Broad-spectrum on pharmacological potential of Phyllanthus niruri in disease treatment: A review

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Abstract

Phyllanthus, the largest genus within the Euphorbiaceae family, encompasses a diverse array of approximately 750 to 1200 species, each exhibiting remarkable diversity and therapeutic potential attributed to their unique bioactive compounds. Among these species, *Phyllanthus niruri* has gained notable recognition for its traditional use in treating jaundice and various hepatic disorders. Scientific investigations have revealed its broad pharmacological spectrum, encompassing activities against a diverse array of maladies such as amoebic dysentery, influenza, dysentery, vaginitis, cancer, and renal calculus, among others. Subsequent studies have unveiled a plethora of active constituents from various plant parts, including alkaloids, flavonoids, tannins, and terpenoids, contributing to its diverse biological activities such as anti-hyperuricaemic, hypolipidaemic, hepatoprotective, antibacterial, hypoglycaemic, analgesic, anti-inflammatory, cardioprotective, antiviral, anti-urolithiatic. This review highlights the applicative perspective of *Phyllanthus niruri*, with a focus on pharmacological and medical potential in treating chronic diseases. Despite its extensive use in traditional medicine, the application and utility in clinical trials remains unexplored, impeding a comprehensive understanding of its therapeutic potential.

Keywords: Phyllanthusniruri, oxidative stress, Hepato-protective, anti-diabetic, anti-cancer

Abbreviations: CAD- Coronary artery disease; CRP- C-reactive protein

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INTRODUCTION

A tropical perennial herb *Phyllanthusniruri* is a species from the family Euphorbiaceae and genus Phyllanthus.vernacularly known as '*Bhumyamalaki'*, '*pitirishi'* inIndia, '*Chancapiedra*' in Spain, '*Zhu zi cao*' in China, '*dukonganank*' in Malaysia.(1). *P.niruri* was widely distributed in tropical regions including Southren East Asia, South India, and most parts of China (2). However, this unpretentious plant is not confined to any sole purpose, its bioactive compounds have sparked interest across various fields, from traditional medicine to modern scientific research. It has been used in traditional medicine for approximately two thousand years and has been reported in herbal findings such as Ayurvedaoriginated in India, Traditional medicine from China, and Indonesian Jamu for jaundice, gonorrhea, frequent menstruation, and diabetes. It also has a broad spectrum of proven pharmacological activity in a diverse array of maladies such as Influenza, amoebic dysentery, vaginal inflammation , various cancers, Diabetes, Diuretic, kidney stones, PCOS and Dyspepsia, hepatotoxicity, hepatitis B, Hyperglycemia, viral and bacterial diseases.(3) Early pioneer Ottowstarted active scientific research on *p. niruri*andmade an evident extraction of lignin phyllanthin in 1861. Furthermore, many scientific researches concluded and exploited the variety of active constituents such as alkaloids, Benzenoids, coumarins, flavonoids, lignan, tannins, terpenoids, sterols, phthalate, lipids, saponins, etc. which are obtained from leaf, stem, aerial parts, and roots of the plant.(3)Despite the extensive array of applications from an ethnomedicinal perspective, most of the potential therapeutic uses of *P. niruri* have yet to progress to the stage of clinical trials. Indeed, there is a lack of integration concerning the existing knowledge about *P. niruri*research. The diversity of preliminary studies on this herb was hindered by an impartial evaluation of its activity, and the mechanisms underlying much of its therapeutic potential remain undefined.

P. niruri could emerge as a significant drug lead, underscoring the continued importance of natural originating products from herbs as fundamental fountains of innovative therapeutic agents and fresh molecular entities. This researchfocuses on thepharmacological perspective of the *p. niruri*specifically towards the research in chronic diseases treatment.

