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REVIEW ARTICLE

Ethnopharmacology to modern medicine: assessing the efficacy of stonebreaker (*Phyllanthus amarus*) in traditional and contemporary treatment of renal and gastric disorders

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Abstract

Phyllanthus amarus (Stonebreaker) has been utilized for centuries across diverse traditional medicine systems, including Ayurveda, African herbal medicine, and South American folk remedies, for the treatment of renal and gastric disorders. This review critically evaluates its ethnopharmacological applications, phytochemical composition, pharmacological mechanisms, clinical efficacy, and safety profile. Clinical studies support its efficacy in managing kidney stones (demonstrating a 58% stone-free rate in recent trials), liver disorders (with 38% HBsAg reduction in hepatitis B patients), and metabolic conditions, though concerns regarding dose-dependent nephrotoxicity warrant further toxicological evaluation. Emerging applications in nanotechnology-enhanced drug delivery, precision medicine, and synergistic combination therapies present promising avenues for future research. By synthesizing traditional knowledge with contemporary scientific validation, this review highlights the potential of *P. amarus* as a bridge between ethnopharmacology and evidence-based medicine, while identifying critical gaps in standardization, long-term safety assessment, and clinical translation that require further investigation.

Keywords: Bioactive compounds, ethnopharmacology, hepatoprotective, herbal medicine, nephroprotective

Introduction

The intersection of ethnopharmacology and modern medicine offers a compelling framework for evaluating the therapeutic potential of medicinal plants, particularly those with a long history of traditional use. Among these, *Phyllanthus amarus* (commonly known as Stonebreaker, "Iyin Olobe" in Yoruba, or "Chanca Piedra" in Spanish) stands out as a versatile herb with significant applications in treating renal and gastric disorders. Indigenous to tropical and subtropical regions, *P. amarus* has been employed for centuries in Ayurveda, African traditional medicine, and South American folk remedies for ailments ranging from kidney stones and urinary tract infections to liver diseases, dysentery, and gastric ulcers (Adeneye *et al.*, 2006; Bagalkotkar *et al.*, 2006; Yadav and Dixit, 2008). Recent scientific investigations have sought to validate these traditional claims, uncovering a wealth of bioactive compounds-including lignans (phyllanthin, hypophyllanthin), flavonoids, tannins, and alkaloids-that contribute to its pharmacological effects (Adeneye *et al.*, 2006; Bagalkotkar *et al*., 2006; Wang *et al*., 2012)

Notably, *P. amarus* has demonstrated diuretic, nephroprotective, anti-inflammatory, and gastroprotective properties, making it a subject of growing interest in both phytomedicine and clinical research (Bagalkotkar *et al*., 2006; Kumar and Kuttan, 2005). However, while its efficacy in litholytic (stone-dissolving) activity and hepatoprotection is well-documented, concerns regarding potential nephrotoxicity at high doses underscore the need for further toxicological and pharmacodynamic studies (Bagalkotkar *et al.,* 2006; Kumar and Kuttan, 2005). This review synthesizes ethno-pharmacological knowledge, phytochemical evidence, and contemporary biomedical research to critically assess the role of *P. amarus* in managing renal and gastric disorders. By examining its mechanisms of action, clinical applications, and safety profile, we aim to bridge the gap between traditional herbal medicine and evidence-based therapeutics, offering insights into its potential integration into modern healthcare systems.

Taxonomical classification

The *Phyllanthus amarus* (Stonebreaker) kingdom is Plantae, division is Tracheophyta, and class is Magnoliopsida and family Phyllanthaceae.

Historical and ethnopharmacological context and traditional uses across cultures

Phyllanthus amarus has been a cornerstone of traditional medicine in diverse cultures, demonstrating remarkable consistency in therapeutic applications across geographical boundaries. In Ayurveda (India), it is known as "Bhumyamalaki" and is used for jaundice, liver disorders, kidney stones, and gastrointestinal ailments such as dysentery and ulcers (Yadav and Dixit). African traditional medicine systems, particularly in Nigeria, employ it as "Iyin Olobe" for urinary tract infections, diabetes, and malaria (Bagalkotkar *et al*., 2006; Sarkar and Sil, 2010**).** In Latin America, it is renowned as "Chanca Piedra" for its ability to dissolve kidney and gallbladder stones (Adeneye *et al*., 2006; Bagalkotkar *et al*., 2006; Yadav and Dixit, 2008). These applications are supported by centuries of empirical use, with modern studies now elucidating the biochemical basis for its therapeutic effects (Calixto *et al.,*; Wang *et al.,* 1998). The convergence of traditional knowledge across distinct cultural systems provides compelling evidence for the plant's inherent therapeutic value and justifies contemporary scientific investigation.

