

## Review on Antimicrobial Screening of Phyllanthus Niruri against Pathogen Responsible For Uti and Its Pharmacological Profile

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**ABSTRACT:** One of the diseases that occur most frequently in hospitals is a urinary tract infection (UTI) but the microbes that cause UTI vary in their susceptibility from continent to continent and occasionally. Phyllanthus niruri Linn., a tiny plant with numerous medicinal uses that is a member of the Euphorbiaceae family, is grown all over the world. It is used in the Indian ayurveda system to treat diabetes, chest pain, ulcers, skin problems, and urinary difficulties. The genus Phyllanthus has been used in traditional medicine for its wide range of pharmacological activities like antimicrobial, antioxidant, anticancer, anti-inflammatory, antiplasmodial, antiviral, diuretic and hepatoprotective. P. niruri has been found to contain active phytochemicals such as flavonoids, alkaloids, terpenoids, lignans, polyphenols, tannins, coumarins, and saponins. This review summarizes the information about morphological, biochemical, pharmacological, biological and toxicological activities with special emphasis on mechanism of anticancer activity of P. niruri. Previous research gaps, such as P. niruri's taxonomic inconsistency, novel phytochemicals and their therapeutic properties, particularly mechanisms of anticancerous activity and market products, have been addressed.

**KEYWORD:** Phyllanthus niruri, Phytochemistry, Hepatoprotective, Antiviral, Phytochemical Analysis.

### I. INTRODUCTION

The second most common infection is urinary tract infection (UTI). Worldwide about 160 million people are infected with urinary tract infection every year costing more than 7 billion US dollars. Escherichia coli is the most common clinical isolate in both outpatients and inpatients, accounting for 75 to 95 percent of uncomplicated UTI isolates. Outpatients are less likely to be infected with Klebsiella, Proteus, Pseudomonas, Enterococcus, and Enterobacter sp<sup>[1]</sup>.

urinary tract infection (UTI) is a critical health problem affecting millions of people every year.

A urinary tract infection (UTI) is an infection that affects the urinary system or a portion of it. It's called a bladder infection (cystitis) when it affects the lower urinary system, and a kidney infection when it affects the upper urinary tract (pyelonephritis)<sup>[2]</sup>. Lower urinary tract infection symptoms include urination pain, frequent urination, and the need to urinate despite having an empty bladder<sup>[3]</sup>. Fever and flank pain are common signs of a kidney infection, in addition to the symptoms of a lower UTI. Urine might very well frequently seem bloody. Symptoms in the elderly and young can be vague or non-specific<sup>[2]</sup>.

Escherichia coli is the most common cause of illness, however other bacteria or fungus can also cause infection. Risk factors include female anatomy, sexual intercourse, diabetes, obesity, and family history. UTIs are not categorized as sexually transmitted infections, ignoring the fact that sexual intercourse is a risk factor<sup>[4]</sup>. UTIs are treated with a short course of antibiotics in uncomplicated instances<sup>[5]</sup>. Many of the medications used to treat this illness are becoming increasingly resistant<sup>[6]</sup>. Antibiotics are rarely needed in people who have bacteria or white blood cells in their urine but no symptoms, although there is an exception during pregnancy<sup>[7]</sup>. A brief course of antibiotics can be taken as soon as symptoms appear, while long-term antibiotics can be administered as a prophylactic precaution in many get infections frequently<sup>[8]</sup>.

The plant kingdom is a treasure trove of potential medications, and there has been a growing understanding of the relevance of medicinal plants in recent years. Plant based medicines are widely available, less expensive, safe and effective, and have few side effects. One of the necessary steps in determining the chemical ingredients that lead to the isolation of bioactive chemicals is phytochemical screening. Various

bioactive phytoconstituents have been identified and described since the mid-nineteenth century. They were known to show the medicinal activity as well as physiological activity<sup>[9]</sup>. Plant-derived biomolecules have been found to be effective in the control of even resistant bacteria and human infections, and their usage has been scientifically validated. Many of these are utilised as active ingredients in modern medicine or as lead compounds in the development of new drugs that's are effective in urinary tract infection (UTI)<sup>[10]</sup>.