Pharmacological properties of *P. niruri*againstdifferent diseases

1. ***Phyllanthus niruri* as an antidiabetic**

The wide use of *Pyllanthusniruri* from ancient history picturises it in managing blood glucose levels and diabetes. With current era of research, scientists have elucidated how plant extract impacts key processes such as glucose absorption, mobilization, and storage. A recent study has demonstrated that ethanolic aqueous fraction of *P. niruri* ameliorated insulin sensitivity through activation of SIRT1, PGC1-α, and AMPK expression in vitro and in vivo.(4)Kumar et al. 2019 observed increased levels of GSH & SOD while decreased NO, LPO levels in various tissues of vital organs of the rats treated with *P. niruri* extracts that showed its anti-oxidant potential. This study also suggested that it downregulated leptin that might be associated with a reduction in insulin resistance.(5) Diabetes is also manifested as a state of dyslipidemia, elevated triglycerides and free radical generation. A study observed decreased level of TBA reactive substances in kidney, brain and liver of diabetic rats indicating that it can reduce lipid peroxidation.(6) *P. niruri* extract showed potent inhibition of Alpha – Amylase activity(7) and α-glucosidase(8)which plays a prominent role in limiting glucose absorption in the gastrointestinal tract and result in a decrease in postprandial glucose levels. Therefore, *P. niruri* demonstrated notable anti-diabetic potential by enhancing glucose uptake in C2C12 cell line derived from muscles and promoting adipogenesis in 3T3-L1 fat cells.(8) In Insulin Dependent Diabetes Mellitus animal model, the extract administration significantly increased hepatic glycogen, hepatic hexokinase activity and lowered plasma glucosecorrelating with improved glucose tolerance while it showed ineffectiveness in NIDDM due to an incapacity to reduce insulin resistance.(9)

2. Anti-uroliathiatic Potential

*Phyllanthus niruri*has been extensively studied for its diuretic properties(10) and treating kidney stones.(11)The phytoconstituents such as terpenes, phenols, flavonoids, etc. of this plant possess the ability to inhibit the cytotoxic effects triggered by calcium oxalate which forms the urolith.(12) Particularly, triterpenes play a role in mitigating the indicators associated with crystal deposition within the kidneys,(13) exhibiting its potential, thus, called as Stone breaker. *P. niruri* in Indian Ayurveda has been long renowned to treat renal calculi. Renal calculi originate when the renal tubular epithelial cells damage and crystallization occurs followed by crystal retention and development of stone. Administration of *P.niruri* extracts has reduced urine protein concentration indicating that membrane damage at glomerular basement is also less.(14)The application of *P. niruri* extract in diabetic rats might result in an augmentation of glomerular diameter, cross-sectional area, and volume, potentially playing a role in mitigating renal atrophy. The diminished concentration of urine protein suggests a reduced likelihood of membrane damage at the glomerular basement.(15)*P. niruri*extract administration has been concluded to maintain regulatory levels of serum electrolytes, uric acid, urine protein, blood urea nitrogen (BUN), creatinine clearance (CCr), and BUN/Cr ratio in diabetic rats. Furthermore, the expression of inflammatory, fibrosis, and apoptotic markers decreased in kidney tissue as a result of *P. niruri* treatment. It was also noted that whilst the expression of Nrf2, SOD1, CAT, and GPx-1 increased, the expression of TBARS and decreased the RAGE. Proliferative markers were discovered to be overexpressed, nevertheless in this study.(16) This might be its possible mechanism of action as an anti-uroliathiatic herbal drug.

3. *P. niruri*offering anti hepatotoxicity:

The hepatoprotective effects of *P. niruri* exhibit antioxidative properties. Initial *in-vitro* investigations into the antioxidative hepatoprotective potential of *P. niruri* revealed that the extracts from n-hexane of this plant determined*phyllanthin* and *hypophyllanthin*which are a group oflignans. These lignans were observed to safeguard rat hepatocytes against hepatotoxicity

induced by substances such as carbon tetrachloride and galactosamine in early studies.(6)One of the prominent studies have demonstrated a protective effect against the cytotoxicity induced by carbon tetra chloride in isolated hepatocyte primary cultures. As CCl4 commonly results in elevated levels of serum enzymes- glutamate oxaloacetate transaminase and glutamate pyruvate transaminase, *P. niruri* emerged as downregulating these enzymes.(6)Recent studies on extracts from *Phyllanthus niruri* and *Andrographis paniculata*, whether administered individually or in combination, exhibited hepatoprotective effects against Isoniazid and Rifampicin-induced hepatotoxicity. Significant reductions were observed in the limits of total bilirubin and serum glutamic oxaloacetic transaminase in groups treated with *P. niruri*.(17)These enzymes serve as markers for liver injury. However, it is important to highlight that while there is a noticeable decrease in enzyme intensity, the exact mechanism underlying this reduction remains elusive. Furthermore, the extent and specific enzymes exhibiting reduced levels seem to differ among various studies, implying the potential involvement of multiple mechanisms in the lowering the liver enzyme levels.Molecular docking studies have identified nine candidate target proteins—JUN, CCND1, VEGFA, AKT1, CREB1, SRC, RELA, MMP2, and EGFR, as well as two key components ellagic acid and quercetin. These compounds demonstrate promising hepatoprotective activities.(18,19)