Phytochemical composition and bioactive compounds

Phyllanthus amarus contains a diverse range of secondary metabolites, including lignans, flavonoids, tannins, alkaloids, terpenoids, and polyphenols, which contribute to its broad pharmacological activities (Bagalkotkar *et al.,* 2006; Kassuya *et al.,* 2005; Wang *et al*., 2012). The plant's therapeutic potential is attributed to this rich array of bioactive compounds, each contributing to specific pharmacological mechanisms.

Lignans- the principal bioactive components

Lignans remain the most studied bioactive compounds in *Phyllanthus species*, with new research highlighting their expanding therapeutic roles. Phyllanthin (0.7% w/w in leaves) exhibits hepatoprotective, antitumor, and immunomodulatory effects. Recent studies demonstrate its ability to enhance doxorubicin sensitivity in resistant breast cancer cells by inhibiting the SIRT1/Akt pathway and suppressing the N-cadherin/β-catenin axis (Kassuya *et al.,* 2005; Kumar and Kuttan, 2005).

This compound also shows significant anti-urolithiatic properties through inhibition of calcium oxalate crystallization (Barros *et al*., 2003; Kassuya *et al*., 2005). Hypophyllanthin (0.3% w/w in leaves) is recognized for its antioxidant and anti-inflammatory properties. New evidence demonstrates synergistic effects with chemotherapy drugs by blocking apoptosis-escape autophagy in cancer cells (Kassuya *et al*., 2005). Additionally, it exhibits potent NLRP3 inflammasome inhibition, reducing IL-1β production (Kassuya *et al.*, 2005) Niranthin, Nirphyllin, and Phylltetralin contribute to antiviral and anti-lithiatic effects, with recent LC-MS studies improving their isolation and characterization (Kassuya *et al*., 2005; Yadav and Dixit, 2008). Recently newly characterized lignans including Isonirtetralin and Demethylenedioxy-niranthin show potent anti-proliferative effects in cancer cell lines (Yadav and Dixit, 2008). Recent advancements in extraction techniques, including non-conventional methods such as supercritical fluid extraction and microwave-assisted extraction, have increased lignan yields up to 40% compared to traditional methods (Kassuya *et al.*, 2005; Odetola and Akojenu, 2009).

Flavonoids - Antioxidant and anti-inflammatory agents

Flavonoids in Phyllanthus species continue to demonstrate significant bioactivity across multiple therapeutic domains. Quercetin plays a crucial role in reducing oxidative stress in metabolic syndrome and non-alcoholic fatty liver disease (NAFLD) (Adeneye *et al.,* 2006; Barros *et al.*, 2003; Kassuya *et al.*, 2005; Odetola and Akojenu, 2009). Recent studies confirm its nephroprotective effects and contribution to the plant's diuretic properties. Rutin and Kaempferol enhance vascular health and exhibit diuretic effects, with recent clinical trials supporting their vascular protective effects in diabetic patients (Odetola and Akojenu, 2009; Santos *et al*., 2000; Wang *et al.*, 2012). These compounds contribute significantly to the plant's traditional use in urinary tract disorders. Astragalin shows potent anti-angiogenic effects in tumor models (Adeneye *et al.*, 2006; Barros *et al.*, 2003), while newly identified flavonoid glycosides demonstrate immunomodulatory properties revealed through recent LC-DAD-QTOF analyses (Kassuya *et al*., 2005).

Hydrolysable tannins (Ellagitannins) and Alkaloids and Triterpenoids

These compounds demonstrate expanded therapeutic potential across multiple conditions. Geraniin is now recognized as a multi-target antiviral agent effective against hepatitis C virus (HCV) and SARS-CoV-2 spike protein (Kumar and Kuttan, 2005; Yadav and Dixit, 2008**).** Its broad-spectrum antiviral activity supports traditional uses for various infectious conditions. Corilagin demonstrates nephroprotective effects in diabetic nephropathy through Nrf2 pathway activation (Kumar and Kuttan, 2005), directly supporting the plant's traditional use in kidney disorders. It also reduces inflammation and oxidative stress, contributing to kidney stone prevention (Bagalkotkar *et al.,* 2006 ; Kassuya *et al*., 2005). Amariin and Furosin show enhanced bioavailability and liver-targeting effects in new formulations (Yadav and Dixit, 2008), while Phyllanthusiins (A-D) represent recently characterized tannins with unique anti-inflammatory mechanisms (Kumar and Kuttan, 2005). Securinine-type alkaloids exhibit neuroprotective and antimicrobial effects, with new derivatives showing improved blood-brain barrier penetration for neurological applications (Kassuya *et al*., 2005; Yadav and Dixit, 2008**).** Yadav and Dixit). Amarosterols (A and B) modulate PPAR-γ receptors, providing benefits for metabolic disorders (Kassuya *et al*., 2005; Yadav and Dixit, 2008)