Developing a medicinal plants business in India's many states has become a major concern. Tamil Nadu, and Sikkim one of the southern states, has been dubbed the "Herbal State" by many stakeholders in the medicinal plant industry. Traditional medicine has received little attention in modern research and development, and less effort has been made to enhance the profession, despite its enormous contribution to society<sup>[11]</sup>. A number of researchers in the field have looked at the antibacterial capabilities of plants. Antibiotics of microbiological origin and other chemotherapeutic drugs have been used to treat bacterial infections for decades. However, many harmful bacteria have acquired resistance to many of the currently available antibiotics as a result of indiscriminate use of these medications<sup>[12]</sup>.

The Euphorbiaceae family contains about 300 genera and 5000 species worldwide. The *Phyllanthus* genus is one of the many genera that make up this massive family. Around 750-800 species of *Phyllanthus* can be found in tropical and subtropical locations around the world<sup>[13]</sup>. *Phyllanthus niruri* is an erect annual herb, it reaches a height of 50–70 cm (20–28 in) and has rising herbaceous branches. The bark is bright green and smooth. It produces a large number of pale green flowers that are frequently flushed with crimson. The fruits are seed-filled capsules that are small and silky. Traditional medicine has utilized *Phyllanthus niruri* to treat a variety of ailments, including urinary blockage and urinary tract infection<sup>[14]</sup>. *Phyllanthus niruri*, also known as gale of the wind, stonebreaker, or seed-under-leaf, is a common tropical plant found in coastal locations. It belongs to the *Phyllanthus* genus in the *Phyllanthaceae* family. Lignans, flavonoids, triterpenes, sterols, alkaloids, and essential oils are found in this plant.

### 1.1 PHYLLANTHUS NIRURI'S BOTANICAL DESCRIPTION

*Phyllanthus niruri* is an erect annual plant that grows to a height of 40 to 70 cm and has ascending herbaceous branching. It is hairless and branches at the base. Because the flower and fruit can be connected with the leaf, the genus *Phyllanthus* means "leaf and flower." It's a plumose leaf with flower and fruit on it.

- **LEAVES**

They are distributed alternately on each side of the stem and are small, green, sub sessile, tightly arranged, elliptic along shaped, obtuse, with short petiole and stipules.

- **FLOWERS**

The flowers are yellowish, tiny, axillary, and abundant. These flowers are monoecious and unisexual, with male blooms having 1-3 sessile stamens and female flowers being solitary.

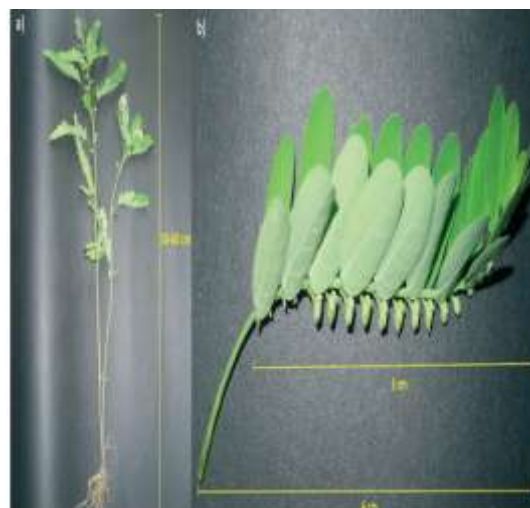


FIGURE:1 PHYLLANTHUS NIRURI<sup>[15]</sup>

- **FRUITS**

Fruit is a capsule, extremely small, depressed globose, and smooth, with a diameter of 2-3mm.

- **STEM**

It has horizontal branches with a height of 30-60cm and a width of 1-2.5mm.

- **ROOT**

It has a branching structure and is quite huge. Botanical classification is described in table 1.

TABLE: 1 BOTANICAL CLASSIFICATION: PHYLLANTHUS NIRURI<sup>[16]</sup>

Kingdom	Plantae
Division	Eukaryota
Class	Magnoliopsida
Order	Euphorbiales
Family	Euphorbiaceae

Genus	Phyllanthus
Species	Niruri

## II. P. NIRURI AS A MEDICINAL PLANT

In herbal medicine systems like Indian Ayurveda, Traditional Chinese Medicine, and Indonesian Jammu, *P. niruri* has a long history of use. Numerous conditions, including dysentery, influenza, vaginitis, tumors, diabetes, diuretics, jaundice, kidney stones, and dyspepsia, are treated using the entire plant. Hepatotoxicity, hepatitis B, hyperglycemia, and bacterial and viral illnesses can all be treated with the herb<sup>[17]</sup>.

