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Review Article

# Ethno-medical and Pharmacological role of *PhyllanthusNiruri:* A Review

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## Abstract

Medicinal plants have been considered as a vital therapeutic aid for the treatment of various ailments of humankind like jaundice, ulcers, skin diseases; diabetes, chest pain and urinary complications etc. There are numerous herbs which are used for the treatment of different disorders with reference to their pleiotropic effects. Present review mainly focuson ethno-medicinal uses of *Phyllanthusniruri Linn*. with reference to their toxicological and pharmacological profile. *P. niruri* (Euphorbiaceae family) is a small herb having extensive range of medicinal properties due to their naturally occurring phytochemical constituents which is used widely across the world. The major phytochemical constituents of *P. niruri are* lignans, phyllanthin, hypophyllanthin, flavonoids, glycosinoidsand tannins which have a wide range of pharmacological activities like antimicrobial, antiviral, hepatoprotective, antioxidant, anticancer, anti-inflammatory, antimalarial and diuretic. Traditionally it was used for eliminating gallstones, kidney stones and also to treaturinary tract infections. The new diagnostic trend of P.nirurifor the treatment of variousliver disorders increases the demand of this herb in the market for developing hepatoprotective medicinal formulations.

**Keywords:** *Phyllanthusniruri Linn. (P.niruri),* Phytoconstituents, pharmacological activity, Hepatoprotective action, Toxicology, Contraindications, Drug Interactions

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## 1. Introduction

*PhyllanthusNiruri* is an annual herb and widely spread in coastal areas of India. It is used in the Indian ayurvedic systems from the ancient times. The Phyllanthus genus contains over 600 species of shrubs, trees and annual or biennial herbs distributed throughout the tropical and subtropical areas. In Indian ayurvedic system *P. niruri* plant extract is used as a medicine and is recommended for bronchitis, anemia, leprosy, asthma, urinary disorders, stimulating liver, improving digestion, increase appetite and produce laxative effects. Maharshi Charaka has considered this herb as Kasahara: alleviates cough, Swasahara: relieves asthma, mootrarogahara: cures urinary disorders, Kaphapittahara: relieves the kaphapittadosha, Kaamalaahara: cures jaundice and Bhavaprakasa Nighantu: cures cough and blood disorders [1, 2]. It is bitter in taste but sweet in the post digestive effect (vipaka) and it is also used as astringent.

In the Unani System of medicine *P. niruri*(PN) herb is good for sores and chronic dysentery. Phyllanthus means “leaf and flower” because the flower, as well as the fruit, seems to become one with the leaf, quite glabrous, stem often branched at the base. *P. niruri* is a winter weed and originated throughout the hotter parts. It is an herb of Euphorbiaceae family that grows up to 60 cm.

Leaves are numerous, sub sessile distichous often imbricating, elliptic, oblong obtuse, stipules present. Flowers are yellowish, very numerous, axillary. The male flowers are one to three in number while the female flowers are solitary in nature. Capsules are 2.5mm in diameter, depressed globose, smooth scarcely lobed[1, 2].This plant has medicinal importance for numerous ailments like dysentery, influenza, vaginitis, tumors, diabetes, diuretics, jaundice, kidney stone, and dyspepsia. The aqueous infusions of the whole plant is employed as a stomachic, appetite, anti-spasmodic, laxative, diuretic [3], carminative, against constipation, fever including malaria, hepatitis B[4], dysentery, gonorrhea, syphilis, tuberculosis, cough, diarrhea, vaginitis [5, 6]. Seeds of PN are used in the treatment of ulcers, wounds, scabies and ringworms. The root of this plant is considered to be an excellent remedy for liver diseases.

The scientific literature demonstrated that *P. niruri* extract helpful in curing hepatitis very effectively [7] and HIV-AIDS [8]. It has various pharmacological properties like anti-inflammatory [9], anti-fungal, anti-viral, anti-bacterial [10], anti-oxidant [11, 12, 13], hepatoprotective [14], hypoglycemic [15, 16], hypotensive, analgesic [17, 18], inhibitory effect on renal stone formation [19]. It is used as an ingredient in almost 175 Ayurvedic formulations. It is also used in the preparation of various health care and personal products like chavanprash, hair oil dye, face cream, tooth powder [19].

