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Medicinal Potential of *Phyllanthus niruri*: A Review of Traditional and Modern Therapeutic Applications

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Abstract

Phytomedicine *Phytanthus niruri* (Bhumi Amla) is a medicinal herb that is commonly used in the traditional medical systems to treat liver diseases, kidney stones, infections, and metabolic diseases. Most of its traditional claims have been proven by recent progress in phytochemical and pharmacological studies. The chapter provides an in-depth overview of its phytoconstituents, traditional uses, and current therapeutic possibilities, such as hepatoprotective, antiviral, antioxidant, anti-inflammatory, antidiabetic, and anti-urolithiatic actions. The chapter also brings out the present research trends, challenges and future prospects of clinical and pharmaceutical applications.

Keywords: *Phytanthus niruri*, Bhumi Amla, hepatoprotective, antiviral, phytochemicals, ethnomedicine, antioxidant.

Introduction

Medicinal plants have always been an important part of the traditional healthcare system and remain a major source of therapeutic agents in the world. Plant-based remedies have been in use since ancient times in various cultural systems, including Ayurveda, Traditional Chinese Medicine (TCM), Unani, and indigenous folk medicine. These systems extensively depend on the medicinal value of botanicals in the prevention and treatment of many diseases. World Health Organization (WHO) estimates that 80 percent of the world population continues to rely on plant-based medicines as their primary healthcare requirement especially in third world countries. The revival of natural products interest in the past decades could be explained by the fact that they are considered to be safe, economical and have minimum side effects in comparison with synthetic medicines. As a result, medicinal plants have taken center stage in the current pharmacological studies in

an effort to identify new bioactive compounds and authenticate the traditional knowledge using scientific procedures [1]. Among the numerous pharmacological activities and the extensive traditional use, *Phyllanthus niruri* is the plant of great interest in the world. *Phyllanthus niruri*, a member of the family Euphorbiaceae, is a small herbaceous plant that is widespread in tropical and subtropical areas, such as India, Southeast Asia, South America, and Africa. It is commonly referred to as Bhumi Amla in Ayurveda and in English as a stonebreaker due to its ancient use in the management of kidney stones and problems with the urinary tract. The plant has found extensive use in Ayurvedic and other traditional systems of medicine in the treatment of hepatic conditions, urinary stones, gastroenterological disorders, diabetes and infectious diseases. This has led to great interest in science in seeking to understand its pharmacological potential and its mechanisms of action due to its wide ethnomedicinal usage [2].

Phytanthus niruri is mentioned in classic Ayurvedic books as having hepatoprotective, diuretic, antiviral, and anti-inflammatory effects. It is widely used in the treatment of liver-related conditions like jaundice, hepatitis and cirrhosis and also in the treatment of UTI and renal calculi. Dysentery, fever, and skin diseases are also treated using the plant. Various preclinical and clinical studies have supported these traditional claims and have emphasized its versatility in therapy. It is important to note that its contribution to the treatment of liver diseases has received a lot of interest because of the rising cases of hepatic diseases that are linked to lifestyle alterations, environmental toxins, and viral diseases [3]. Scientific studies over the past few years have been more keen on confirming the traditional uses of *Phytanthus niruri* using a systematic phytochemical and pharmacological research. The development of analytical methods, including high-performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GC-MS), and nuclear magnetic resonance (NMR) spectroscopy, have enabled the identification and characterization of a large number of bioactive compounds that can be found in the plant. Such studies have found that *Phytanthus niruri* is abundant in a wide variety of phytoconstituents, among which are lignans, flavonoids, alkaloids, tannins, terpenoids and polyphenolic compounds. Among these, there are lignans like phyllanthin and hypophyllanthin that can be regarded as major active constituents of the majority of its pharmacological actions [4]. These bioactive constituents are majorly attributed with the therapeutic efficacy of *Phyllanthus niruri*, which demonstrate considerable biological activity as antioxidant, hepatoprotective, antimicrobial, antiviral, anti-inflammatory, and anti urolithiatic activity. Of particular interest is the antioxidant action of the plant because oxidative stress is an important factor in the etiology of many chronic disorders, such as liver diseases, cardiovascular diseases, and cancer. Phytochemical scavenging of reactive oxygen species (ROS) and up-regulation of native

antioxidant enzymes aid *Phytanthus niruri* in reducing oxidative damage and preserving cellular homeostasis [5].

The hepatoprotective feature is one of the most researched pharmacological aspects of *Phyllanthus niruri*. Experimental research has shown that the extracts of the plant can shield the liver against toxic damage as in the case of carbon tetrachloride (CCl₄) and paracetamol and alcohol. The hepatoprotective effect is thought to be based on stabilization of membranes of hepatocytes, inhibition of lipid peroxidation and protection of antioxidant mechanisms. Moreover, the plant has demonstrated impressive antiviral effect against hepatitis B virus (HBV), which further substantiates the use of the plant in liver diseases, traditionally [6]. The other significant pharmacological factor of *Phyllanthus niruri* is that it possesses antiurolithiatic (anti-kidney stone) effect, hence its popular name as a stonebreaker. Research has shown that the plant has the ability to prevent the formation, growth and aggregation of calcium oxalate crystals, which are the major components of kidney stones. It also induces diuresis thus allowing the small calculi in the urinary tract to be expelled. The clinical implications of these findings are substantial, as urolithiasis is a frequent and recurrent disease, and has few non-invasive methods of treatment [7].