Hepatotoxicity, hepatitis B, hyperglycemia, and bacterial and viral illnesses can all be treated with the herb<sup>[43]</sup>. *P. niruri* has been utilized in Ayurvedic medicine for more than 2000 years and has a variety of traditional uses for diabetes, gonorrhoea, jaundice, and frequent menstruation. In Jammu, a well-known traditional

herbal remedy used in Indonesia to cure a variety of ailments, is a significant medicinal plant. The herb is employed as a hepatoprotective and antiviral agent in jamu preparations. *P. niruri*, also known as Dukong anak in Malaysia, is taken internally for coughs, gonorrhoea, kidney diseases, and diarrhea<sup>[18]</sup>.

The leaves and fruit have been used to treat gallstones and jaundice in traditional medicine systems such as Ayurvedic and Unani medicine. In Malay traditional medicine, *P. niruri*, vernacularly known as 'dukong anak', is used for kidney disorders and cough<sup>[18]</sup>. In South India, where the herb is known as Bhumyamalaki, it is thought to treat constipation, gonorrhoea, and syphilis<sup>[17]</sup>. This herb, known locally as 'pitrishi,' has gained a reputation in northern India as a home remedy for asthma, bronchitis, and even tuberculosis<sup>[19]</sup>. In cases of chronic dysentery, the young shoots of this herb may be used as an infusion<sup>[20]</sup>.

### 2.1 PHYTOCHEMICAL ANALYSIS

Ramandeep and colleagues discovered the various phytochemicals listed below in table 2 in the year 2017.

**TABLE 2: PHYTOCHEMICAL SCREENING OF PHYLLANTHUS NIRURI PLANT EXTRACT**<sup>[51]</sup>

No	Phytochemicals	Method	Observation
1	Saponins	Emulsion formation test	Formation of emulsion
2	Alkaloids	Mayer's reagent test	No characteristic changes
3	Phenols	Ferric chloride test	Blue colored appears
4	Terpenoids	Sulfuric acid test	Reddish brown color
5	Flavonoids	Ammonia test	Yellow color disappeared on standing

Shilpa and her colleagues discovered the phytochemicals listed in table 3 in 2018.

**TABLE 3: PHYTOCHEMICAL SCREENING OF PHYLLANTHUS NIRURI IN DIFFERENT EXTRACTS**<sup>[26]</sup>

Phytochemical	Aqueous extract	Methanolic extract	Ethanol extract
Alkaloids	+	+	+
Saponins	+	+	+
Phenols	+	+	+

<b>Flavonoids</b>	+	+	+
<b>Terpenoids</b>	-		+

In 2011, Paithankar and colleagues discovered the various phytochemicals listed in table 4 below.

