IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
July 2021 Vol.:21, Issue:4

Pharmacological Account: *Phyllantus niruri*

IJPPR
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ISSN 2349-7203
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Submitted: 23 June 2021
Accepted: 30 June 2021
Published: 30 July 2021

Keywords: *Phyllanthus niruri*, Pharmacological Activity, Medicinal Plant

ABSTRACT

The medicinal plant *Phyllanthus niruri* Linn. (Euphorbiaceae), its large range of phytochemicals, and their pharmacological properties are discussed in this analysis. Flavonoids, alkaloids, terpenoids, lignans, polyphenols, tannins, coumarins, and saponins have all been reported as active phytochemicals in *P. niruri***.** Many clinical trials have shown that extracts of this herb have therapeutic effects. Anti-hepatotoxic, Antilithic, Antihypertensive, Anti-HIV, and Anti-hepatitis B are some of the most intriguing therapeutic properties. As a result, research into the chemical and structural properties of the bioactive phytochemicals found in *P. niruri* is required many phytochemicals have shown preclinical therapeutic efficacies for a wide range of human diseases, including HIV/AIDS and hepatitis B. are very useful for more research on this plant.[1.3]

INTRODUCTION:

Nature has produced a plethora of natural sources of conventional medicines that have been used as cures for a variety of ailments and diseases for many years. Natural product databases have registered more than 200.000 compounds from almost every part of the world among the broad variety of living organisms available on Earth, including higher plants, animals, fungi, and marine organisms. Plants have a variety of functions. Plants have been the source of medicinal compounds that has been researched the most. One of the ancient Egyptian scripts (2600 BC) mentions the use of plants as the main constituents of conventional medicines (pills, infusions, and ointments). Furthermore, several manuscripts pertaining to the prescription of various herbal medicines were documented by ancient Chinese scientists (100 BC) and Greek physicians (100 AD). Later, in the eighth century, Avicenna, a popular Persian scientist, established and implemented the foundations of modern-day pharmacy and medicine science for the first time, with a focus on the application of plant-derived medicine.

Natural compounds are secondary metabolites generated by an organism, with several of these metabolites being found to be specific to that organism. They may not be necessary for metabolism, but they may be related to environmental adaptation or as a potential protection mechanism for the organism's survival. Due to its broad range of therapeutic uses in traditional medicine, *Phyllanthus niruri* L is one of the most common natural herbal *remedies* for many symptoms. All hemispheres' tropical and subtropical areas Traditional medicine has used the Phyllanthus genus for its wide variety of pharmacological activities, such as antimicrobial activity. *Phyllanthus niruri*, a small annual herb found throughout, is an antioxidant, anticancer, anti-inflammatory, anti-plasmodial, antiviral, diuretic, and hepatoprotective member of the Euphorbiaceae family.[2]

In traditional South and Southeast Asian medicine, a wide variety of diarrhoea, dyspepsia, and genitourinary diseases, including but not limited to jaundice, are treated. *Phyllanthus niruri* is a tropical annual shrub that has been used to treat kidney stones and infections. Preparations of *P. niruri* are used as folk remedies for renal and vesicular calculi in Brazil, where the plant is known as "Chanca Piedra" or "stone breaker." Gallstones and jaundice have been treated with leaves and fruit in traditional medicine systems such as Ayurvedic and Unani medicine. *P. niruri*, also known as dukonganak in Malay, is used to treat kidney problems and cough in Malay traditional medicine.[4] The herb is believed to treat constipation, gonorrhoea, and syphilis in South India, where it is known as Bhumyamalaki.

This plant, locally known as 'pitirishi,' has developed a reputation in northern India as a home remedy for asthma, bronchitis, and even tuberculosis. In cases of chronic dysentery, the young shoots of this herb may be used as an infusion. *P. niruri,* also known as ‘zhu zi cao,' has long been used in traditional Chinese medicine to treat liver damage caused by a variety of hepatotoxic agents. Indeed, after the landmark animal research by Venkateswaran and colleagues, which demonstrated for the first time *in vivo* the possible antihepatitis B activity of *P. niruri,* this herb has piqued scientific interest, resulting in a slew of studies examining its therapeutic potential**.**[6]