Along with its hepatoprotective and anti urolithiatic effects, *Phyllanthus niruri* also has significant antimicrobial and antiviral effects. The plant extracts are found to be effective in a broad spectrum of bacterial and fungal pathogens such as *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans*. The antimicrobial effect is explained by the presence of phenolic compounds and flavonoids disrupting cell membranes of microorganisms and blocking vital metabolic activities. Moreover, its antiviral effects on viruses like hepatitis B and C have provided novel opportunities in the production of antiviral therapeutics derived out of plants [8]. Although *Phyllanthus niruri* has a promising pharmacological profile, there are few issues in the translation of its traditional and experimental applications into approved clinical therapies. The absence of standardized formulations and dosage regimens is one of the biggest restrictions, as it may result in differences in therapeutic effects. Moreover, the bioavailability and pharmacokinetics of its active constituents have not been studied completely. As such, more studies are needed to perfect extraction processes, standardize phytochemical composition and to carry out well designed clinical trials to establish its safety and effectiveness in humans [9]. Moreover, the growing interest in herbal medicine has raised concerns regarding the sustainable harvesting and conservation of medicinal plants. Overexploitation of *Phyllanthus niruri* in its natural habitat may lead to ecological imbalances and loss of biodiversity. Therefore, sustainable cultivation practices and conservation strategies are essential to ensure the long-term availability of this valuable medicinal resource. Integration of traditional knowledge with modern scientific approaches can play a crucial role in promoting the rational use and conservation of medicinal plants [10].



Fig. 1. Graphical abstract illustrating phytochemical composition, mechanisms, and therapeutic applications of *Phyllanthus niruri*

Botanical Description and Distribution.

Phyllanthus niruri L. *Phytanthus niruri* L. is a small herbaceous, due to its nature, annual plant which belongs to the family Phytanthaceae (it used to belong to Euphorbiaceae). It is well known to have medicinal value and is widely known as Bhumi Amla in India, as stonebreaker in English and by vernacular names in different places. The plant can be described by its fine morphology, the ability to adapt to various environmental conditions and a great amount of ethnobotanical significance. The ease of access and extensive use in traditional medicine systems is due to its botanical characteristics and wide distribution.

Taxonomical Classification

Phyllanthus niruri can be classified as follows

Kingdom: Plantae

Subkingdom: Tracheobionta (vascular plants)

Superdivision: Spermatophyta (seed plants)

Family: Aurelaceae (oreo).

Class: Magnoliopsida (dicotyledons)

Order: Malpighiales

Family: Phyllanthaceae

Genus: *Phyllanthus*

***Phyllanthus niruri* L.**

Phylae *Phyllanthus* is a genus with more than 600 species that are found worldwide and most of them are medicinal. *P. niruri* is, however, one of the most studied ones, owing to its pharmacological importance.

1. Morphological Characteristics

Phytanthus niruri is a small erect-decumbent annual herb that generally ranges in height of 3060 cm. The plant has a slender, smooth and green stem which in most cases are branched at the base. The most conspicuous characteristic of this species is its phyllanthoid branching in which the branchlets are like compound leaves that make the plant look like mimosa. The leaves are small, simple, and not rosette like, but alternately on the branchlets. Their shape is oblong or elliptic with a length of about 5-12 mm and a width of about 2-5 mm. The surface of the leaves is smooth, light green in color and the margins are entire. Sessile leaves or very short petioles give the leaves a compact outlook of the plant. The plant is monoecious with both male and female flowers growing on the same plant. The flowers are small, inconspicuous and greenish-white. Usually these are located in the axils of the leaves on the lower surface of the branchlets. Male flowers tend to be more and have three stamens and female flowers have a superior ovary with three lobes. *Phyllanthus niruri* fruit is a small globose capsule, 2-3 mm in diameter. It is depressed, smooth and has six seeds that are segmented. The seeds are small, triangular and light brown in color. The fruiting structure is distinctive in the sense that, the capsules are seen to be lower in the leaves which is an important identifying mark of the plant. There is a relatively shallow root system with a slender taproot that has few lateral branches. The plant has a very simple root structure but exhibits an impressive resilience and adaptability to a variety of soils and environmental conditions.

2. Anatomy and Microscopy

Phylogenetically *Phyloganthus niruri* has characteristic anatomical characteristics that can be used in identification and quality control of the drug in pharmacognostic research. The anatomy of the leaf shows a well-developed dorsiventral structure with an epidermis, mesophyll, and vascular bundles. Crystals of calcium oxalate, which are usually found in the form of druses are normally present in the leaf tissues. The epidermis, cortex, and a well-developed vascular system make the stem look typical about having two cotyledons. The vascular bundles are organized in a ring whereby the xylem and phloem tissues can be easily identified. Lignified fibers and parenchymatous cells are known to add structural properties to the plant. Analysis of powdered drugs of *P. niruri* commonly displays diagnostic characteristics of fragments of epidermal cells, stomata, trichomes (when present), and crystalline inclusions. Such microscopic features play a crucial role in

authentication and standardization of the plant material employed in herbal preparations.

3. Geographical Distribution

Phyllanthus niruri is a common plant in tropical and subtropical areas of the world. It usually occurs in India, Sri Lanka, China, Thailand, Indonesia and Brazil and also in various regions of Africa and South America. The plant grows in warm climates and has moderate to high rainfall and is commonly seen growing as a weed in disturbed areas. *P. niruri* is widely found in India with a distribution spread across all the states especially in the states of Rajasthan, Uttar Pradesh, Maharashtra, Tamil Nadu and Kerala. It normally propagates in open fields, roadsides, gardens, farm lands, and wastelands. The plant likes wet soils that are well drained but is also able to adjust to relatively dry soils and hence the plant is very versatile in terms of habitat. The plant is extensively grown in Southeast Asia as well as in wild in the tropical forests and grasslands. *Phyllanthus niruri* has been utilized in South America, especially in the Amazon region, traditionally by indigenous people in treating kidney stones and liver diseases. Its ecological flexibility and ethnomedicinal applicability is manifested by its presence in various geographical areas.

4. Ecological/Climatic Needs

Phyllanthus niruri thrives best in tropical and subtropical environments with temperatures of between 20° C to 35° C. It likes open spaces that have sufficient sunlight, but can also withstand partial shade. It is a fast-growing annual plant and is normally in full bloom in the rainy season, which means that the plant finishes its life cycle within a few months. It does not require a very fertile soil and can be planted in different soils such as sandy, loamy and clay soils. It however exhibits an improved growth in well-drained soils with slightly acidic to neutral soils. Its capacity to propagate in marginal and disrupted soils has made it a ubiquitous weed in the fields and towns.