**TABLE-4 CHEMICAL CONSTITUENTS PRESENT IN DIFFERENT PART OF PLANT** <sup>[50]</sup>

ROOT	Leaf, stem	Aerial parts	leaf	Essential oil
1.Lupeol, Rt 12.Nor-securinine, Rt 2.(+)Gallocatechin, Rt Cult 3.(-) Epigallocatechin, Rt Cult 4.(-)Epicate chin-3-gallate, Rt Cult 5. (-)Epicate chin, Rt Cult 6. Gallic acid, Rt cult 7. (-)Epigalloca techin-3-Ogalla te, Rt Lrhamnoside, Rt 8. Fisetin-41-Oalpha-L-rhamo nicide, Rt 9. Lupeol acetate, Rt 10 (+)-Catechin, Rt cult	1.Phylochrysin, Lf, St 2.Rutin, Pl, Lf 3. Phyllanthine, Rt, Lf, St 4. Quercetin, Lf, Pl 5. Nirtetralin, Pl, Lf 2.4-Methoxy-nor securinine, Aer, Rt, St	1.Dotriacontanoic acid, Aer 2.Nirphyllin, Aer 3.Phyllanthin, Aer 4.Phyllin, Aer 5.Phyllinurin, Aer 6.Phylltetrin, Aer 7.Triacontan-1-al, Aer 8.Triacontan-1-ol, Aer 9.Nirurine, Aer 10. 24-Isopropyl Cholesterol, Aer	1. 2,3-dimethoxy-isolintertralin, Lf 2. 4 Hydroxylintertralin, Lf 3. Astragalin, Lf 4. Beta sitosterol, Lf 5.Demethylenedioxy niranthin, Lf 6. Hydroxy niranthin, Lf 7.Lintetralin, Lf 8.Niranthin, Lf 9.Quercitrin, Lf 10.Salicylic acid methyl ester, Lf EO 11.Seco-4-hydroxylintertralin 12. Hypophyllanthin, Lf Aer 13. Iso-quercetin, Lf 14. Linnanthin, Lf	1. (-) Limonine, Lf EO 4.5% 2. Ascorbic acid, Lf 0.41% 3. Linoleic acid, Sd Ol 21% 8. Linolenic acid, Sd Ol 51.4% 4.Ricinoleic acid, Sd Ol 1.2% 5.Phylltetralin, Pl, Lf 0.14% 6.&Phyllanthin, Lf, Aer 7. Kaempferol-4-o-alpha-L-rhamnoside, Aer 0.9%, Rt 8. Cymene, Lf EO 11% 5. Hypophyllanthin, Pl 0.05-0.17% 9. Geranin, Pl .23%

### III. PHARMACOLOGICAL ACTIVITY

#### • ANTI MICROBIAL ACTIVITY OF PHYLLANTHUS NIRURI

The development of microorganisms was spoiled by P. niruri and Piper beetle extracts were tested for food suppression by ethanolic extracts of dried P. niruri<sup>[21]</sup>. Lactobacillus isolated from the plant's surface was used to boost the antibacterial activity of fermented P. niruri. When compared to the crude extract, the antibacterial activity was increased by 80-170 percent. When the extract was fermented with lactobacillus, the potency was raised by 49%<sup>[22]</sup>.

The methanol extract of P. niruri is strong against Bacillus pumillus, Bacillus cereus, E. coli and Vibrio cholera at conc of 750µg/ml/disc. It was compared to the conventional medicine

chloramphenicol at a concentration of 10g/ml/disc, indicating that it could be a source of antibacterial agent<sup>[23]</sup>.

On rabbits infected with E. coli, Phyllanthus niruri extracts of alkaloids were studied. WBC, neutrophils, and Haemoglobin, as well as lymphocytes, were found to have increased concentrations, but enzyme concentrations remained unchanged<sup>[24]</sup>.

#### • ACTION OF KIDNEY STONES & URIC ACID

The creation, nucleation, development, and aggregation of calcium oxalate crystals in the kidney is a prevalent condition that includes urinary calculi formation, nucleation, growth, and aggregation. Phyllanthus niruri extract inhibits the growth and aggregation of calcium oxalate [CaOx] crystals in calculi. In male wister rats' urine

samples, the extract prevents CaOx crystal aggregation in the early phases of stone formation. It's best to deal with stone formation as soon as possible<sup>[27]</sup>. The treatment of *P. niruri* [5% [v/v]] extract decreased the CaOx metastable limit, and it can also prevent the production of CaOx crystals and nucleation<sup>[28]</sup>.

The extract has the ability to stop calculi from growing and change the shape and texture of calculi. It can form a matrix-like material on the surface of prepared calculi and change the appearance and texture of the calculus when handled<sup>[29]</sup>. The extract is also given to hypercalcemic patients to help lower calcium levels in the urine<sup>[22]</sup>. Lignans with uricosuric activity in the extract also decrease excess uric acid in hypouricemic patients<sup>[30]</sup>.