Phytochemical studies on this plant have shown that it is rich in tannins, flavonoids, alkaloids, terpenes, coumarins, lignans, and phenylpropanoids, dating back to 1861 when Ottow isolated the lignan phyllanthin and as recently as the isolation of possible anti-HBV phytochemicals nirtetralin and niranthin, which are responsible for the pharmacological activity of *P. niruri*. The following table lists the different compounds that have been isolated from this herb for research purposes. Despite its broad variety of ethnomedicinal applications, most of these possible therapeutic applications have yet to be researched to the point of clinical trials. In reality, there is a lack of coordination when it comes to the current state of knowledge in *P. niruri* study. The heterogeneity of primary studies on *P. niruri* has also made it difficult to determine the plant's potential objectively, and the mechanisms underlying much of the herb's therapeutic activity are still unknown. *P. niruri* may be a promising drug candidate, as natural products derived from plants are still essential sources of novel therapeutic agents and chemical entities. Furthermore, the previous overreliance on combinatorial chemistry, which does not always produce large and pharmacologically viable libraries, has reemphasized the value of investigating natural products. Exploration of these natural products could lead to the creation of novel natural product-like libraries, which, when combined with the use of high-throughput screening assays, could yield new drug candidates for further growth.[8] The therapeutic potential of common, multipurpose herbs such as *P. niruri* offers more accessible and affordable drugs that not only target a wide variety of chronic diseases but also have fewer side effects than synthetic agents. To allow for more precise future targeting Research on this plant must be harnessed, scientific evidence must be consolidated, and any information gaps must be resolved. The aim of this review is to summarize and compile the existing state of scientific evidence on the pharmacological properties of *P. niruri* available on PubMed from 1980 to 2015. It will define areas for further advancement of this herb as a cost-effective supplement or even a novel alternative

therapeutic agent, as well as include information about how to get started and future research in the development of new *Phyllanthus* based drugs.

Pharmacognosy of *Phyllanthus niruri*:

Phyllanthus niruri L is a small-size indigenous plant (shown in Figure 1.1) that grows in tropical and subtropical areas, such as South America, Africa and Asia, including Indonesia (Calixto *et al.*, 1998, Mellinger *et al*., 2005, Elfahmi *et al*., 2006). It has small solitary, auxiliary and apetalous off-white-greenish flowers and green leaves that are up to 7-12 cm in length (Bagalkotkar *et al*., 2006). Different names are given to *Phyllanthus niruri* L, such as Chanca Piedra in Spanish, QuebraPedra in Brazil, Pitirishi in India, and Meniran in Indonesia.[10]

Figure No. 1: Whole plant of *Phyllanthus niruri* L

Kingdom - Plantae

Clade - Tracheophytes

Clade - Angiosperm

Clade - Eudicots

Chemical constituents of P*hyllanthus niruri*:

Table No. 1(a): Chemical constituents of *Phyllanthus niruri*

Class	*Compound*	*Activities*	*Reference*
Alkaloid	Nor-securinine	Anti-fungal	(Joshi et al., 1986) (Sahni et al., 2005)
	4- (Methoxy-d3) securinine		(Mulchandani and Hassarajani, 1984)
	Nirurine		(Petchnaree et al., 1986)
Coumarin	Ellagic acid	Aldose reductase inhibitor, ACE-inhibitor	(Ueno et al., 1988, Shimizu et al., 1989)
	Methyl brevifolincarboxylate	Vasorelaxan, anti-platelet	(Iizuka et al., 2007) (Iizuka et al., 2005, Than et al., 2006)
	Brevifolin carboxylic acid	Aldose reductase inhibitor	(Shimizu et al., 1989, Ishimaru et al., 1992, Than et al., 2006]
	Ethyl Brevifolin carboxylate	Aldose reductase inhibitor	(Shimizu et al., 1989)
Flavonoid	Rutin	Hepatoprotective	(Sabir and Rocha, 2008) (Janbaz et al., 2002) (Colombo et al., 2009)
	Quercetin		(Subeki et al., 2005, Than et al., 2006]
	Quercitrin		(Sabir and Rocha, 2008)
	Astragalin		(Kale Kumud et al., 2001)
	Catechin		(Ishimaru et al., 1992)
	Niruriflavone	Antioxidant	(Than et al., 2006)
Lignan	Phyllanthin	Hepatoprotective,	(Syamasundar et al., 1985, Satyanarayana et al., 1988)
	Hypophyllantin	Hepatoprotective	(Syamasundar et al., 1985)
	Niranthin	Anti-inflammatory, anti-viral	(Satyanarayana et al., 1988, Huang et al., 2003, Kassuya et al., 2006)