4. Anti-microbial Activity:

The ethanolic extracts of *P. niruri* demonstrated efficacy against *Escherichia coli*, *S. aureus*, and *S. typhi*.(20)Extracts derived from nearly five species, *P. niruri* included, exhibit activity against prevalent pathogens like *K. pneumonia* and *S. paratyphia*.*(21,22)*Some findings revealed that the DMSO extract of leafof *P. niruri* exhibited significantly impactful effect on *S. typhi* and *S. aureus*, suggesting a potential cure for typhoidandother staphylococcal infection. Njoroge et al. demonstrated that the water, methanol and dichloromethane diluted extracts of *P. niruri* possess bacteriolytic effect on various pathogenic bacteria and fungus.*(23)*This supports the historical application of *P. niruri* in traditional medicine for the treatment of typhoid fever and its use as an intestinal anesthetic.(24,25) Similarly, ethanol, methanol and aqueous extract of *P. niruri*showed

potency against *Vibrio cholera*and *Aspergillus niger*, in another study.(26) Within *P. niruri*, the presence of beta-sitosterol demonstrates anestheticand antinociceptive potential, proving effective against several microbial species.*(27)*These combined discoveries emphasize the potential therapeutic advantages of *P. niruri* in treating diverse microbial infections, providing a rationale for its incorporation into traditional medicine.(28)

The antimicrobial efficacy of the ethanol extract derived from various components of *P. niruri* was investigated, revealing distinct specificity in their actions. The leaf extract displayed significant inhibition of Micrococcus purpurea growth, comparable to the standard antibiotic ampicillin. Both seed and leaf extracts exhibited increased sensitivity against *A. calcoaceticus*. The root extract demonstrated strong inhibition against *Z. mobilis,* whereas the seed extract hindered the growth of S. epidermidis.*(29)*Significantly, the seed and leaf extracts of *P. niruri* demonstrated considerable inhibition zones compared to other plant parts when evaluated against *P. chrysosporium* and *P. chrysogenum*. Recent discoveries affirm that *P. niruri*harbors potent bioactive compounds effective against *E. coli* infection. The administration of this extract at doses up to 1500 mg revealed no adverse effects on liver and kidney functions.(30)

Metabolites and substances found in the *P. niruri* plant encompass fatty acids, steroids, ethyl ester forms of hexadecanoic acid (palmitic acid), linolenic acid, and linoleic acid. These components collectively contribute to antioxidant and anti-inflammatory functions. Additionally, these compounds exhibit various pharmacological activities, including antiparasitic or nematicide effects, hemolytic activity, antiandrogenic, antihistamine, anti-acne, along with antimicrobial activity.(31)

Anti-cancer effect:

The selective anti-proliferative effects of four distinct *Phyllanthus* plant species on four different cancer cell lines, specifically PC-3, MCF-7, A549, and MeWo.(32,33) Notably, these effects were observed without inducing cytotoxicity in their corresponding normal cells. The methanol extracts (MEs) from these plants demonstrated superior anti-proliferative efficacy against cancer cells compared to aqueous extracts, achieving notable effects at relatively low doses. This

Phyllanthus plants exhibited a targeted inhibition of cancer cell growth, selectively influencing cell cycle modulation and apoptosis induction through caspase activation.(34) The study emphasizes the crucial role of polyphenol compounds in inhibiting the invasion, migration, and adhesion of cancer cells, along with their involvement in apoptosis induction. Consequently, *P. niruri* emerges as a prospective candidate for the creation of robust apoptosis-inducing anticancer agents, bolstered by prior research.(35)

5. Cardioprotective, anti-platelet activity:

A single pivotal animal study has been undertaken to explore the mitigating effects *of P. niruri*distillate in the prevention of cardiotoxicity induced by drug doxorubicin. Prior administration of *P. niruri*distillate demonstrated a substantial safeguarding effect on rat myocardia against doxorubicin toxicity. This protection was evident through the normalization of cardiac biomarkers, reinstatement of cytoplasmic levels of antioxidants both the non-enzymatic and enzymatic, and a reduction in peroxidation of rat cardiac tissue.