#### • LIVER PROTECTIVE, DETOXYFICATION & ANTIOXIDANT ACTIVITY

The *P. niruri* hexane extract can reduce the cytotoxicity caused by carbon tetrachloride and galactosamine in rat hepatocytes. Phyllanthin and hypophyllanthin protect against cell lesions caused by CCl<sub>4</sub> and hepatotoxicity caused by GalN<sup>[31]</sup>. Nimesulide-induced hepatic damage can be lessened by *Phyllanthus niruri*. It was discovered that the levels of three enzymes, glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, and alkaline phosphatase, are reduced in the extract treated group by measuring their levels in serum. Based on these findings, intraperitoneal treatment was shown to be more effective than oral delivery, and we may conclude that *P. niruri* protects the liver against nimesulide-induced liver damage by combining these findings<sup>[32]</sup>.

Hepatotoxicity is caused by taking too much paracetamol, just like a viral infection. In the *P. niruri*-treated group, serum glutamic pyruvic transaminase levels were lower<sup>[33]</sup>. In rats, serum glutamate pyruvate transaminase and glutamate oxaloacetate transaminase levels were reduced in *in vivo* experiments<sup>[34]</sup>.

Higher dosages of alcohol are hazardous, and when combined with polyunsaturated fatty acids, they cause oxidative stress and hepatotoxicity [35]. *P. niruri* extract, as determined by the antioxidant potentials of liver enzymes and histological tests, can effectively lower this<sup>[36]</sup>.

#### • ANTI-INFLAMMANTORY, ANTI-SPASMODIC, AND PAIN-RELIEVING

The ability of *Phyllanthus niruri* to cure wounds when applied topically and orally has been

assessed. It has been demonstrated that *P. niruri* plays a substantial part in wound contraction and epithelialization. When the extract was administered topically and orally to rats whose wound healing had been inhibited by dexamethasone, a substantial increase in wound contraction was seen<sup>[37]</sup>.

#### • ANTI CANCEROUS & CELLULAR PROTECTIVE ACTIONS

When 7, 12 dimethyl benzanthracene (100 g/100 ml acetone) and croton oil were used to introduce malignant cells into mouse skin cells, *P. niruri* showed a significant ability to block the growth and initiation of the cancerous cells (1 percent)<sup>[38]</sup>. and there is drastic increase in the catalase, reduced glutathione and protein levels in the skin. The chemopreventive activity of *P. niruri* with DMBA causes cutaneous papilloma genesis in albino mice<sup>[39]</sup>.

#### • ACTIVITY OF P. NIRURI AGAINST HEPATITIS B VIRUS AND HUMAN IMMUNODEFICIENCY VIRUS

Chronic hepatitis B is a major problem of worldwide concern. More than 2 billion people all over the world have been infected by the HBV, and out of these, 400 million people are chronic carriers of the virus. Chronic carriers of infection with HBV are more likely to have impaired quality of life and life expectancy because the disease has the potential to progress and lead to fibrosis, cirrhosis, liver failure and hepatocellular carcinoma after initial infection. It is estimated that annually more than 600 000 individuals die from HBV-related liver disease on a global basis<sup>[54]</sup>. The extract was also found to inhibit woodchuck (Marmotamonax) hepatitis virus (WHV) DNA polymerase by binding to the surface antigen of WHV *in vitro*. The extract was non-toxic to mice and was tested for antiviral activity in woodchucks. A clinical trial on six long-term WHV carrier woodchucks was performed where five treated animals displayed a faster decrease in WHV surface antigen titer than one untreated control. The extract effectively reduced and eliminated surface antigen titer and DNA polymerase activity in serum of infected animals when administered intra-peritoneally. Ten weeks after the discontinuation of treatment, treated animals continue to exist free of detectable markers of WHV up to 45 weeks. The alkaloidal extract of *P. niruri* in tested concentrations also exhibited inhibitory activity against cytopathic effects caused by both the strains of HIV on human MT-4 cells<sup>[55]</sup>.

- **IMMUNE MODULATORY ACTIONS**

When tested with peritoneal mouse macrophages, an arabinogalactan (AG) that was produced from *P. niruri* tea preparations was discovered to have immunological characteristics. Using human stomach juices, the glycoside had the same action in both acidic and neutral gastrointestinal environments. HCL remedy<sup>[40]</sup>.