*P.niruri* has different names or vernacular names in different area and languages.

**Assamese:** Holpholi; Poram-lokhi
**Bengali:** Noar
**Hindi:** Chalmeri, Harfarauri, Bhuiaonla.
**Kannada:** Kirunelli, NelaNelli,
**Konkani:** Bhuin-avalae
**Telugu:** Ratsavusirike, NelaUsiri,
**Tamil:** Arunelli, KeelaNelli
**Malayalam:** Arinelli,Kizhanelli,Nellipuli
**Marathi:** Rayavali, Bhuiavli
**Oriya:** Narakoli
**Sanskrit:** Amala, Bhumyamlaki, Sukshmadala, Vitunika, Bhoodatri.

## 2. Geographical Distribution

It is found flourishing throughout tropical and subtropical regions of Asia, America, and China. Phyllanthusniruri is an annual herb which grows in the wild after first showers of monsoon in Jharkhand, Bihar, and Chhattisgarh etc. However, it has also been reported to grow commonly in coastal areas. In Indian states it usually grows during the second week of June and starts bearing fruits up to mid-July or August [1, 19].

## 3. Phytoconstituents

The phytochemicals like flavonoids, alkaloids, terpenoids, lignans, polyphenols, tannins, coumarins and saponins, have been identified from various parts of *P. niruri*. An extract of this herb has been proven to have therapeutic effects in many clinical studies which is shown in the fig 1 [20].

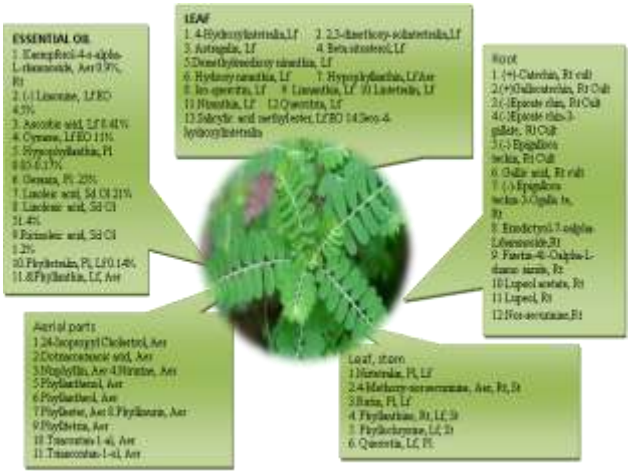


Fig.1 Phytoconstituents present in different parts of *P. niruri* Linn.

## 4. Commercially available market formulation of *P.niruri*

Alternative and traditional system of medicines showing well therapeutic efficacy with less side effects and ADR, which is the basic need of today scenario. The 80% of people from the developing countries use of herbal formulations due to their less side effects and high curing power. A literature survey was carried out to find out the current scenario of *P. niruri*and their various market formulations which is compiled in the table given below.

## 5. Pharmacological activity

The scientific literature demonstrated that *P.niruri* has been reported to possess the antioxidant, anti-

infection, anti-asthmatic, anti-diuretic, anti-soresis and many more beneficial activities which is shown in fig 2.

| SN | Name of the product | Company name |
|---|---|---|
| 1. | Phyllanthusniruri (BhumiAmalaki) cap | Safe Herbs (herbal supplements) Gujarat, INDIA |
| 2. | BhumiAmla cap | BACFO Pharmaceuticals (INDIA) Pvt Ltd |
| 3. | Phyllanthusniruri (BhumiAmala) cap | Planet Ayurveda (INDIA) Pvt Ltd |
| 4. | BhumiAmala (Phyllanthusniruri) cap Hepatic support | WDPL Pvt Ltd |
| 5. | ChancaPiedra caps classic series | Innovation Research Scientific Integrity (ARO) Calgary, Canada |
| 6. | ChancaPiedra herbal supplement | Swanson Premium, Fargo, North Dakata. |