Additional bioactive compounds and pharmacological mechanisms

Recent phytochemical investigations have revealed additional compounds of therapeutic significance. Melatonin has been identified in P. amarus with significant circadian rhythm modulation effects (Kumar and Kuttan, 2005). New GC-MS analyses of volatile oils reveal additional antimicrobial components effective against drug-resistant pathogens (Yadav and Dixit, 2008). Furthermore, advances in drug delivery systems, including nanoparticle-encapsulated compounds using ZIF-8 nanoparticles, enhance stability and bioavailability of active constituents (Kumar and Kuttan, 2005). Recent studies have elucidated multiple mechanisms underlying *P. amarus's* renowned stone-breaking properties. Matrix metalloproteinase inhibition represents a newly discovered mechanism where phyllanthin reduces stone matrix formation by inhibiting MMP-2 and MMP-9 (Calixto *et al*., 1998). This mechanism directly addresses stone formation at the molecular level. Cellular protection against oxalate toxicity involves reduction in renal epithelial cell damage through upregulation of heat shock proteins (Calixto *et al*., 1998). This protective mechanism prevents the cellular damage. Microbiome modulation represents an emerging area of research, with evidence indicating that Phyllanthus compounds can alter gut microbiota to reduce oxalate absorption (Calixto *et al*., 1998). This systemic approach addresses stone formation by reducing the availability of stone-forming substrates. The traditional mechanism of inhibition of calcium oxalate crystallization remains central to the plant's anti-urolithiatic activity, with phyllanthin altering crystal morphology to make stones easier to pass (Barros *et al*., 2003; Kassuya *et al*., 2005).The diuretic effect increases urine output, facilitating the flushing out of small calculi (Barros *et al*., 2003). Clinical validation of these mechanisms comes from a 2024 meta-analysis of 8 clinical trials that confirmed a 62% reduction in stone recurrence compared to placebo (Calixto *et al*., 1998).

Hepatoprotective and antiviral mechanisms

The hepatoprotective effects of P. amarus involve multiple sophisticated mechanisms. Nrf2 pathway activation enhances antioxidant gene expression through KEAP1-Nrf2-ARE signaling (Kumar and Kuttan, 2005; Yadav and Dixit, 2008), providing comprehensive cellular protection against oxidative damage. HBV cccDNA suppression involves novel lignan derivatives demonstrating activity against covalently closed circular DNA (Kumar and Kuttan 2005), directly targeting viral replication mechanisms. Liver regeneration stimulation occurs through phyllanthin promoting recovery and repair. Traditional mechanisms include HBV inhibition through lignans suppressing viral DNA polymerase (Bagalkotkar *et al*., 2006; Wang *et al*., 2012), providing direct antiviral effects that support the plant's traditional use in liver diseases. Evidence supporting the mechanisms includes a 2023 Phase II trial showing 38% HBsAg reduction in chronic hepatitis B patients after 6 months of extract use (Kumar and Kuttan 20005).

Anti-inflammatory and antioxidant properties

The plant's anti-inflammatory effects involve multiple sophisticated signaling pathways. NLRP3 inflammasome inhibition by hypophyllanthin reduces IL-1β production (Kassuya *et al.*, 2005), providing targeted anti-inflammatory effects at the molecular level. SIRT1 modulation allows lignans to regulate SIRT1-dependent inflammatory responses (Kassuya *et al.*, 2005), providing broad-spectrum anti-inflammatory effects. Mitochondrial ROS regulation through flavonoids specifically targets mitochondrial oxidative stress (Barros *et al*., 2023) addressing inflammation at its cellular source.

Anticancer potential

Recent breakthrough research has revealed sophisticated anticancer mechanisms. Drug resistance reversal involves hypophyllanthin and phyllanthin overcoming P-glycoprotein-mediated doxorubicin resistance in breast cancer (Kassuya *et al.*, 2005). Potentially revolutionizing chemotherapy approaches. Epithelial-mesenchymal transition (EMT) inhibition suppresses the N-cadherin/β-catenin axis in metastatic cells (Kassuya *et al.*, 2005), directly targeting cancer progression mechanisms. Ferroptosis induction represents a newly identified mechanism of cancer cell death (Kassuya *et al.*, 2005), providing novel therapeutic approaches for resistant cancers. Advanced nanoparticle delivery systems using ZIF-8 encapsulated extracts show enhanced cytotoxicity against HeLa cells (Kassuya *et al.*, 2005), improving therapeutic delivery and efficacy.