5. Cultivation and Propagation

Phyllanthus niruri is mostly grown in the wild, but it can also be grown as a medicinal plant. The plant is grown by using seeds and the seeds can easily germinate in good environmental conditions. Planting is normally done at the beginning of the monsoon season where enough water is available to grow. Growing is not very demanding with the plant having very few agricultural needs. Watering regularly, spacing and occasional weeding are adequate to grow well. The plant takes 3-4 months to mature after which it can be used as a source of medicine. 4. Traditional Medicinal Uses *Phyllanthus niruri* L. has been widely employed in traditional systems of medicine for centuries due to its broad spectrum of therapeutic properties. Its extensive ethnomedicinal applications across different

cultures highlight its importance as a versatile medicinal herb. Traditionally known as Bhumi Amla in India and “stonebreaker” in many parts of the world, the plant has been utilized in both codified systems like Ayurveda and in indigenous folk practices for the management of various ailments, particularly those related to the liver, kidneys, and infectious diseases. The traditional knowledge associated with *P. niruri* has served as a foundation for modern pharmacological research, which increasingly aims to validate and standardize its medicinal uses.

Ayurveda and Aboriginal Systems

Phyllanthus niruri plays a significant role in the Ayurvedic system of medicine because of the well-known therapeutic properties. It falls under the category of herbs that have hepatoprotective (liver-protecting), diuretic and digestive-enhancing effects. The Ayurvedic texts state that the plant is referred to as balancing the three doshas of Vata, Pitta, and Kapha, although it is specifically helpful in calming Pitta aggravated, which is mostly attributed to liver disorders and inflammatory diseases. Treatment of hepatitis, liver enlargement (hepatomegaly) and liver ailments like jaundice (Kamala) is one of the main applications of *P. niruri* in Ayurveda. The plant is thought to enhance bile secretion, liver functioning as well as detoxification. It is usually prescribed by ayurvedic practitioners as a single herb or polyherbal formulations to restore hepatic health. Fresh plant extracts or decoctions (Kashayam) are usually given orally as a treatment of jaundice with patients being told to take the preparation on a regular basis over a few days to see an effect. The other important use of *P. niruri* in Ayurveda is in the treatment of urinary calculi (Ashmari), or kidney stones. The plant is believed to be a strong diuretic and lithotriptic, i.e. it dissolves and expels stones in the urinary tract. It is normally used as decoctions or powdered formulations (Churna) usually together with other herbs which assist in the functioning of the kidneys. The diuretic effect of the plant enhances the production of urine which aids in flushing out small calculi and hinders the additional aggregation of crystals.

Besides hepatic and renal diseases, *P. niruri* is also employed in the treatment of digestive conditions like dyspepsia, constipation and anorexia nervosa. It is considered to increase digestive fire (Agni) and the absorption of nutrients. The laxative and carminative effects of the plant are mild, which leads to its effectiveness in the treatment of gastrointestinal discomfort. *P. niruri* has many modes of administration in Ayurveda, which varies based on the disease being managed. Widely used preparations are decoctions, powders, fresh juice (Swarasa), and occasionally tablets or capsules in contemporary Ayurvedic medicine. The dosage and treatment period are usually decided by the constitution of the patient (Prakriti), the intensity of the illness and the health condition of the patient. In addition to Ayurveda, *P. niruri* has other traditional systems of use like Unani and Siddha medicine. It is also appreciated in these systems due to its hepatoprotective,

diuretic, and anti-inflammatory effects. The plant has been a very common traditional knowledge through generations, as the indigenous community in India and other parts of the world have traditionally used the plant as a readily available effective remedy to the common ailments in the form of locally prepared formulations largely depending on the traditional knowledge.

Ethnomedicinal Applications

Phythanthus niruri has found ethnomedicinal application in many areas, such as Asia, Africa and South America, where it has been integrated into local medicine. These conventional applications are usually founded on empirical observations and cultural dogmas, and most of them have been proved by initial scientific studies. *P. niruri* is most often used ethnomedicinally in treatment of fever and infections. The plant is also an antipyretic agent that can be used to lower the body temperature and relieve symptoms of febrile conditions in many traditional communities. Whole-plant decoctions are typically taken to treat fever, especially related to infectious diseases, like malaria and viruses. It is thought that the effectiveness of the plant in fighting infections is due to its antimicrobial and antiviral properties. *P. niruri* has been used traditionally as a way of controlling the level of glucose in the blood in the management of diabetes. As dietary interventions in the management of diabetic patients, indigenous practitioners tend to prescribe the use of plant extracts or infusion. It is believed that the hypoglycemic effect of the plant is linked to the fact that the plant can stimulate the insulin secretion or glucose metabolism. Despite its common use in traditional form, scientific confirmation is in progress, and various studies have shown potential to use it as an antidiabetic.

Another significant field of *P. niruri* ethnomedicine is in urinary disorders. Besides treatment of kidney stones, the plant is also used in the treatment of urinary tract infections (UTIs), dysuria (painful urination), and other renal complications. Its diuretic effect aids in clearing toxins and pathogens in the urinary tract, and its anti-inflammatory effect is less irritating and painful. The plant is also used in treatment of different skin ailments such as wounds, ulcers, rashes and fungal infections. To enhance the healing process and prevent infection, in most traditional practices fresh plant paste is applied topically to the affected areas. Its application in dermatological diseases is supported by the presence of bioactive compounds with antimicrobial and anti-inflammatory properties. The plant is also used in treating insect bites and allergic skin reactions in some cultures. Furthermore, *P. niruri* is reported to be used in folk medicine to treat respiratory diseases, including cough and asthma and treat conditions, including hypertension and anemia. It is taken as an all-purpose health tonic to enhance immunity and vitality in some areas. These varied uses have been used to show the broad therapeutic uses of this plant and its significance within traditional healthcare systems. Due to the increasing interest in ethnomedicinal practices, scientific attempts have also been made to prove these

traditional assertions. Initial research has shown evidence to support most of the traditional applications of *P. niruri*, especially its antimicrobial, hepatoprotective, antidiabetic and anti-inflammatory properties [5]. Nevertheless, these encouraging results do not exclude the necessity of further in-depth clinical trials that will help to determine standard doses, safety, and pharmacological actions.