Table No. 1(b): Chemical constituents of P*hyllanthus niruri*

Nirtetralin	Anti-inflammatory, anti-viral	(Satyanarayana et al., 1988, Huang et al., 2003, Kassuya et al., 2006)
Phyltetralin	Anti-inflammatory	(Satyanarayana et al., 1988, Kassuya et al., 2006)
Lintetralin		(Satyanarayana et al., 1988)
2,3-desmethoxy seco-isolintetralin		(Singh et al., 1989)
2,3-desmethoxyseco-isolintetralin diacetate		(Singh et al., 1989)
Linnanthin		(Singh et al., 1989)
Demethylenedioxynirathin		(Singh et al., 1989)
Nirphyllin		(Singh et al., 1989)
Phyllnirurin		(Singh et al., 1989)
Seco-4-hydroxylintetralin		(Satyanarayana et al., 1988)
Seco-isolariciresinol trimethyl ether		(Satyanarayana et al., 1988)
Hydroxyniranthin,		(Satyanarayana et al., 1988)
Methylenedioxybenzyl-3',4'-dimethoxybenzylbutyrolactone		(Satyanarayana et al., 1988)
cubebin dimethyl ether		(Elfahmi et al., 2006)
Urina tetralin		(Elfahmi et al., 2006)

Table No. 1(c): Chemical constituents of *Phyllanthus niruri*

Tannin	Geraniin	ACE-inhibitor, anti-viral	(Huang et al., 2003)
	Repandusinic acid	Anti-viral	(Ogata et al., 1992)
	Corilagin		(Colombo et al., 2009)
	Isocorilagin		(Than et al., 2006)
	Gallic Acid	ACE-inhibitor	(Than et al., 2006)
Other	1-O-galloyl-6-O-luteoyla-D-glucose	Anti-malaria	(Subeki et al., 2005)
	β-glucogallin	Anti-malaria	(Subeki et al., 2005)
	Niruriside	Anti-viral	(Qian-Cutrone et al., 1996)
	β-sitosterol		(Subeki et al., 2005)

Pharmacological activities:

a) Antioxidant and hepatoprotective activity:

Models, as evidenced by the reduction in liver enzyme levels. *P. niruri's* antioxidant preparations *in-vitro* found that leaf and fruit extracts of *P. niruri* inhibited iron overload

microsomal lipid peroxidation and had strong DPPH radical scavenging activity. Aqueous extracts were found to be more effective at quenching ROS than alcoholic extracts, with DPPH and ABTS scavenging activities comparable to ascorbic acid. Another research found that crude aqueous extracts of *P. niruri* leaves inhibited Fe (II)-induced lipid peroxidation in a dose dependent manner. This may indicate that it could be used to treat iron toxicity in the brain and liver. Furthermore, hepatoprotective activity may be attributed to its high content of antioxidative flavonoids, tannins, lignans, and terpenes. One of the first *in-vitro* studies on *P. niruri's* antioxidative hepatoprotective function found that the hexane extract contained lignans including phyllanthin and hypophyllanthin, which protected rat hepatocytes from carbon tetrachloride and galactosamine-induced hepatotoxicity. *P. niruri* has also been shown to have a hepatoprotective effect in animal and cell culture.[12]

Other research on the antioxidant properties of methanolic and aqueous *P. niruri* aqueous extracts iron chelating properties can provide a novel neuroprotective therapy for Fe(II)-related oxidative stress in the brain. Which is involved in Alzheimer's disease pathobiology? Another research found that crude aqueous extracts of *P. niruri* leaves inhibited Fe(II)-induced lipid peroxidation in a dose-dependent manner, suggesting that it may be used to treat brain and liver iron toxicity.