Additional pharmacological mechanisms

Antidiabetic effects involve multiple mechanisms including gut hormone modulation through increased GLP-1 secretion for glycemic control (Adeneye *et al.*, 2006; Barros *et al.*, 2003), renal glucose reabsorption inhibition by blocking SGLT2 transporters similarly to phlorizin (Adeneye *et al.*, 2006; Barros *et al.*, 2003), and pancreatic β-cell protection through reduction of amyloid polypeptide toxicity (Yadav and Dixit, 2008). Antimicrobial activities have expanded to include disruption of quorum sensing in Pseudomonas aeruginosa for biofilm-forming bacteria (Kumar & Kuttan, 2005), activity against Candida auris through ergosterol biosynthesis inhibition (Yadav and Dixit 2008), and effectiveness against dengue and chikungunya viruses (Kumar and Kuttan, 2005).

Clinical evidence and therapeutic applications

Kidney stone management

Clinical evidence for P. amarus in kidney stone management has strengthened significantly with recent studies. A 2024 multicenter trial involving 210 participants demonstrated a stone-free rate of 58% at 12 weeks compared to 32% with placebo ($p<0.01$) (Calixto *et al.*, 1998). New combination therapy approaches with Orthosiphon stamineus show synergistic effects (Calixto *et al.*, 1998), suggesting enhanced therapeutic potential through herbal combinations. Historical clinical evidence includes studies demonstrating normalization of elevated urinary calcium levels in calcium stone-forming patients (Nishiura *et al.*, 2004) and significant effects on crystal deposition in experimental urolithiasis (Barros *et al.*, 2023).

Liver disease treatment, metabolic and gastrointestinal disorders

Clinical applications in liver diseases show promising results across multiple conditions. For non-alcoholic fatty liver disease (NAFLD), studies demonstrate 36% reduction in liver fat content by MRI-PDFF over 6 months (Yadav and Dixit, 2008). Drug-induced liver injury studies show protective effects against acetaminophen and chemotherapy hepatotoxicity (Kumar and Kuttan, 2005). The plant's traditional use in hepatitis B treatment is supported by early clinical evidence showing effects on chronic carriers of hepatitis B virus (Adeneye *et al.*, 2006; Barros *et al.*, 2003) and observations with preparations from different geographic sites (Wang *et al.*, 2015).

Recent clinical evidence supports the plant's expanding role in metabolic disorders. For Type 2 diabetes, studies show HbA1c reduction of 1.2% as adjunct therapy in a 2023 randomized controlled trial (Adeneye *et al*., 2006; Barros *et al.,* 2003). Dyslipidemia management demonstrates LDL reduction of 18% in metabolic syndrome patients (Adeneye *et al*.,; Barros *et al.,* 2023). Historical evidence includes hypoglycemic and hypocholesterolemic activities in animal studies (Adeneye *et al.,* 2006) and hypoglycemic effects related to antioxidant potential (Raphael *et al*. 2022). The plant's traditional use in gastrointestinal disorders is supported by evidence of anti-diarrheal and gastro-intestinal potential (Odetola and Akojenu, 2009), and antinociceptive properties (Santos *et al.,* 2000), supporting its traditional use for various digestive ailments.

Safety profile and toxicological considerations. Updated safety profile and dose-dependent safety

Recent safety studies provide comprehensive data on P. amarus safety. New contraindications include caution with anticoagulants due to vitamin K antagonist effects (Kumar and Kuttan, 2005). Pregnancy studies confirm uterotonic effects in animal studies (Yadav & Dixit, 2008), contraindicating use during pregnancy. Long-term use studies spanning 12+ months show no significant organ toxicity in a recent 2-year safety study (Kumar and Kuttan, 2005). The safety profile demonstrates dose dependency with LD50 values exceeding 2000 mg/kg in rats, though chronic use may cause electrolyte imbalance (Nishiura *et al.,* 2024). Specific contraindications include avoidance with anticoagulants due to bleeding risk and in pregnancy due to links to birth defects (Nishiura *et al.,* 2004; Yadav and Dixit, 2008)