Pharmacological Activities

Phyllanthus niruri L. has become a pharmacologically versatile medicinal plant with a broad range of biological activities confirmed by in vitro, in vivo, and limited clinical investigations. The presence of various types of bioactive compounds including lignans (e.g., phyllanthin and hypophyllanthin), flavonoids, tannins, alkaloids, and polyphenols has contributed to its therapeutic potential. These components have interacted with a variety of biochemical pathways, which have led to the hepatoprotective, antiviral, antioxidant, anti-inflammatory, anti-diabetic, anti-urolithiatic as well as antimicrobial effects of the plant. The subsections below will give a comprehensive account of the significant pharmacological actions of *P. niruri*.

1. Hepatoprotective Activity

The hepatoprotective effect of *Phyllanthus niruri* is one of the most researched pharmacological properties of this plant. Various experimental findings have shown that the plant extract offers a great deal of defense against toxin-induced liver damage caused by chemicals like carbon tetrachloride (CCl₄), paracetamol, alcohol and other hepatotoxins. *P. niruri* extracts have been demonstrated to decrease high serum levels of liver enzymes like alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP), which are significant biomarkers of hepatic injury. Hepatoprotective effect of *P. niruri* has taken various routes including prevention of lipid peroxidation, hepatocyte membrane stabilization, and finally the increase of antioxidant defense systems like superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH). The plant also facilitates the regeneration of the liver through the increased protein synthesis and repair of the cell. Phytochemicals like lignans (e.g. phytanthin) are thought to be key contributors to these effects. These results are a strong indication of the conventional application of *P. niruri* in liver ailments treatment [6], [7].

2. Antiviral Activity

Phyllanthus niruri has shown significant antiviral activity, especially against Hepatitis B virus (HBV) which is a significant cause of chronic liver disease across the world. Research has found that the extracts of the plant have the ability to suppress HBV replication by blocking viral DNA polymerase activity as well as disrupting viral gene transcription. This leads to a decrease in the viral load and prevention of viral replication of the host cells. One of the other anti-viral effects of

P. niruri is its possible effect on other viruses such as hepatitis C virus (HCV) and human immunodeficiency virus (HIV), although more studies are needed to demonstrate its clinical utility. The antiviral properties are mainly ascribed to lignans, flavonoids and tannins, which disrupt the process of viral entry, replication, and assembly. The results indicate that *P. niruri* has the potential to be an effective natural antiviral agent and its traditional use in the treatment of viral infections can be supported [8].

3. Antioxidant Activity

Oxidative stress is the imbalance between the formation of reactive oxygen species (ROS) and antioxidant defense mechanisms of the body that is a decisive factor in the pathogenesis of many chronic diseases such as liver diseases, cardiovascular diseases, diabetes, and cancer. Phytochemicals High phytochemical concentrations of flavonoids, polyphenols, and other antioxidants make *phyllanthus niruri* a strong antioxidant. The extracts of the plants have been proved to scavenge free radicals including superoxide anions, hydroxyl radicals, and hydrogen peroxide, thus inhibiting oxidative damage of cellular components, including lipids, proteins, and DNA. It also increases the work of the native enzymes of antioxidant activity which adds to the enhanced cell defense. The antioxidant properties of *P. niruri* do not only justify its hepatoprotective properties, but also its overall therapeutic effectiveness in the prevention and treatment of oxidative stress-related diseases [9].

4. Anti-inflammatory and Analgesics Effects

Inflammation is a complicated biological reaction of injury or infection and is commonly accompanied by pain and tissue damage. *Phyllanthus niruri* has been found to exhibit considerable anti-inflammatory and analgesic effects in different pathological models. The plant extract suppresses the synthesis of major inflammatory agents including prostaglandins, leukotrienes, and pro-inflammatory cytokines (e.g., TNF-alpha, IL-1, and IL-6). Inhibition of cyclooxygenase (COX) and lipoxygenase (LOX) pathways that produce inflammatory mediators is believed to be the mechanism of action of the anti-inflammatory effect. The plant also regulates immune functions and lessens oxidative stress, which also has a role in its anti-inflammatory action. The analgesic effect of *P. niruri* is linked to the fact that it decreases the pain perception via the peripheral and central pathways. These characteristics enable it to be applicable in the treatment of inflammatory diseases like arthritis, and in the treatment of pain related to different diseases [10].

5. Antidiabetic Activity

Elevated blood glucose levels and compromised insulin action are hallmarks of diabetes mellitus, a chronic metabolic disease. In both experimental and early clinical research, *Phyllanthus niruri* has demonstrated encouraging antidiabetic effects. According to reports, the plant extract increases insulin sensitivity, lowers

blood glucose levels, and improves glucose tolerance. *P. niruri*'s hypoglycemic impact can be explained by a number of mechanisms, such as increased peripheral glucose absorption, inhibition of carbohydrate-digesting enzymes including α -amylase and α -glucosidase, and stimulation of insulin production from pancreatic β -cells. Its antioxidant qualities also aid in lowering oxidative stress, a major contributor to the onset of problems from diabetes. According to these results, *P. niruri* may be used as an adjuvant treatment for diabetes mellitus [11].

6. Anti-urolithiatic Activity

One of *Phyllanthus niruri*'s most well-known and practically significant qualities is its antiurolithiatic (anti-kidney stone) action. Kidney stones have historically been treated and prevented with the herb, and scientific research has shown strong support for this practice. The main component of the majority of kidney stones, calcium oxalate crystals, are prevented from forming, growing, and aggregating by the *P. niruri* extract. The method of action includes reducing oxalate levels, preventing crystal adherence to renal epithelial cells, and modifying the content of urine. The herb also has diuretic qualities, which boost urine production and help the urinary tract expel tiny stones. Some studies have also suggested that *P. niruri* may alter the structure of existing stones, making them more fragile and easier to dissolve. These effects collectively contribute to its effectiveness in managing urolithiasis [12].