Methyl brevifolin carboxylate, derived from *P. niruri*, exhibited vasorelaxant properties on rat aortic rings by impeding noradrenaline-induced vasoconstriction. This effect was associated with a reduction in calcium ion influx through receptor-operated Ca2+ channels. Additionally, this compound displayed inhibitory effects on platelet aggregation.(36,37)

6. Hypolipidaemic activity:

Research on the lipid-lowering effects of *P. niruri* has predominantly utilized rat models, overlooking the acknowledged reliability of rabbit models in hyperlipidemic studies. Despite the widely accepted credibility of rabbit models, no investigations involving them have been undertaken. Moreover, a notable gap exists in the absence of comprehensive *in-vitro* or molecular studies exploring the precise mechanism responsible for lipid reduction. Nevertheless, compelling evidence from animal studies supports the assertion that *P. niruri* possesses hypolipidemic properties associated with antioxidants.(9,25,38)

*P. niruri*has been observed to regulate redox changes, disrupt lipoprotein export linked to alcoholic liver disease, and mitigate lipid peroxidation caused by oxidative stress induced by alcohol. The literature highlights the importance of comparative studies that investigate the hypolipidemic effectiveness of various *P. niruri* extracts. Inconsistencies persist regarding the specific extract utilized, encompassing variations such as ethanolic, methanolic, aqueous, and unspecified extracts, along with variations in decoction concentrations.*(39)*Furthermore, the relevance of animal studies is emphasizing the need for a broader understanding before contemplating clinical trials. The pathobiological distinctions between rodent Triton-induced hyperlipidemia and human pathology underscore the importance of expanding research to include various mammalian models.(40)

Phytochemical screening emerges as a pivotal component in pinpointing the potential bioactive compounds responsible for its hypolipidemic activity. In studies involving Triton- and cholesterol-induced hyperlipidemic rats, *P. niruri* exhibited significant reductions in major serum lipid biomarkers, corroborating prior findings on alcoholic extracts lowering low-density lipoprotein levels. This effect was associated with various positive changes, including reduced lipidaemic parameters, reactivation of lipolytic activity, and restoration of hepatic lipoprotein lipase activity.(40)

These investigations are derived from proportion of dosageused in hypolipidemic activity of extracts of *P. niruri*, connected with some studies suggesting superior efficacy compared to glibenclamide. However, limitations are visible, as weight gain, akin to the side effects of thiazolidinediones, was observed in one study. Further research is imperative to assess potential adverse effects, particularly in the context of *P. niruri* as an antidiabetic agent, particularly when addressing urgent blood glucose and weight control in obese patients. The interplay between its hypolipidemic action and its potential application in patients with alcoholic liver disease is intricately connected to its capacity for lipid peroxidation quenching, possibly attributable to its high polyphenolic content.

7. *P. niruri*: long way to go in reproductive well being

Researches have concluded that Phyllanthus species offers benefits in enhancing reproductive health. The traditional use of *Phyllanthus* species in various reproductive disorders and fertility enhancement has been emerging from ancient practices since history. However, the research conducted by Asare et al., 2012, showed that hydrous leaf extract of *P. niruri*,taken for prolonged duration, generated testicular degradation as well as hormonal imbalances, and might lead to male infertility.(41)Researchers have not yet discovered any beneficial impact of administration of the aqueous extract of *P.niruri* during gestation but it resulted in alterations in maternal kidney function and a decrease in offspring weight. These findings indicate that the extract may have adverse effects during pregnancy.(42)

The availability of strong evidences of *Phyllanthus*species's protective role motivate researchersexplorethe function of every species (Table 1). Reproductive and metabolic dysfunctions resulting from letrozole-induced PCOS in rats were addressed by 7-14 days of *P.muellerianus* therapy. This treatment enhanced lipid profile, improved blood glucose levels, restored estrus cyclicity, alleviated oxidative stress, and sex hormone levels, and prevented ovarian damage. These findings indicate the potential of this plant as an alternative therapeutic option for individuals with PCOS facing reproductive and metabolic challenges.(43)

On the other hand, there are not enough evidences why *P. niruri* has detrimental effects despite of its inherent properties such as anti-oxidant, anti-inflammatory. Further expeditions are required to unveil its medicinal utility in reproductive health of men and women. Future research endeavours should focus on elucidating the underlying mechanisms of action, conducting rigorous clinical trials thereby paving the way for novel therapeutic interventions in the management of PCOS and infertility.