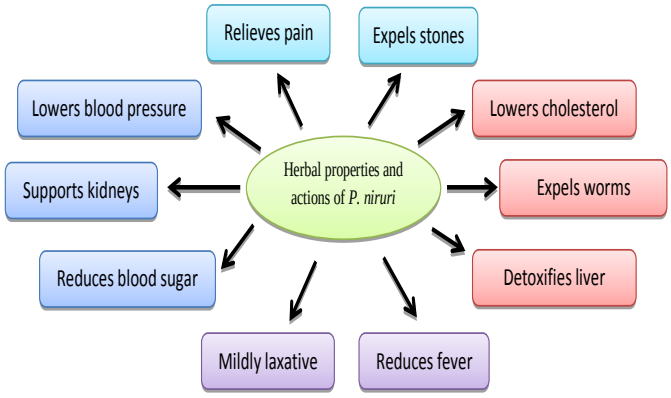


Fig 2: Herbal properties and Pharmacological action of *P.niruri Linn.*

### 5.1 Anti-spasmodic, pain relieving and anti-inflammatoryactivity

The isolated tannin Corilagin (β-1-O-galloyl-3,6-(R)-hexahydroxydiphenoyl-D-glucose) from *P. niruri*exhibits anti-hyperalgesic activity at a dose of 3 mg/kg in capsaicin and glutamate models of mice that may be due to interaction with the glutamatergic system [21]. The methanolic extract of *P. niruri* at different concentration administered i.p. to mice against acetic acid induced writhing and formalin induced pedal edema showed antinociceptive effects and significantly improves nociception [22]. Research done in Brazil at the Federal University of Santa Catarina in 1984 on *P.niruri* revealed an alkaloid (phyllanthoside) in the leaves and stem with strong antispasmodic activity. It served as a relaxing agent for smooth muscles and they concluded that its spasmolytic action probably accounted for the efficacy of *P.niruri* in expelling stones [23].

### 5.2 Anti-diabetic Activity

An alcoholic extract of *P.niruri* was found to reduce significantly the blood sugar in normal rats and in alloxan induced diabetic rats. Plant extract did not produce any toxicity as seen from liver and kidney function test and in hematological parameters. The results indicate potential anti-diabetic action of *P.niruri* [24]**.**

### 5.3 Hepatoprotective and antioxidant activity

The study has been investigate the mechanism of the protective action of a novel antioxidant protein molecule Phyllanthusniruri protein (PNP) , against tertiary butyl hydroperoxide (TBHP) induced cytotoxicity and cell death. Reduction in GSH/GSSG ratio and activities of antioxidant enzymes have also been found to be prevented by this protein. Moreover, TBHP exposure caused injury in cellular mitochondria, disrupted mitochondrial membrane potential, induced reciprocal regulation of Bcl-2 family proteins and facilitated cytochrome c release in the cytosol. From the scientific literature it has been concluded that PNP possesses cyto-protective activity against TBHP-induced oxidative cellular damage and prevents hepatocytes from apoptotic death [25].

The extract from *P.niruri* plays a protective role against liver cirrhosis induced by thioacetamide (TAA) in rats. The therapeutic effect of the extract was investigated using body and liver weights; liver biochemical parameters (SGOT, SGPT, ALP, and TBS) total antioxidant capacity, lipid peroxidation, and oxidative stress enzyme levels which show that significant decrease in hepatotoxicity induced by thioacetamide. Silymarin and *P. niruri* treatments effectively restored these measurements closer to their normal levels. Progression of liver cirrhosis induced by TAA in rats can be intervened using the *P. niruri* extract and these effects are comparable to those of Silymarin [26, 27].