7. Antimicrobial Activity

Broad-spectrum antibacterial action against a variety of bacterial and fungal diseases is demonstrated by *Phyllanthus niruri*. Both Gram-positive and Gram-negative bacteria, such as *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, as well as fungi like *Candida albicans*, have been demonstrated to be susceptible to the plant's extracts. The presence of phenolic chemicals, flavonoids, and tannins, which damage microbial cell membranes, suppress enzyme function, and obstruct vital metabolic processes, is mainly responsible for the antibacterial activity. The plant has long been used to treat wounds, skin infections, and gastrointestinal issues because of its capacity to fight microbial infections. Additionally, *P. niruri* is a viable candidate for the development of novel therapies due to the increased interest in plant-based antimicrobial medicines brought about by the rising prevalence of antibiotic resistance [13].

Mechanisms of Action

Phyllanthus niruri L. has a variety of medicinal actions that are mediated by a complex web of molecular and metabolic processes. *P. niruri* modulates multiple physiological systems at once because it uses multi-target methods to carry out its pharmacological activities, in contrast to many single-target synthetic medicines. Its

diverse phytochemical composition, which includes lignans (phyllanthin, hypophyllanthin), flavonoids, tannins, alkaloids, and polyphenolic chemicals, is largely responsible for this complex mechanism of action. These bioactive components have a variety of therapeutic effects via interacting with enzymes, molecular targets, and cellular signaling pathways. Below is a discussion of the main mechanisms that underlie its pharmacological actions.

1. Antioxidant Defense Mechanisms

Phyllanthus niruri's capacity to fight oxidative stress through strong antioxidant activity is one of its primary modes of action. An imbalance between the body's antioxidant defense system and the production of reactive oxygen species (ROS) results in oxidative stress, which damages cells and causes chronic illnesses like diabetes, cardiovascular disease, and liver ailments. By boosting the activity of important enzymes like glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD), *P. niruri* strengthens natural antioxidant defenses. These enzymes are essential for stopping lipid peroxidation and neutralizing free radicals. Furthermore, the plant's polyphenolic chemicals directly scavenge ROS, preventing oxidative damage to cellular macromolecules like proteins, lipids, and DNA. *P. niruri* is thought to activate transcription factors at the molecular level, such as nuclear factor erythroid 2-related factor 2 (Nrf2), which controls the expression of genes driven by antioxidant response elements (AREs). Its hepatoprotective and cytoprotective properties are mostly attributed to this activation, which also strengthens cellular resistance to oxidative stress.

2. Enzyme Inhibition and Antiviral Mechanisms

Another important mechanism of action of *Phyllanthus niruri* involves the inhibition of specific enzymes, particularly those associated with viral replication. The plant has demonstrated significant antiviral activity, especially against Hepatitis B virus (HBV), by targeting viral DNA polymerase. By inhibiting this enzyme, *P. niruri* prevents the replication of viral DNA, thereby reducing viral load and limiting the spread of infection. In addition to polymerase inhibition, the plant's bioactive compounds may interfere with other stages of the viral life cycle, including viral entry, transcription, and protein synthesis. Tannins and lignans present in the plant are known to bind to viral proteins and enzymes, disrupting their function and impairing viral replication. Furthermore, *P. niruri* may enhance host immune responses by stimulating antiviral defense mechanisms, such as the production of interferons and activation of immune cells. This dual action—direct inhibition of viral enzymes and indirect enhancement of host immunity—makes it a promising candidate for antiviral therapy.

3. Modulation of Inflammatory Cytokines

Inflammation is a key underlying factor in many chronic diseases, including liver disorders, arthritis, and metabolic syndromes. *Phyllanthus niruri* exerts its anti-inflammatory effects by modulating the production and activity of pro-inflammatory cytokines and mediators. The plant has been shown to inhibit the expression of cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6), which play crucial roles in initiating and sustaining inflammatory responses. This inhibition is achieved through the suppression of key signaling pathways, including the nuclear factor-kappa B (NF- κ B) pathway, which regulates the transcription of inflammatory genes. Additionally, *P. niruri* inhibits the activity of enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX), which are involved in the synthesis of inflammatory mediators like prostaglandins and leukotrienes. By reducing the production of these mediators, the plant effectively alleviates inflammation and associated pain. The modulation of inflammatory pathways also contributes to its hepatoprotective and nephroprotective effects, as chronic inflammation is a major contributor to tissue damage in these organs.

4. Regulation of Metabolic Pathways

Phyllanthus niruri also influences various metabolic pathways, particularly those involved in glucose and lipid metabolism. This regulatory effect underlies its antidiabetic and metabolic health benefits.

The plant has been reported to enhance insulin secretion from pancreatic β -cells and improve insulin sensitivity in peripheral tissues. It also inhibits key carbohydrate-metabolizing enzymes such as α -amylase and α -glucosidase, thereby reducing glucose absorption and postprandial blood glucose levels. Additionally, *P. niruri* may modulate signaling pathways such as the AMP-activated protein kinase (AMPK) pathway, which plays a central role in energy homeostasis. In lipid metabolism, the plant has been shown to reduce levels of total cholesterol, triglycerides, and low-density lipoprotein (LDL), while increasing high-density lipoprotein (HDL). These effects contribute to its cardioprotective potential and overall metabolic benefits.

5. Anti-urolithiatic Mechanisms

The antiurolithiatic activity of *Phyllanthus niruri* is mediated through multiple mechanisms that prevent the formation and promote the dissolution of kidney stones. The plant inhibits the nucleation, growth, and aggregation of calcium oxalate crystals, which are the primary constituents of most renal calculi. One of the key mechanisms involves the alteration of urinary biochemical parameters, such as reducing oxalate and calcium levels while increasing magnesium and citrate concentrations, which inhibit stone formation. Additionally, *P. niruri* prevents the adhesion of crystals to renal epithelial cells, thereby reducing the likelihood of stone

retention and growth. The plant also exhibits diuretic activity, which increases urine output and facilitates the flushing of small crystals and stones from the urinary tract. Some studies suggest that it may even modify the structure and morphology of existing stones, making them more fragile and easier to disintegrate.