Conclusion

Phyllanthus niruri has garnered considerable attention due to its pharmacological efficacy highlighting its hepatoprotective, antioxidant, antiviral, anti-inflammatory, antidiabetic, and anti-urolithiatic attributes. Yet, the lack of consolidated knowledge underscores the need for further

research to elucidate the mechanisms underlying its pharmacological actions and potential side effects. Further research is imperative to comprehensively unravel its molecular mechanisms, optimize dosage, evaluate safety profiles, and identify potential synergistic interactions with conventional medications. A longitudinal study to focus on its incorporation in herbal tea lays a good idea to bring benefits in layman life. Furthermore, exploring the potential of combination therapies and assessing the treatment's efficacy against other combinatorial medical conditions could broaden its therapeutic utility.

4

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All authors have read and agreed to the published version of the manuscript.

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TABLES

Table:1 Pharmalogical uses *of P. Niruri*

S.no	Disease	Chemical used	Obtained from	Therapeutic property	References
1.	Bruises/open lesions	Astragalin, Beta-Sitosterol, Salicylic Acid Methyl Ester, Quercitrin	Leaves	anti-inflammatory and antioxidant properties	(45)
2.	Cough and common cold	Corilagin, Geraniin, Nirurine	Whole plant	anti-inflammatory, antimicrobial, antioxidant, bronchodilatorproperties, immunomodulatory, and antitussive (cough-suppressing) effects	(46)
3.	Diabetes mellitus	Quercetin, Gallic Acid, Gallotannins, Corilagin, Repandusinic Acid	Whole plant	anti-diabetic and hypoglycemic activity, α-glucosidase inhibitory activity	(8)
4.	Jaundice	Hypophyllanthin Phyllanthin, Niranthin, Quercetin, Rutin, Geraniin, Corilagin, Ellagic Acid	Roots and leaves	hepatoprotective properties, antioxidant,anti-choleretic activity	(47)
5.	Malarial fever	Alkaloids: Securinine	Whole plant	anti-tumour, antimalarial, antimicrobial and neuropharmacological activity, anti-spasmodic activity, anti-malarial and anti-bacterial activity	(48)
6.	Diuretic	Quercetin, Rutin, and Kaempferol, Astragalin	Fruits, leaves and shoots	anti-aggregant, anticancer, anti-fungal, anti-dermatophytic, anti-glaucomic, anti-inflammatory and anti-spasmodic activity	(49,50)
7.	Dysentery	Quercitrin, Isoquercitrin, Kaempferol, Fisetin-4-O-Glucoside, Phyllanthin, Niranthin, Rutin, Astragalin, CorilaginHypophyllanthin, Geraniin	Shoots	anti-inflammatory and antimicrobial properties, antibacterial activity	(51)

8.	Ulcers on the skin	Ellagic Acid, Gallic Acid, Beta-sitosterol, 4-Methoxy-Securinine.	Fruits, leaves and roots	wound healing and anti-ulcer properties	(52)
9.	Sexually transmitted diseases	Quercetin, Rutin, And Kaempferol, PhyllanthinHypophyllanthin, Triacontanal, Ellagic Acid,	Leaf and Root	antimicrobial, anti-inflammatory, antiviral activity, immunomodulatory effects, hepatoprotectivean d anti-genotoxic activities	(53)
10.	Heart/stroke attacks	Quercetin, Phyllanthin, Rutin, Hypophyllanthin, Gallic Acid	Whole plant	ameliorative, antioxidant activity, anti-hyperglycemia and antihyperlipidemic, cardioprotective action	(54)
11.	Renal failure	Gallic Acid, Ellagic Acid	Whole plant	ROS scavenging and antioxidant, gastroprotective, antioxidant activity, anti-inflammatory activities	(49)