- **LIPID LOWERING ACTIVITY**

The serum lipid levels can be lowered with *Phyllanthus niruri*. When fed orally to hyperlipemic rats, the extract reduces lipid levels (250 mg/kg b.w.)<sup>[41]</sup>. In tests using Wistar rats, methanol extract of *P. niruri* alterations caused by chlorpyrifos (CPF)-evoked *niruri* was found to be protective against the erythrocyte fragility and lipoperoxidative erythrocyte fragility<sup>[42]</sup>.

- **ANTI FERTILITY ACTIVITY**

When the anti-fertility properties of *Phyllanthus niruri* were examined on male albino rats, the fructose levels of seminal fluids, sperm count, sperm motility, and sperm viability all significantly decreased. By lowering the testosterone levels in the treated rats, it has anti-fertility activity<sup>[43]</sup>.

- **ANTI MALARIAL ACTIVITY**

One of the most significant health issues in tropical and subtropical nations is malaria. The medicinal plants exhibit malaria-repelling qualities. When fed with ethanol extracts, *P. niruri* and *Mimosa pudica* shown antiparasmodial action in albino mice<sup>[44]</sup>. Higher antiparasmodial activity was seen in *P. niruri*'s ethanolic extract of a month-old invitro-grown callus than in extract made from a fresh apical stem extract<sup>[45]</sup>.

- **ANTI ULCER ACTIVITY**

Another polysaccharide and the acidic heteroxylan both exhibited anti-ulcer efficacy. These substances lessened the 65 and 78 percent ethanol-induced stomach lesions. *P. niruri* has demonstrated effectiveness in treating peptic ulcers<sup>[46]</sup>.

- **NEMATOCIDAL ACTIVITY**

*Meloidogyne incognita* and *Rotylenchulus reniformis* were two nematocides that the two prenylated flavones that were extracted from the hexane extract of *P. niruri* exhibited nematocidal efficiency against. The two substances have a moderate amount of nematocidal activity<sup>[47]</sup>.

- **TOXICOLOGY**

The low toxicity of *Phyllanthus niruri* was demonstrated by its toxicity to fish and batrachians in extracts based on alcohol and water. Mammals are not at all poisonous to it.

- **ANTICANCER ACTIVITY OF PHYLLANTHUS NIRURI**

Strategy of chemoprevention is significant in controlling the process of carcinogenesis. Medicinal herbs have shown great potential as chemo preventive agents. Hence, these can be exploited as medicines, which could behave as chemo preventive agents<sup>[48]</sup>. *Phyllanthus niruri* accentuates two-stage skin carcinogenesis in Swiss albino mice models because it extends the formation of cancer in the skin and reduces its multiplicity and yield. This activity of *P. niruri* was due to the fusion of its cytoprotective effect on normal cells and cytotoxic effect on pre-neoplastic and/or neoplastic cells. The notable decrease in the occurrence and number of skin papillomas was attributed to potent phytochemicals, that is, quercetin and rutin. They used a hydroalcoholic extract of *P. niruri* at dose 1000 mg/kg b. wt.<sup>[48]</sup>. Corilagin from *P. niruri* was isolated and investigated for anticancer activity along with the mechanism of action against ovarian cancer cell lines, SKOv3ip<sup>[49]</sup>. The research group reported that corilagin inhibited tumor progression at IC50 values factor  $\beta$ 1/Akt/extracellular signal-regulated kinase (ERK)/Smad signaling pathways. The effect of *P. niruri* extract against human cancer cell lines has been summarized in.

#### IV. CONCLUSION

The plants' widespread use in traditional and complementary medicine for a wide range of diseased conditions has resulted in a large number of scientific studies. The current study confirms that *P. niruri* extracts have pharmacological potential in a wide range of conditions. *Phyllanthus niruri* plant extract, which is also prescribed as medicine, is used to treat conditions such as bronchitis, anaemia, leprosy, asthma, urinary disorders, and others. Lignans, phyllanthin, hypophyllanthin, flavonoids, glycosides, tannins, alkaloids, ellagitannins, triterpenes, phenyl propanoids, steroids, ricinolic acid, niruriside, and phytetralin are also found in *Phyllanthus niruri*. *Phyllanthus niruri* is used to treat diuretic, hypoglycemia, and hypertension, as well as kidney, gallbladder, and liver diseases such as cancer and jaundice. The Euphorbiaceae family has so much potential that it deserves to be studied further.

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