased by 70%, indicating reduced oxidative stress.

Table 3 Modulation of Antioxidant Enzymes by *P. amarus* Extract

Parameter	APAP-only	APAP + 300 μg/mL Extract	Normal Control
SOD (U/mg protein)	12.4 ± 1.1	28.7 ± 2.3*	32.5 ± 2.8
CAT (U/mg protein)	8.6 ± 0.9	20.1 ± 1.8*	22.4 ± 2.1
GSH (μM/mg protein)	1.5 ± 0.2	4.8 ± 0.4*	5.2 ± 0.5

3.5. Inhibition of Apoptosis in Hepatocytes

AO/EB staining revealed that *P. amarus* extract (300 μg/mL) reduced APAP-induced apoptosis from 45% to 12% ($p < 0.001$). Fluorescence microscopy confirmed preserved nuclear morphology in treated cells, supporting the anti-apoptotic effects of the extract.

Table 4 Anti-apoptotic Effects of *P. amarus* Extract on APAP-induced Hepatocyte Damage

Treatment Group	Apoptotic Cells (%)	Nuclear Morphology Observations	p-value vs APAP-only
Normal Control	3.2 ± 0.8	Intact, uniform chromatin	<0.001
APAP-only (20 mM)	45.1 ± 3.6	Chromatin condensation, fragmentation	-
APAP + *P. amarus* (300 μg/mL)	12.4 ± 1.9*	Mostly intact nuclei, minimal condensation	<0.001

*Values represent mean ± SD (n=6 independent experiments); *p < 0.001 compared to APAP-only group

4. Discussion

The present study demonstrates that *Phyllanthus amarus* ethanolic extract possesses significant hepatoprotective, antioxidant, and anti-apoptotic properties against acetaminophen (APAP)-induced hepatotoxicity. These findings align with recent research on hepatoprotective phytochemicals while providing novel insights into the mechanisms of *P. amarus* action.

The phytochemical analysis revealed high levels of phenolics (58.4 ± 3.2 mg GAE/g) and flavonoids (32.7 ± 2.1 mg QE/g), consistent with previous reports on *P. amarus*. The presence of phyllanthin (1.8%), hypophyllanthin (1.2%), and gallic acid (2.5%) supports its pharmacological efficacy, as these compounds are known for their antioxidant and anti-inflammatory properties [27]. Similar findings were reported by Patel et al. [28], who identified lignans and flavonoids as key bioactive constituents in *P. amarus* responsible for liver protection.

The MTT assay confirmed the extract's low cytotoxicity (IC_{50} > 800 μg/mL), with cell viability exceeding 85% at 200 μg/mL. These results are comparable to recent studies on *P. amarus* safety in hepatic cells [29]. The high IC_{50} value suggests a favorable therapeutic window, reinforcing its potential as a natural hepatoprotective agent.

Pretreatment with *P. amarus* (300 μg/mL) significantly restored cell viability (82.5 ± 4.1%) and reduced LDH leakage by 62%. The marked decrease in ALT (60%) and AST (55%) levels indicates membrane stabilization, corroborating findings by Zhang et al. [30] on herbal extracts mitigating drug-induced liver injury. These results suggest that *P. amarus* may interfere with APAP bioactivation, possibly by inhibiting cytochrome P450-mediated *N*-acetyl-p-benzoquinone imine (NAPQI) formation, similar to the mechanism proposed for silymarin [31].

The extract significantly elevated SOD (2.3-fold), CAT (2.4-fold), and GSH (3.2-fold) levels while reducing MDA by 70%. This indicates a robust antioxidative mechanism, likely due to flavonoid-mediated free radical scavenging, as reported in recent studies [32]. The GSH restoration is particularly crucial, as APAP toxicity depletes hepatic GSH stores, leading to oxidative stress [33]. Our findings align with research on *P. niruri*, a related species, which also exhibited GSH-replenishing effects [34].

The AO/EB staining confirmed a dramatic reduction in apoptosis (from 45% to 12%), with preserved nuclear integrity. This suggests that *P. amarus* may modulate apoptotic pathways, possibly via Bcl-2 upregulation or caspase-3 inhibition, as seen with other hepatoprotective plants [35]. Recent work by Li et al. [36] on *P. amarus* polyphenols supports this, demonstrating inhibition of mitochondrial-dependent apoptosis in hepatocytes [37].

This study validates *P. amarus* as a potent hepatoprotective agent, acting through antioxidant reinforcement, membrane stabilization, and apoptosis inhibition. Its efficacy against APAP-induced toxicity highlights its potential as an adjunct therapy for drug-induced liver injury. Future studies should explore its molecular targets and clinical applicability.

5. Conclusion

The present study provides compelling evidence that the ethanolic extract of *Phyllanthus amarus* exhibits significant hepatoprotective effects against acetaminophen-induced toxicity in human LO2 hepatocytes through multiple synergistic mechanisms. The phytochemical characterization revealed a rich composition of bioactive compounds, particularly phenolics (58.4 ± 3.2 mg GAE/g) and flavonoids (32.7 ± 2.1 mg QE/g), which likely contribute to its therapeutic potential. The extract demonstrated an exceptional safety profile with minimal cytotoxicity (IC50 >800 µg/mL), supporting its suitability for therapeutic applications.

At the cellular level, *P. amarus* extract effectively protected hepatocytes by: (1) maintaining membrane integrity (62% reduction in LDH leakage, 55-60% decrease in ALT/AST levels), (2) enhancing endogenous antioxidant defenses (2.3-2.4-fold increase in SOD/CAT activity, 3.2-fold GSH elevation), and (3) inhibiting apoptotic pathways (72.5% reduction in apoptosis). These multi-target actions collectively mitigate the key pathological events in APAP-induced hepatotoxicity - oxidative stress, cellular necrosis, and programmed cell death.

The findings validate the traditional use of *P. amarus* in liver disorders while providing scientific evidence for its mechanism of action. Particularly noteworthy is its ability to restore glutathione levels and reduce lipid peroxidation, suggesting potential advantages over single-target therapies. Future studies should focus on isolating the most active constituents, evaluating in vivo efficacy, and exploring potential synergistic effects with conventional treatments like N-acetylcysteine. This research positions *P. amarus* as a promising candidate for development as a standardized phytopharmaceutical or adjunct therapy for drug-induced liver injury, particularly in resource-limited settings where affordable hepatoprotective agents are urgently needed.

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Compliance with ethical standards

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