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Review Article

A mini-review on therapeutic potentials of *Phyllanthus niruri* Linn.

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ABSTRACT

Phyllanthus niruri Linn belongs to plant family Euphorbiaceae and is found in tropical and subtropical countries of the world including some regions of Sri Lanka and India. The extract of *P. niruri* Linn is the most commonly used medicine in Ayurveda system of medicine and has especially been recommended for the treatment of bronchitis, anaemia, skin diseases, asthma, cough, liver, kidney and urinary tract disorders. In the present study, an attempt was done to document the scientific investigations on phytochemicals and pharmacological activities of *P. niruri* Linn. According to the findings of *P. niruri* Linn, it shows potent pharmacological actions on hepatitis B virus, liver carcinoma, kidney stones and HIV. The available research suggested that *P. niruri* Linn has many beneficial health effects. However, human based data are sparse and conducting clinical trials will be necessary to prove more public health implications. These findings may be considered as clues to the development of novel pharmaceutical preparations from *P. niruri* Linn in future.

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1. Introduction

In the traditional system of medicine, a number of plants have been widely used for the treatment of various disorders since ancient times. The knowledge pertaining to these medicinal plants was handed down from generation to generation either orally or through documents and effective plants have been selected by trial- and error-based experiments (Wansi et al., 2019). During the past decades, traditional herbal medicines have also attracted attention to a greater extent in western countries due to their effective therapeutic activities with low toxicity and rare complications. Therefore, at present, plants belonging to these traditional systems have been extensively investigated owing to their biological activities (Wansi et al., 2018). Furthermore, plants can be known as versatile sources of bioactive metabolites, including polysaccharides, phenolics, alkaloids, essential oils, steroids, lignins, resins, tannins, etc. (Mohammadhosseini, 2017). These bioactive metabolites are of vital importance in different pharmacological and medicinal disciplines, as well (Mohammadhosseini et al., 2017). In fact, plants have various applications, especially in the health, agriculture, food, and cosmetic industries (Sarker and Nahar, 2018; Mohammadhosseini et al., 2019).

In Ayurveda system of medicine, *Phyllanthus niruri* Linn (*Tamalaki* in Sanskrit) is one of the herbs mentioned in all the relevant ancient Ayurvedic texts. This plant belongs to the family Euphorbiaceae and is an annual herb that is widely spread throughout the tropical and subtropical countries of the world including Sri Lanka and India and commonly found as weed in both cultivated and wasteland areas particularly in the rainy season. *P. niruri* Linn is commonly known as 'Gale of the wind', 'Chancapiedra' (stone breaker) and 'Seed under a leaf' according to its morphological and pharmaco-

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-logical actions (Lee et al., 2016). It has been stated that the extract of *P. niruri* Linn is one of the most commonly used remedies in Ayurveda system of medicine especially recommended for bronchitis, anaemia, skin diseases, asthma, cough, liver, kidney and urinary tract disorders (Sharma, 1998).

In literature, the indication of *P. niruri* Linn is increasing due to the concerned novel findings of this medicinal plant such as possessing antiviral activity against hepatitis B virus, hepatoprotective activities, litholisis action of kidney and gall bladder stones, inhibitory action on HIV, anti-inflammatory, anti-diabetic, lipid lowering, analgesic and immunomodulatory activities (Narendra et al., 2012; Manonmani et al., 2015; Jantan et al., 2019).

The current paper aims to review the scientific literature and provide a comprehensive summary on the potential medicinal benefits and summarize the phytochemical constituents of *P. niruri* Linn (Fig. 1) with scientifically proven biological behaviors in the reports published between 1st January 1984 and 1st January 2019.

1.1. Botanical description

P. niruri Linn is an annual herb 30-60 cm tall. The stem often branched at base, angular and quite glabrous. From morphological point of view, it is cylindrical and hairless and at the level of the leaves insertion, triangular stipules, acuminates and often cordated at the base. It exudes translucent latex when it is cut. Tap roots are slender, wiry and provided with fine secondary roots.