This is important because the treatment options for paracetamol poisoning are limited and sometimes unsuccessful, relying heavily on Nacetyl cysteine. Furthermore, the iron chelating property of aqueous extracts can provide a novel neuroprotective therapy for Fe(II)-related oxidative stress in the brain, which is the normalisation of liver enzyme profiles and nonenzymatic antioxidant levels was observed in studies focusing on the *in vivo* hepatoprotective activity of *P. niruri* against paracetamol-induced hepatotoxicity through the decrease in iron-induced peroxidation of hepatocyte biomembranes linked to Alzheimer's disease pathobiology facilitate apoptosis by activating the ERK and mitogen activated protein kinase (MAPK) pathways, according to research on aspirin and iron hepatotoxicity. As a result, *P. niruri's* scavenging activity can interfere with ROS-induced apoptosis by inactivating these pathways. However, no molecular studies on this subject have been carried out.[12]

b) Antidiabetic (hypoglycemic) action:

Diabetes Chronic hyperglycemia causes oxidative stress, which is a well-known factor in the development of diabetes and its complications. *P. niruri* extracts have shown dose-dependent

changes in fasting blood sugar, glucose tolerance, and pancreatic tissue architecture in animals, which may be attributed to inhibition of enzymatic pathways in intestinal carbohydrate digestion and glucose storage. The extract's bioactive agents are thought to have insulin-mimicking activity or to mimic insulin production, as evidenced by the extract's ability to increase liver hexokinase activity and enhance hepatic glycogen quality. Despite these findings, the anti-diabetic efficacy of Phyllanthus is still unknown, with reports from various species of the genus varying. According to a review of current research, the authors used a range of approaches to cause diabetes, including different extraction methods and dosages. This has always made it difficult to compare studies to determine the true functional properties of *P. niruri* as an antidiabetic agent, despite the fact that it has long been used as a traditional treatment for non-insulin dependent**.**[16]

c) Immunomodulatory activity:

P. niruri extract significantly improved various indices of activation and functions of murine bone marrow related macrophages, including phagocytosis, lysosomal enzyme activity, and TNF alpha release, while also modulating macrophage nitric oxide release. In a concentration-dependent manner, *P. niruri* increased the expression of major histocompatibility complex II and markers for dendritic cell extracts of *P. niruri* have proven to be potent murine lymphocytes mitogens and are able to induce surface activation maker (CD69), B and T lymphocyte proliferation.*P. niruri* extract stimulated naive splenocyte cultures produced more interferon gamma (IFN gamma) and interleukin 4 (IL4), which increased in a concentration-dependent manner. Pretreatment maturation (CD40), activation (CD83), and costimulation (CD86). *P. niruri* treated dendritic cells also presented Ova antigen to Ova-specific CD8 (+) T cells more efficiently in a transgenic T-cell activation model.[14]

d) Antiplasmodial and nematicidal properties:

P. niruri extracts have anti-plasmodial properties, according to *in-vivo* and *in-vitro* tests. This may be because *P. niruri* extracts are high in terpenes. Methanolic extracts, in particular, showed chemosuppressive activity comparable to chloroquine and greater prophylactic activity than pyrimethamine. A analysis of *P. niruri's* nematicidal activity against *Meloidogyne incognita* and *Rotylenchulus reniformis* found two prenylated flavanones to be responsible for *P.niruri's* nematicidal activity.[13,19]

e) Antibacterial activity:

An agar well diffusion analysis of the antimicrobial activity of aqueous and ethanolic extracts of the leaves and roots of four Indian herbs, including *P. niruri*, revealed that the ethanolic extract was more effective against *Escherichia coli* and *Staphylococcus aureus*, while the aqueous extract was more effective against *Proteus vulgaris* and *Bacillus subtilis* but had low anticoliform activity. Methanol extracts of *P. niruri* were found to be twice as potent as aqueous preparations, with a MIC of about one-third that of aqueous extracts. Furthermore, both aqueous and methanolic extracts of *P. niruri* showed strong antibacterial activity against Listeria *monocytogenes,* the bacterium that causes listeriosis, implying that *P. niruri* may be used as a food preservative. Both the ethanolic and aqueous extracts of *P. niruri* failed to inhibit the growth of *P. niruri* in a disc diffusion analysis. However, a subsequent strain of Gram negative bacteria showed statistically greater inhibitory activity against Gram positive bacteria. As compared to the ethanolic extract, the phenolic extract has a higher content of phenolic compounds. The apparent discrepancy in findings between this research and Cheah and colleagues' study from 2011 may be due to the use of different solvents. This may imply that the aqueous extracts were contaminated.[18]

f) Anti-malarial activity:

From the study of anti-malaria screening of crude extracts of *Phyllanthus niruri* L, Subeki and co-workers isolated 1-O-galloyl-6-O-luteoyl-α-d-glucose from an aqueous extract, which demonstrated a strong inhibitory activity against *Plasmodium falciparum* growth *in-vitro,* with the IC50 of 1.4 µg/ml. The same study also successfully identified several compounds from the fractionation of an aque-(2→1)-O-β-dxylopyranoside, β-glucogallin, β-sitosterol, and gallic acid. Some compounds that have been identified were quercetin 3-O-β-d-glucopyranosyl a inhibitory effect towards *Plasmodium falciparum* growth. Nonetheless, the study has not been able to elucidate the mechanism of inhibition of the active compounds.[16]

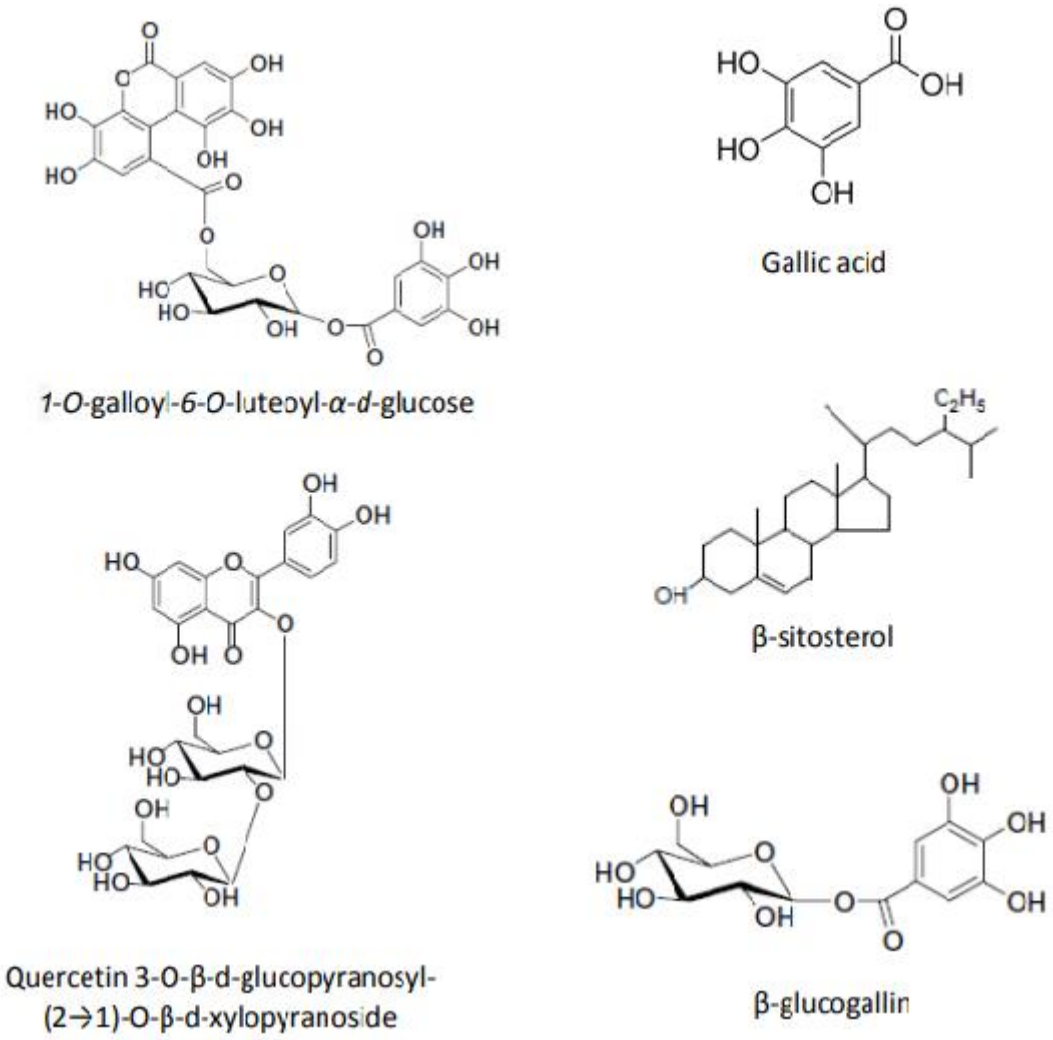

Figure No. 2: Importance constituents of *Phyllanthus niruri* L

g) Anti-cancer activity:

Phyllanthus niruri L extracts have shown considerable potency in inhibiting cancer cell proliferation *in-vitro*, making them a possible source of new anti-cancer agents. However, until recently, the active compounds isolated from *Phyllanthus niruri* L had not been tested for anti-cancer activity, despite the fact that the plant's secondary metabolites, which include lignans, flavonoids, and terpenes, are known to have one or more actions against cancer cell lines. Tang and colleagues (2010) hypothesised that the cytotoxic property of the methanol and ethanol extracts was due to the existence of polyphenol compounds such as ellagitanin, gallo tannins, flavonoids, and phenolic acid as a major constituents. Furthermore, in melanoma and prostate cancer cells, ethanol extracts were found to be capable of altering the cancer cell cycle by inducing apoptosis through caspase activation. In human lung and breast

cancer, the extract has also been shown to slow cancer progression by inhibiting metastatic activity.[19]

h) Anti-viral action:

Hepatitis B is a form of hepatitis that affects the liver. Phyllanthus plants have been used in Asia for thousands of years as a natural remedy. *P. niruri* has been used to treat jaundice and hepatitis B virus and has been shown to suppress the hepadnavirus. Plants in the phyllanthus genus suppress duck hepatitis B virus by inhibiting DNA polymerase by 50%. In the developing age, hepatitis B is the most common disease. By binding to the endogenous DNA polymerase and the hepatitis B surface antigen *in vitro*, *Phyllanthus niruri* extract can prevent Hepatitis B. The extract was tested against the wood chuck hepatitis virus (WHV) in wood chucks, and it effectively inhibited the virus, resulting in the removal of both surface antigen and DNA polymerase activity. *Phyllanthus niruri* is a low-toxic plant that has been shown to be toxic to batrachians and fish when extracted with alcohol and water. Mammalian toxicity is extremely low.[20]

CONCLUSIONS:

The current study examines a number of scientific researches that has used the plant *P. niruri*. The plants' widespread usage in traditional and complementary medicine for a wide range of diseases has resulted in a large number of scientific researches, many of which have used animal models. As described in Appendix 1, the present review reveals that *P. niruri* extracts have pharmacological potential in a wide range of diseases. *P. niruri* appears to have been explored for its antiviral, hepatoprotective, hypolipidaemic, and antibacterial properties among the diseases studied. The favourable result seen in the articles examined here is likely owing to the fact that there may be many bioactive components within crude extracts used in these investigations. It is commonly acknowledged that crude extracts contain a variety of bioactive chemicals, each of which may have varying effects on bodily tissues. Despite this, only a few research have looked into the pharmacological potential of these bioactive chemicals, with the majority focusing on the activity of methanolic and aqueous crude extracts. Investigators are unable to distinguish whether the findings are linked to the effect of a single bioactive molecule or synergy between numerous bioactive compounds, hence therapeutic discoveries utilising crude extracts have little translational relevance. This also applies to the extraction method used to prepare crude extracts varying extraction procedures and the use of solvents with various polarities produce different bioactive chemicals, which

limits our ability to compare results across investigations. We discovered significant variation in study protocols and, in some cases, contradictory results during our review, implying that some research may not produce repeatable data. Furthermore, the lack of information in some research prohibits us from replicating them and making an unbiased assessment of the plant's therapeutic potential. When assessing pharmacological potential of novel therapeutic agents, it is essential that authors provide a comprehensive account of the experimental design and protocol and ensure proper standardization of material and techniques, an aspect that appears to be lacking in some studies in this review. While the overall data show that *P. niruri* has a lot of medicinal promise, such findings should be regarded with caution. Larger sample numbers, toxicological studies, mechanism studies, and molecular analysis are all parts of this herb's research that need to be studied. The majority of current information focuses on the relationship between known phytochemicals and their biological functions. There aren't enough mechanisms of action research to figure out how bioactive phytochemicals from *P. niruri* interact with their molecular targets. Before conclusive choices on *P. niruri's* potential can be made, more robust scientific approaches are required. Before clinical trials may be considered, this is an important step.

ACKNOWLEDGEMENTS:

The authors of this review article are thankful to the Principal, Government College of Pharmacy, Karad for allowing us to present this paper. We are also thankful to AICTE for providing research fellowship to complete our research work and convert our research work into publications.

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