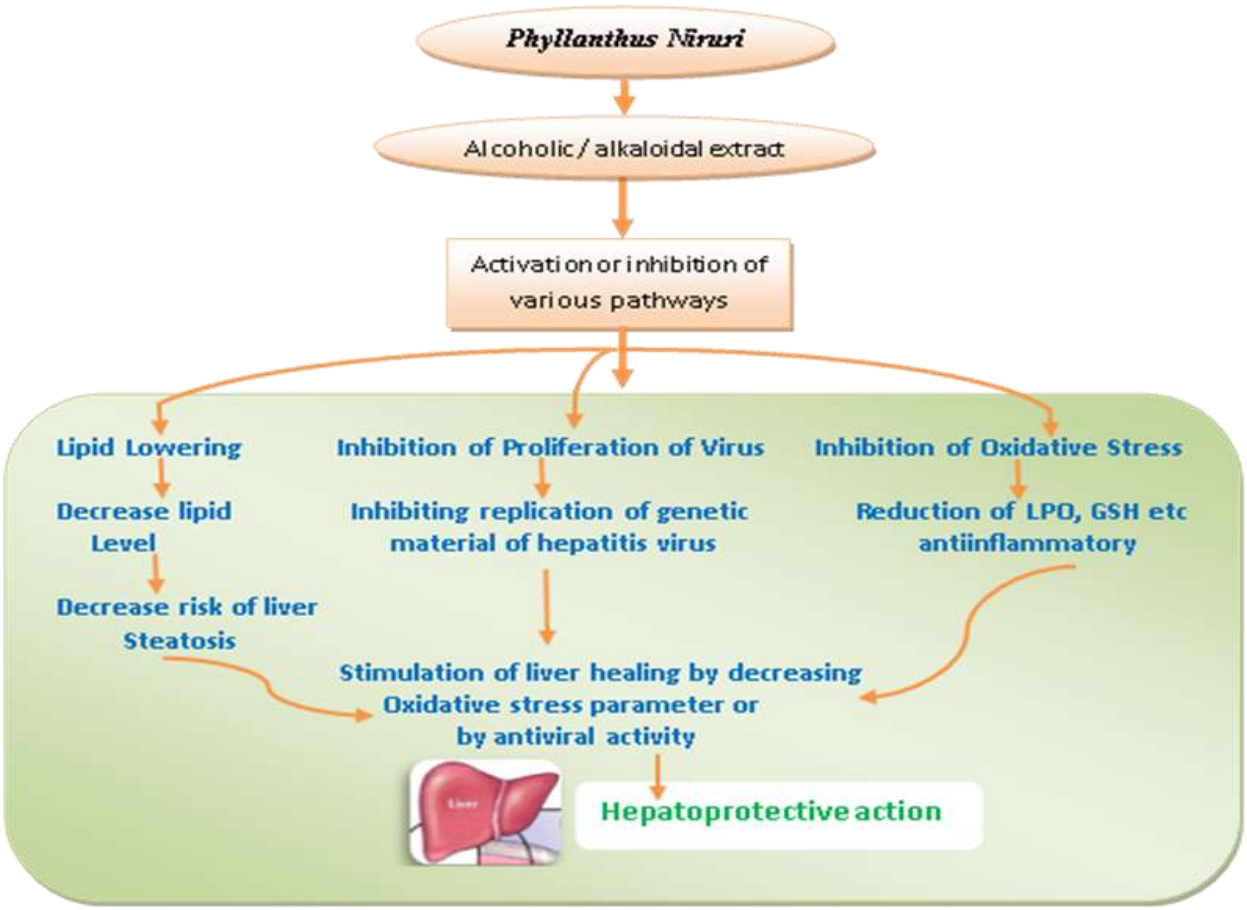


Figure 3: Illustration of mechanism of action of P. niruri Linn. For hepatoprotective activity

The partially purified protein fraction of *P. niruri* was injected i. p. in mice either prior to (preventive) and levels of different liver marker enzymes in serum and different antioxidant enzymes, as well as lipid peroxidation in total liver homogenates were measured. *P. niruri* significantly reduced the elevated glutamate pyruvate transaminase (GPT) and alkaline phosphatase (ALP) levels in the sera of toxicity induced mice, compared with the control group which shown their antioxidant potential. Lipid peroxidation levels were also reduced in mice treated with *P. niruri* protein fraction compared with the APAP (acetaminophen) treated control group. Among the antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST) levels were restored to almost normal levels compared with the control group. *P. niruri* treatment also enhanced reduced hepatic glutathione (GSH) levels caused by APAP administration. The results demonstrated that the protein fraction of *P. niruri* protected liver tissues against oxidative stress in mice, probably acting by increasing antioxidative defensive [28].