6. Synergistic and Multi-target Effects

A notable feature of *Phyllanthus niruri* is its ability to exert synergistic effects through the interaction of multiple bioactive compounds. Unlike single-compound drugs, the combined action of various phytochemicals in the plant enhances its therapeutic efficacy and reduces the likelihood of adverse effects. These synergistic interactions allow *P. niruri* to target multiple pathways simultaneously, making it effective in the treatment of complex, multifactorial diseases such as liver disorders, diabetes, and chronic infections. The multi-target nature of its action also reduces the risk of drug resistance, particularly in the case of antimicrobial and antiviral therapies.



Figure: 3 Mechanism of anti-urolithiatic activity.

Modern Applications and Research Trends

The transition of *Phyllanthus niruri* from a traditionally used medicinal herb to a scientifically validated therapeutic agent has opened new avenues in modern biomedical research. With growing interest in plant-based drug discovery, this species has attracted attention for its diverse pharmacological properties and rich phytochemical profile. Contemporary research efforts are focused on translating its bioactive constituents into clinically effective formulations, improving delivery systems, and integrating its use with conventional medical practices. These

developments highlight the evolving role of *P. niruri* in modern healthcare and pharmaceutical sciences.

1. Drug Development

One of the most significant modern applications of *Phyllanthus niruri* lies in drug development. The identification and isolation of bioactive compounds such as phyllanthin, hypophyllanthin, flavonoids, and polyphenols have provided a strong foundation for the development of novel therapeutic agents. These compounds exhibit potent hepatoprotective, antiviral, antioxidant, and anti-inflammatory activities, making them promising candidates for pharmaceutical research. In the context of hepatoprotective drug development, *P. niruri* has shown considerable potential in protecting liver cells against toxin-induced damage and improving liver function. Researchers are actively exploring its role in developing herbal formulations and phytopharmaceuticals for the treatment of liver diseases such as hepatitis, fatty liver disease, and cirrhosis. Standardized extracts of the plant are being evaluated for their efficacy, safety, and pharmacokinetic properties, with the aim of producing reliable and reproducible therapeutic agents.

The antiviral potential of *P. niruri*, particularly against Hepatitis B virus (HBV), has also gained attention in drug discovery programs. Its ability to inhibit viral DNA polymerase and suppress viral replication has encouraged researchers to investigate its application in developing plant-based antiviral drugs. In an era where viral resistance to conventional drugs is a growing concern, natural compounds from *P. niruri* offer a promising alternative or complementary approach. Furthermore, advances in computational biology and molecular docking studies have facilitated the identification of specific interactions between *P. niruri* phytochemicals and biological targets. These *in silico* approaches are accelerating the drug discovery process by predicting the binding affinity and activity of plant-derived compounds, thereby reducing the time and cost associated with traditional drug development. Despite these promising developments, challenges remain in terms of standardization, quality control, and large-scale clinical validation. Variability in phytochemical composition due to geographical, environmental, and processing factors can affect the consistency of herbal formulations. Therefore, establishing standardized extraction methods and quality assurance protocols is essential for successful drug development.

2. Nanotechnology-Based Delivery

A major limitation in the therapeutic application of *Phyllanthus niruri* is the poor bioavailability of its bioactive compounds. Many phytochemicals exhibit low solubility, rapid metabolism, and limited absorption, which can reduce their clinical efficacy. To address these challenges, recent research has focused on the application of nanotechnology-based drug delivery systems. Nanoparticle-mediated delivery systems offer several advantages, including improved solubility, enhanced stability,

controlled release, and targeted delivery of active compounds. Various nanocarriers such as liposomes, polymeric nanoparticles, solid lipid nanoparticles, and nanoemulsions are being explored for encapsulating *P. niruri* extracts or isolated phytochemicals. These nanocarriers facilitate the efficient transport of bioactive molecules to specific tissues or organs, thereby increasing therapeutic efficacy while minimizing side effects. For instance, liver-targeted nanoparticle systems can enhance the hepatoprotective action of *P. niruri* by delivering higher concentrations of active compounds directly to hepatic cells. Similarly, antiviral compounds can be delivered more effectively to infected tissues, improving treatment outcomes. Nanotechnology also enables sustained and controlled release of drugs, which reduces the frequency of administration and improves patient compliance. Additionally, surface modification of nanoparticles with ligands or antibodies allows for precise targeting of diseased cells, further enhancing the specificity of treatment. Recent studies have demonstrated that nanoformulations of *P. niruri* exhibit superior pharmacological activity compared to conventional extracts, highlighting the potential of nanotechnology in optimizing herbal therapies. However, further research is required to evaluate the long-term safety, toxicity, and regulatory aspects of these nano-based systems before their widespread clinical application [15].

3. Integrative Medicine

The concept of integrative medicine, which combines conventional medical treatments with complementary and alternative therapies, has gained significant momentum in recent years. *Phyllanthus niruri* is increasingly being incorporated into integrative healthcare approaches, particularly for the management of chronic diseases such as liver disorders, diabetes, and kidney stones.

In integrative medicine, *P. niruri* is often used as an adjunct therapy alongside standard pharmaceutical treatments. For example, in patients with chronic liver diseases, herbal formulations containing *P. niruri* may be used in combination with antiviral or hepatoprotective drugs to enhance therapeutic outcomes and reduce drug-induced side effects. Similarly, in the management of urolithiasis, the plant may be used alongside conventional treatments to prevent recurrence and promote stone dissolution. The use of *P. niruri* in integrative medicine is supported by its multi-target mechanisms of action, which allow it to address various aspects of disease pathology simultaneously. Its antioxidant, anti-inflammatory, and immunomodulatory properties contribute to overall health improvement and disease prevention. Moreover, the growing patient preference for natural and holistic therapies has further driven the adoption of medicinal plants in integrative healthcare systems. Healthcare practitioners are increasingly recognizing the value of combining traditional knowledge with modern medical practices to provide comprehensive and patient-centered care. However, the integration of *P. niruri* into

mainstream medicine requires careful consideration of factors such as herb-drug interactions, dosage standardization, and clinical validation. While the plant is generally considered safe, its concurrent use with conventional drugs may lead to interactions that could affect therapeutic efficacy or safety. Therefore, evidence-based guidelines and clinical studies are essential to ensure the safe and effective use of *P. niruri* in integrative medicine.