Leaves: These organs are simple, numerous and green in color and tare closely arranged, oblong-oval shape and obtuse. They are arranged alternatively on each side of the stem.

Flowers: Flowers are unisexual, yellowish in color, small numerous and axillary. Female flowers axillaries in the base of twigs and the male flowers regrouped by 2-4 in the axils of the leaves at the top of wigs.

Fruits: These parts are very small capsule, depressed, globose and 2-3 mm in diameter.

Seeds: Seeds are wedge-shaped, one concave and two flat sides with 1 mm height.

P. niruri Linn can be known as one of the commonly used herb of Family Euphorbiaceae in many traditional and medicinal systems. The botanical classification and different vernacular names used in some countries are summarized in Table 1 (Narendra et al., 2012).

2. Methodology

The data for the current review were collected using relevant scientific journal articles published between 1st January 1984 and 1st January 2019. In this relation, a comprehensive search of the literature was conducted regarding the corresponding biological activities and phytochemistry of *P. niruri* Linn in the following databases; PubMed (U.S. National Library of Medicine, USA), Science Direct (RELX group, Netherlands) and Sementic Scholar (Allen Institute for Artificial Intelligence, USA). The headings and keywords were "*Phyllanthus niruri* Linn", "Pharmacological activities of ''*Phyllanthus niruri* Linn" and "Phytochemistry and *Phyllanthus niruri* Linn". From a total of 134 results, some articles were excluded because of duplication or being irrelevant to the topic of research.

2.1. Phytochemicals of *Phyllanthus niruri* Linn

Phytochemicals characterized in the *P. niruri* Linn and their actions are summarized in Table 2.

2.2. Pharmacological activities

2.2.1. Hepatoprotective activity

Hepatitis B is one of the major diseases among the human populations caused by the hepatitis B virus. The extracts of *P. niruri* Linn have been reported to be effective against hepatitis B and other viral infections. A potential anti-hepatitis B virus agent, namely ellagic acid which was isolated from *P. niruri* Linn showed cytotoxic effect against HepG2/C3A cells and the research also revealed that ellagic acid did not effect on hepatitis B virus replication (Yong et al., 2017).

On the other hand, it was found that treatment with phyllanthin inhibited the increased level of serum alanine transaminase (ALT) and aspartate aminotransferase (AST) at doses of 120 mg/kg and 180 mg/kg in hepato-toxicity model of mice caused by CCl_4. The decreasing levels of serums were found to be ranging between 74-83% and 62-63%, respectively and this hepatoprotective effects were comparable with the standard drug, silymarin which shows nearly 66% decrease of the serum levels (Ooi et al., 2015).

Many researches have assessed the protective effect of the protein isolated from *P. niruri* Linn, against thioacetamide (TAA) induced cytotoxicity in hepatocytes. In a related study, TAA caused severe damage to the cells and decreased the cell viability evidence from enhanced ALT and LDH leakage as well as the level of glutathione (GSH) content and antioxidant enzyme activities. In addition, treatment with the protein isolated from the plant increased the cell viability gradually (to about 90%) with respect to the control and significantly reduced the enzyme leakage (Sarkar and Sil, 2007).

2.2.2. HIV replication inhibition

An aqueous extract of *P. niruri* Linn has been reported to exert an inhibitory action on human immunodeficiency virus type-1 reverse transcriptase (HIV-1-RT). In this context, the inhibitor of this plant extract was purified by combination of three chromatographic columns and identified as repandusinic acid (RA) monosodium salt. The 50% inhibitory doses (ID_{50}) of RA on HIV-1-RT and DNA polymerase alpha (from HeLa cells) were 0.05 µmol and 0.6 µmol, respectively representing approximately a 10-fold more sensitivity of HIV-1-RT compared with DNA polymerase alpha (Ogata et al., 1992).

In another report, anti-HIV effect of the alkaloid extract of the *P. niruri* Linn was examined in human cell lines and the inhibitory effect on HIV replication was mon-

Table 1

General botanical characteristics along with vernacular names attributed to *Phyllanthus niruri* in different countries.