Pharmacological studies demonstrated its prooxidant-antioxidant system of liver and the hepatoprotective potential of aqueous extract of the herb *P.niruri*on NIM (Nimusulide)-induced oxidative stress *in-vivo* using a murine model and by determining the activities of hepatic anti-oxidant enzymes superoxide dismutase (SOD) and catalase (CAT), levels of reduced glutathione (GSH) and lipid peroxidation (malonaldialdehyde, MDA). Aqueous extract of *P. niruri* (50 or 100 mg/kg body weight)has shown antioxidant action against NIM-induced oxidative stress in the liver [29, 30]. Methanolic and aqueous extract of leaves and fruits of *P. niruri* showed inhibition of membrane lipid peroxidation (LPO), scavenging of 1, 1-diphenyl-2picrylhydrazyl (DPPH) radical and inhibition of reactive oxygen species (ROS) *in-vitro.* Antioxidant activity of the extracts was also demonstrable *in vivo* by the inhibition of the carbon tetrachloride ($CCl_4$)-induced formation of lipid peroxides in the liver of rats by pretreatment with the extracts. $CCl_4$–induced hepatotoxicity in rats, as judged by the raised serum enzymes, glutamate oxaloacetate transaminase (GOT) and glutamate pyruvate transaminase (GPT), was

prevented by pretreatment with the extracts, demonstrating the hepatoprotective action of *P. niruri* [31].

The aqueous extracts of leaves showed inhibition against thio-barbituric acid-reactive species (TBARS), induced by different pro-oxidants (10 gm. $FeSO_4$ and 5 µM sodium nitroprusside) in rat liver, brain and kidney homogenates. The hepatoprotective activity of the extracts were also demonstrated in vivo against paracetamol-induced liver damage, as evidenced by the decrease in serum glutamate oxaloacetate transaminase (GOT), and glutamate pyruvate transaminase (GPT), and increased catalase activity in the liver in treatment groups, compared to the control[32].

The protective role of a 35 KD protein (PNP) isolated from this herb against iron-induced cytotoxicity in murine hepatocytes. Exposure of hepatocytes to iron ($FeSO_4$) caused elevation of reactive oxygen species (ROS) production, enhanced lipid peroxidation and protein carbonylation, depleted glutathione levels, decreased the antioxidant power (FRAP) of the cells and reduced cell viability however this was reverse in the case of PNP treatment by providing protection to the cells from apoptosis and by stabilizing the mitochondria and arresting the release of cytochrome c. It also suppressed caspase activation and cleavage of PARP. Moreover, this protein has strong free radical scavenging activity and thereby scavenged ROS extensively [32].

**5.4 Anti-cancerous and cellular protective actions**

*P.niruri* has high potential to inhibit the growth and initiation of cancerous cells which were introduced into mouse skin cells with 7, 12 dimethyl benz (a) anthracene (100µg/100ml acetone) and croton oil (1%) and there is significant increase in the catalase, reduced glutathione and protein levels in the skin.*P.niruri* extract show inhibitory action for cancerous cells with good therapeutic efficacy [33].

**5.5 Lipid lowering activity**

Anti hyperlipidemic activity of *P.niruri*alcoholic extracts in triton induced hyper-lipidaemia was examined in rats. In an experiment with cholesterol fed rats, *P. niruri* at a dose of 100 mg/kg lowered the elevated level of low-density lipoprotein lipids in hyperlipidemia experimental animals [34].

**5.6 Antimalarial activity**

The ethanolic, dichloromethane and lyophilized aqueous extracts of *Cassia occidentalis* root bark, *Morindamorindoides* leaves and whole plants of *P.niruri* were evaluated for their antimalarial activity in vivo, in 4-day, suppressive assays against *Plasmodium berghei* ANKA in mice. No toxic effect or mortality was observed in mice treated, orally, with any of the extracts as a single dose, of 500 mg/kg body weight, or as the same dose given twice weekly for 4 weeks (to give a total dose of 4 g/kg). The most active ethanolic extract, that of *P.niruri*, reduced parasitaemia by 73%. Each lyophilized aqueous extract was less active than the corresponding ethanolic extract [35].