Safety and Toxicity

The safety profile of *Phyllanthus niruri* L. has been a subject of growing scientific interest, particularly in the context of its expanding use in herbal medicine, nutraceuticals, and integrative healthcare systems. Traditionally, the plant has been consumed in various forms—such as decoctions, powders, and fresh extracts—without significant reports of severe adverse effects. This long-standing history of use suggests a relatively favorable safety margin. However, as with any biologically active substance, a comprehensive evaluation of its toxicity, dosage limits, and potential side effects is essential for its safe and effective application in modern medicine.

1. General Safety Profile

Phyllanthus niruri is generally regarded as safe when used at recommended therapeutic doses. Preclinical studies involving animal models have demonstrated low acute and subacute toxicity, with no significant mortality or major organ damage observed at moderate dosage levels. These findings support its traditional use as a non-toxic medicinal herb for the treatment of various ailments, including liver disorders, kidney stones, and infections. In clinical settings, herbal formulations containing *P. niruri* have been administered to patients with minimal adverse effects. Most reported side effects are mild and transient in nature, indicating a good tolerability profile. The plant's widespread use in traditional medicine across different cultures further reinforces its reputation as a safe therapeutic agent.

2. Acute and Subacute Toxicity Studies

Toxicological evaluations of *P. niruri* extracts have shown that the plant exhibits a high margin of safety in acute toxicity studies. In experimental models, even relatively high doses of aqueous or ethanolic extracts did not produce significant toxic effects or mortality. The median lethal dose (LD₅₀) values reported in various studies are considerably higher than the doses typically used for therapeutic purposes, indicating low acute toxicity. Subacute and subchronic toxicity studies, which involve repeated administration of the plant extract over a period of weeks or months, have also demonstrated minimal adverse effects. Parameters such as body weight, food intake, hematological indices, and biochemical markers (including liver and kidney function tests) generally remain within normal ranges.

Histopathological examinations of vital organs, such as the liver, kidneys, and heart, have not revealed significant structural abnormalities at standard doses. These findings suggest that *P. niruri* is relatively safe for short-term use. However, variations in study design, extraction methods, and dosage regimens necessitate cautious interpretation of these results.

3. Chronic Toxicity and Long-Term Safety

Despite encouraging results from acute and subacute studies, data on the long-term safety and chronic toxicity of *Phyllanthus niruri* remain limited. Chronic toxicity studies are essential to evaluate the potential cumulative effects of prolonged use, particularly in patients who consume the plant as part of long-term treatment for chronic conditions such as liver disease or diabetes. Some concerns have been raised regarding the possibility of bioaccumulation of certain phytochemicals, which could lead to subtle toxic effects over extended periods. Additionally, the impact of prolonged exposure on reproductive health, endocrine function, and genetic stability has not been fully elucidated. Therefore, well-designed long-term studies, including clinical trials, are required to establish the safety of continuous use.

4. Adverse Effects and Side Effects

Although *P. niruri* is generally well tolerated, excessive consumption or inappropriate use may lead to mild adverse effects. The most commonly reported side effects include gastrointestinal disturbances such as nausea, abdominal discomfort, diarrhea, and loss of appetite. These symptoms are typically mild and resolve upon discontinuation or dose adjustment. In rare cases, individuals may experience allergic reactions, particularly if they are sensitive to plant-derived compounds. Symptoms such as skin rash, itching, or mild respiratory discomfort may occur, although such reactions are uncommon. It is important to note that the occurrence of side effects may depend on factors such as dosage, duration of use, individual sensitivity, and the form of preparation (e.g., crude extract vs. standardized formulation). Therefore, adherence to recommended dosages and proper medical guidance is essential to minimize the risk of adverse effects.

5. Herb–Drug Interactions

With the increasing use of *P. niruri* in integrative medicine, the potential for herb–drug interactions has become an important consideration. The plant's bioactive compounds may interact with conventional pharmaceuticals by influencing drug metabolism, absorption, or excretion. For example, *P. niruri* may affect the activity of liver enzymes involved in drug metabolism, such as cytochrome P450 enzymes. This could potentially alter the pharmacokinetics of co-administered drugs, leading to either reduced efficacy or increased risk of toxicity. Patients taking medications for liver diseases, diabetes, or hypertension should exercise caution when using *P.*

niruri concurrently. Additionally, the plant's hypoglycemic and hypotensive effects may enhance the action of antidiabetic and antihypertensive drugs, potentially leading to excessive lowering of blood glucose or blood pressure levels. Therefore, careful monitoring and dose adjustments may be necessary when combining herbal and conventional therapies.

6. Safety in Special Populations

The safety of *Phyllanthus niruri* in specific populations, such as pregnant and lactating women, children, and elderly individuals, has not been extensively studied. Due to the lack of sufficient clinical data, its use in these groups should be approached with caution. Pregnant women, in particular, should avoid the use of *P. niruri* unless prescribed by a qualified healthcare professional, as the potential effects on fetal development are not well established. Similarly, its safety during breastfeeding remains unclear, and the possibility of transfer of bioactive compounds through breast milk cannot be ruled out. In pediatric and geriatric populations, dosage adjustments may be required due to differences in metabolism and physiological function. Clinical supervision is recommended to ensure safe use in these vulnerable groups.

7. Standardization and Quality Control

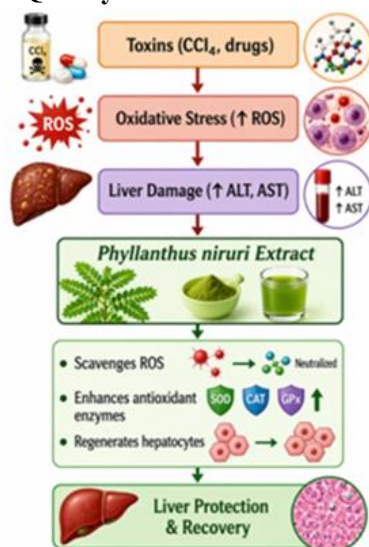


Fig. 3. Proposed mechanism of hepatoprotective activity of *Phyllanthus niruri*.