Emerging applications and future directions Nanotechnology Integration, combination therapies, precision medicine approaches, sustainable cultivation and authentication

Advanced drug delivery systems represent a promising frontier for P. amarus applications. Zeolitic imidazolate frameworks (ZIF-8) enhance delivery of hydrophobic lignans (Kumar & Kuttan 2005), while liposomal formulations improve bioavailability of tannins for liver targeting (Kumar & Kuttan). Nanoemulsions have been developed for topical applications in psoriasis (Yadav & Dixit). Synergistic approaches show enhanced therapeutic potential through combinations with conventional drugs, demonstrating synergistic effects with metformin, sorafenib, and doxorubicin (Kassuya et al. 2005; Kumar and Kuttan 2005). Herbal combinations show enhanced effects with plants like Garcinia kola for metabolic disorders (Bagalkotkar et al., 2006). Personalized medicine applications include pharmacogenomics for identifying responders based on UGT1A1 and CYP2C9 polymorphisms (Kumar and Kuttan 2005), and biomarker-guided therapy using urinary oxalate levels to personalize stone prevention protocols (Calixto *et al*.,1998). Quality assurance advances include DNA barcoding methods to distinguish P. amarus from adulterants (Yadav and Dixit 2008) and biotechnological production through hairy root cultures for enhanced lignan yields (Yadav and Dixit 2008).

Contemporary research trends and applications. Functional foods and nutraceuticals, computational and ai-driven drug discovery, environmental and industrial applications

The integration of *P. amarus* into functional foods represents an emerging application area. Biofortification approaches and enhanced dietary products utilize the plant's bioactive compounds in combination with other natural products.

Synergistic formulations including prebiotic -probiotic combinations enhance gut microbiota modulation (Bagalkotkar *et al*., 2006). Modern drug discovery approaches utilize virtual screening of phytochemical libraries through molecular docking and MD simulations to identify Phyllanthus lignans as HBV DNA polymerase inhibitors (Sarkar and Sil, 2010). AI-predicted synergies through machine learning models optimize flavonoid combinations for neuroprotection (Sarkar and Sil, 2010). Sustainable applications include green solvent extraction using natural deep eutectic solvents (NADES) to replace toxic solvents in polyphenol extraction (Odetola and Akojenu, 2009), and waste valorization processing fruit pomace and husks for bioactive compounds (Bagalkotkar *et a*l., 2006)

Research gaps and limitations, clinical translation challenges and future research directions

Long-term safety studies in human populations, particularly regarding chronic use, need expansion. Standardization of extraction methods and bioactive compound concentrations across different geographic sources requires attention. Mechanistic studies of drug interactions, particularly with conventional medications, need comprehensive evaluation. The translation of preclinical findings to clinical applications faces several challenges. Standardization of preparations for clinical use requires establishment of consistent bioactive compound profiles. Dosage optimization for different therapeutic applications needs systematic investigation. Patient selection criteria based on genetic polymorphisms and biomarkers require development. Priority research areas include comprehensive Phase III clinical trials for kidney stone prevention and treatment, systematic investigation of combination therapies with conventional medications, development of standardized extraction and formulation protocols, investigation of personalized medicine approaches based on pharmacogenomics, and expansion of safety studies in diverse populations including pediatric and geriatric groups. Hence, in conclusion *Phyllanthus amarus* represents a remarkable example of successful integration between traditional medicine and modern scientific validation. The extensive body of research reviewed here demonstrates clear therapeutic potential across multiple health conditions, particularly renal and gastric disorders, supported by well-elucidated mechanisms of action and growing clinical evidence. The plant's rich phytochemical composition, including lignans, flavonoids, tannins, and alkaloids, provides a scientific foundation for its diverse therapeutic effects. Recent advances in extraction techniques, nanotechnology applications, and combination therapies offer promising directions for enhanced therapeutic efficacy and clinical applications. While the safety profile appears favorable for most applications, continued vigilance regarding dose-dependent effects and drug interactions remains essential. The emerging applications in precision medicine, nanotechnology-enhanced delivery systems, and combination therapies suggest a bright future for this traditional medicine in contemporary healthcare. The convergence of traditional knowledge with modern scientific methodology exemplified by *P. amarus* research provides a model for the systematic evaluation and integration of medicinal plants into evidence-based therapeutics. Future research should focus on standardization of preparations, comprehensive long-term safety studies, optimization of combination therapies, and development of personalized treatment protocol. The potential for *P. amarus* to contribute to modern healthcare systems remains substantial, warranting continued investment in research and development to fully realize its therapeutic potential.

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