**5.7 Anti-fertility activity**

One of the scientific data demonstrated that *P. niruri*shows anti-fertility activity by reducing fructose levels of seminal fluids, sperm count, sperm motility and viability in male albino rats. It shows anti fertility activity by decreasing the testosterone levels of the treated rats[36].

**5.8 Anti-microbial activity**

The ethanolic extracts of dried *P.niruri* inhibited the growth of micro-organisms (food borne & spoilage micro-organisms) [37]. The antimicrobial activity of fermented *P.niruri* by using lactobacillus isolated from the surface of the plant was enhanced. The antimicrobial activity was enhanced 80-170 % when compared to the crude extract. The potency was increased by 49% when the extract was fermented with lactobacillus [38]. The methanol extract of *P. niruri* is strong against *Bacillus pumillus, Bacillus ceraus, E. coli* and *Vibrio cholera* at concentration of 750µg/ml/disc. It is tested against standard drug chloramphenicol at concentration 10µg/ml/disc shows potential source of antimicrobial agent [39]. The *P.niruri* extract of alkaloids were tested on rabbits infected with *E. Coli*. The results examined were found to have increased concentration of WBC, neutrophils and decreased hemoglobin, lymphocytes more over there are no changes in enzyme concentration. The antibacterial efficiency of the methanolic extract of *P.niruri* was investigated against pathogenic bacteria responsible for common infections of skin, and urinary and gastrointestinal tracts.

The extract demonstrated antibacterial activities against all the Gram-positive and Gram-negative bacteria tested. The results obtained suggested that at higher concentrations the extract would eradicate the growth of bacterial cells. The bacterial cells, after exposure to the extract, showed complete alteration in their morphology, followed by collapse of the cells beyond repair. The study revealed that the methanolic extract of *P. niruri* may be an effective antibacterial agent to treat bacterial infections since the extract exhibited significant antimicrobial potency, comparable with that of the standard antibiotic chloramphenicol [40, 41].

**5.9 Anti-hepatitis activity**

*P.niruri* has been reported to exhibit marked anti-hepatitis B virus surface antigen activity in *in-vivo* and *in-vitro* studies. Infectious hepatitis is due to the inability of the body's immune system to eliminate the virus from the liver cells. An infection with the virus is documented by detectable levels of various viral antigens in the blood, including HbaAg (the surface antigen of the virus) as well as antibodies to the core of virus (HBc antibodies). In one of the clinical trial study, 37 patients with chronic viral hepatitis B were treated with a daily dose of 600mg of Phyllanthusniruri for 30 days. 59% of the patients lost the HBsAg two weeks after the end of the treatment. The authors postulated that *P.niruri* might inhibit proliferation of the virus by inhibiting replication of the genetic material of the virus [42].The experimental data demonstrated that nirtetralin B isolated from *P.niruri* extract exhibits anti-hepatitis B virus activity both in vitro and in vivo [43].

**5.10 Anti-HIV effect**

Aqueous extract of *P.niruri*is reported to have inhibitory effect on human immunodeficiency virus. The scientific investigation examines the anti-HIV effects of the alkaloidal extract of *P. niruri* in human cell lines and inhibitory effect on HIV replication was monitored in terms of inhibition of virus induced cytopathogenecity in MT-4 cells. The alkaloidal extract of *P.niruri* showed suppressing activity on strains of HIV-1 cells cultured on MT-4 cell lines. The CC50 for the extract was found to be 279.85 µgmL-1 whereas the EC50 was found to be 20.98 µgmL. Interestingly the Selectivity Index (SI) was found to be 13.34, which showed a clear selective toxicity of the extract for the viral cells [44].P.*niruri* are responsible for the reported inhibitory effect of its aqueous extract on HIV. The literature reviews have examined anti-HIV effects of the alkaloidal extract from *P.niruri* on human cell lines. An alkaloid extract of *P.niruri* showed suppressive activity on strains of HIV-1 cultured on the huT-4 cell line [45].