Another important aspect of safety is the quality and standardization of *P. niruri* preparations. Variability in phytochemical composition due to differences in geographical origin, cultivation practices, harvesting time, and extraction methods can influence both efficacy and safety. Contamination with heavy metals, pesticides, or microbial agents is also a concern in herbal products. Therefore, adherence to good agricultural and collection practices (GACP) and good

manufacturing practices (GMP) is essential to ensure the safety and quality of herbal formulations. Standardization of extracts based on specific bioactive markers, such as phyllanthin content, can help in achieving consistent therapeutic outcomes and minimizing variability.

Results & Discussion

Table 1: Phytochemical Constituents and Biological Activities

Compound Class	Major Compounds	Biological Activity
Lignans	Phyllanthin, Hypophyllanthin	Hepatoprotective, antiviral
Flavonoids	Quercetin, Rutin	Antioxidant, anti-inflammatory
Alkaloids	Nirurine	Antimicrobial
Tannins	Ellagitannins	Antioxidant
Terpenoids	Lupeol	Anti-inflammatory

Table 2: Traditional vs Modern Therapeutic Applications

Traditional Use (Ayurveda)	Modern Scientific Validation
Jaundice treatment	Hepatoprotective activity confirmed
Kidney stone removal	Anti-urolithiatic effects proven
Fever and infections	Antimicrobial activity
Diabetes control	Hypoglycemic effects
Digestive disorders	Anti-inflammatory & antioxidant

Table 3: Pharmacological Activities and Mechanisms

Activity	Mechanism of Action	Target System
Hepatoprotective	Enzyme regulation, antioxidant defense	Liver
Antiviral	Inhibition of viral DNA polymerase	Viral infections
Antioxidant	Free radical scavenging	Cellular level
Anti-inflammatory	Cytokine suppression	Immune system
Antidiabetic	Insulin sensitivity improvement	Endocrine system

Table 4: Recent Research Trends

Research Area	Key Findings	Year Range
Hepatoprotection	Liver enzyme normalization	2017–2023
Antiviral studies	HBV inhibition	2018–2024
Nanotechnology	Nanoformulations improve delivery	2020–2026

Antidiabetic research	Blood glucose reduction	2019–2025
Antioxidant studies	ROS reduction confirmed	2016–2024

Challenges and Future Perspectives

Despite the significant therapeutic promise of *Phyllanthus niruri*, several scientific and translational challenges continue to limit its full clinical and pharmaceutical utilization.

Challenges

• Lack of Standardized Formulations

One of the major limitations in the therapeutic application of *P. niruri* is the absence of standardized extracts. Variability in extraction methods, solvent systems, and plant part selection leads to inconsistent concentrations of active phytoconstituents such as phyllanthin and hypophyllanthin. This lack of uniformity affects reproducibility, dosage accuracy, and clinical reliability.

• Limited Clinical Trials

Although numerous in vitro and in vivo studies support its pharmacological activities, there is a scarcity of well-designed, large-scale human clinical trials. Most available studies are preliminary, with limited sample sizes and short durations, restricting the translation of experimental findings into evidence-based clinical practice.

• Variability in Phytochemical Composition

The phytochemical profile of *P. niruri* is highly influenced by environmental factors such as soil conditions, climate, geographic location, and harvesting time. This natural variability results in fluctuations in bioactive compound content, thereby affecting therapeutic efficacy and consistency across different batches.

Future Perspectives

• Clinical Validation and Translational Research

Future studies should prioritize randomized controlled trials (RCTs) to validate the safety and efficacy of *P. niruri* in human populations. Long-term toxicity studies and pharmacokinetic profiling are also essential for regulatory approval and clinical acceptance.

• Isolation and Characterization of Novel Bioactive Compounds

Advanced analytical techniques such as LC-MS/MS, NMR spectroscopy, and metabolomics should be employed to identify and characterize new bioactive molecules. These compounds may serve as lead candidates for the development of novel drugs targeting liver disorders, viral infections, and metabolic diseases.

- **AI-Driven Drug Discovery Approaches**

Integration of artificial intelligence (AI) and machine learning (ML) can accelerate drug discovery from *P. niruri*. Computational tools such as molecular docking, virtual screening, and predictive modeling can help identify potential therapeutic targets, optimize drug design, and reduce development time and cost.

- **Development of Standardized Herbal Formulations**

Establishing pharmacopeial standards, quality control protocols, and Good Manufacturing Practices (GMP) will be crucial for ensuring consistency, safety, and efficacy in herbal formulations derived from *P. niruri*.

- **Nanotechnology-Based Drug Delivery Systems**

Emerging research in nanotechnology can enhance the bioavailability and targeted delivery of phytoconstituents. Nanoformulations such as nanoparticles, liposomes, and phytosomes offer promising strategies to improve therapeutic outcomes.

Conclusion

Phyllanthus niruri (Bhumi Amla) represents a scientifically promising medicinal plant whose therapeutic relevance spans both traditional healing systems and modern biomedical research. This review highlights that its long-standing use in Ayurveda and ethnomedicine—particularly for liver disorders, kidney stones, infections, and metabolic diseases—has been increasingly validated through contemporary pharmacological studies. The plant's rich phytochemical profile, including lignans, flavonoids, tannins, and polyphenols, underpins its diverse biological activities such as hepatoprotective, antiviral, antioxidant, anti-inflammatory, antidiabetic, and anti-urolithiatic effects. These multi-target mechanisms make *P. niruri* a valuable candidate for developing plant-based therapeutics and integrative healthcare solutions. However, despite strong preclinical evidence, the transition from traditional remedy to standardized clinical application remains incomplete due to limitations such as lack of standardized formulations, variability in phytochemical composition, and insufficient large-scale clinical trials. Addressing these gaps through rigorous clinical validation, advanced analytical techniques, and emerging approaches like AI-driven drug discovery and nanotechnology-based delivery systems will be critical. In conclusion, *Phyllanthus niruri* holds substantial potential as a natural, cost-effective, and multifunctional therapeutic agent. Future interdisciplinary research integrating traditional knowledge with modern scientific innovation can facilitate its translation into evidence-based medicine, contributing significantly to global healthcare and sustainable drug development.

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