**6. Toxicology**

*P.niruri* is low toxic, and it showed toxicity to batrachians and fishes when extract is alcohol and water based. It is very less toxic to mammals. The study was carried out to determine toxicity on administered the aqueous leaf extract of *P. niruri* to female Sprague-Dawley rats. Fifteen female rats weighing 150–200 g were divided into 3 groups [46, 47]. Rats in Group 1 were given a single low dose (LD) of 2000 mg/kg b.w. of the extract by oral gavage within 24 hrs. Rats in Group 2 were given a single high dose (HD) of 5000 mg/kg b.w. of the extract by oral gavage within 24 hrs. Rats in Group 3 were not given any extract but drinking water and served as the control group (C). All the rats were observed for signs of toxi-dromes for 14 days. On the 15th day, all the rats were sacrificed [46]. Body organs were harvested for macroscopic examination. Urine and blood samples were drawn and analyzed. Hematological tests performed included full blood count and hemoglobin. Biochemical examinations included bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, albumin, globulin, alkaline phosphates (ALP), γ-glutamyltrans peptidase (GGT), urea, and creatinine. The results of the three groups were not significantly different. Examination of the various body organs did not show any abnormality. Thus no toxicity was observed at the levels administered. The LD50 of the aqueous extract is > 5000 mg/kg. b.w [46, 47, 48].

**7. Contraindications**

- *P. niruri*has demonstrated hypotensive effects in animals and humans. People with a heart condition and/or taking prescription heart medications should consult their doctor before taking this plant. It may be contraindicated for some individuals with heart conditions and/or

heart medications may need monitoring and adjusting.

- *P. niruri* has been considered in herbal medicine to be abortive (at high dosages) as well as a menstrual promoter. While not studied specifically in humans or animals, animal studies do indicate it has uterine relaxant effects. It should therefore be considered contraindicated during pregnancy.
- *P. niruri* has been documented with female antifertility effects in one mouse study (the effect was reversed 45 days after cessation of dosing). While this effect has not been documented in humans, the use of the plant is probably contraindicated in women seeking pregnancy or taking fertility drugs. This effect has not been substantiated sufficiently to be used as a contraceptive, however, and should not be relied on for such.
- *P. niruri*has demonstrated hypoglycemic effects in animals and humans. It is contraindicated for people with hypoglycemia. Diabetics should consult their doctor before taking this plant as insulin medications may need monitoring and adjusting.
- *P. niruri*has been documented in human and animal studies with diuretic effects. Chronic and acute use of this plant may be contraindicated in various other medical conditions where diuretics are not advised. Chronic long-term use of any diuretic can cause electrolyte and mineral imbalances; however, a human study with P. niruri (for up to three months of chronic use) has not reported any side effects. Consult your doctor if you choose to use this plant chronically for longer than three months concerning possible side effects of long term diuretic use [48,49].

### 7.1 Drug Interactions

- May potentiate insulin and antidiabetic drugs.

- This plant contains a naturally-occurring phytochemical called geraniin. This chemical has been documented with negative chronotropic, negative inotropic, hypotensive and angiotensin-converting enzyme inhibitor effects in animal studies with frogs, mice and rats. As such, this plant may potentiate antihypertensive drugs, beta-blocker drugs and other heart medications [50].

## Conclusion

*P. niruri*is spread throughout the tropical and subtropical countries of the world and widely accepted as a good traditional medicine for the treatment of various disorders and is recommended for bronchitis, anemia, leprosy, asthma, urinary disorders etc. *P.niruri*has several bioactive molecules such as lignans, phyllanthin, hypophyllanthin, flavonoids, glycosides, tannins, alkaloids, ellagitannins, tri-terpenes, phenyl propanoids, steroids, ricinolic acid, niruriside and phyltetralin. *P.niruri* is used as a conventional medicine for treating kidney stones, gallbladder stones, liver related diseases such as liver cancer & jaundice, apart from these it also shows anti-inflammatory, anti-tumor, anti-nociceptive and anti-oxidant properties. The pleiotropic effect of *P.niruri*directly demonstrated that it is largely accepted for the preparation of different kind of pharmaceutical formulations with good therapeutic approach. *P. niruri*has been marketed by major companies and could be further explored in near future as a source of useful herbal formulations.

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## Disclosure Statement

No competing financial interest exist

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