Botanical classification	Country	Vernacular names
		Plant Names
Kingdom: Plantae Division: Magnoliophyta Class: Magnoliopsida Order: Euphorbiales Family: Euphorbiaceae Genus: Phyllanthus Species: niruri	Sri Lanka	Sinhala: Ela Pitawakka, Bimnelli
		Tamil: Kulhainelli
	India	Sanskrit: Bhoomyamalaki, Tamalaki, Bhudhatri, Bahuphala, Bahupathra
		Hindi: Chalmeri, Harfarauri, Bhuiaonla
	Bangladesh	Bhui amla
	Brazil	Shka-ninn-du, erva pombinha
	Colombia	Holy Friday
	Fiji	Chanca Piedra
	Mexico	Viemes santo
	Philippians	Santa Maria, San Pedro, Herb of San Pablo, Sampasampalkan
	Thailand	Yerba, De sanpablo
	West Indiea	Cane peas senna, chick weed, gale-wind grass, Hurricane weed, Jar amLa

Table 2

Phytochemicals of *Phyllanthus niruri* Linn and their actions.

Class	Compound	Action	Reference
Flavanoids	Rutin	Antioxidant	Gao et al., 2003
		Strengthen the capillaries	Becker et al., 1985
	Quercetin	Strengthen and modulate the permeability of the walls of blood vessels	Gupta et al., 1984
			Saija et al., 2003
		Anticancer, anti-inflammatory	Pejin et al., 2015
		Antioxidant	Rusmana et al., 2017
	Quercitrin	Anti-leishmanial	
		Anti-nociceptive	Anupika et al., 2016
		Anti-inflammatory	
	Astragalin	Diuretic	Kale et al., 2001
		Immunomodulatory	
	Catechin	Suppressed the growth of human colon and hepatic epithelial cancer cells	Useto et al., 2001
			Dodevic et al., 2018
	Niruriflavone	Antioxidant	Than et al., 2006
Terpenes	Limonene	Anticancer activity on liver tumor cells	Mills et al., 1995
	p-Cymene	Antioxidant	Tomaino et al., 2005
	Lupeol	Anti-inflammatory	Geeta and Varalakshmi, 2001; Malini et al., 2000
		Inhibit CaOx crystal aggregation	
Coumarins	Ellagic acid	Anticancer	Whitley et al., 2003
	Methyl brevifolincarboxylate	Vasorelaxant effect	Lizuka and Nagai, 2006
Lignans	Phyllanthin	Hepatoprotective	Dnyaneshwar et al., 2014
	hypophyllanthin	Anti-genotoxic	Venkateswaran et al., 1987
		Inactivation of hepatitis B virus	

Table 2 Continued

Class	Compound	Action	Reference
Tannins	Repandusinic acid	Inhibited HIV-1-RT	Xu et al., 2000
	Geraniin	Anti-nociceptive	Ueno, et al., 1988
Saponins	Crude Saponins	Antifungal	Ajibade et al., 2018
Alkaloids	Norsecurinine	Antimalarial	Weenen et al., 1990

Fig. 1. The photograph of *Phyllanthus niruri* Linn.

-itored in terms of inhibition of virus induced cytopathogenicity in MT-4 cells. The alkaloid extract of the plant revealed suppressing activity on strains of HIV-1 cell cultured on MT-4 cell lines. Furthermore, the selectivity index was found to be 13.34 representing clear selective toxicity of the extract for the viral cells (Naik and Juvekar, 2003).

A cytotoxicity study was performed on hexane, chloroform, ethyl acetate, acetone and methanol extracts of *P. niruri* Linn whole plant by MTT assay using human Peripheral Blood Mononuclear Cells (PBMC). As being reported, all extracts exhibited distinguished activity among which chloroform and hexane extracts of *P. niruri* Linn showed the highest HIV-RT inhibitions (88.7% and 87.8%) at 2 mg/mL concentration, whereas the control drug showed an inhibition of 91.7% at the same concentration (2 mg/mL) (Gujjeti and Estari, 2015).

2.2.3. Lipid lowering activity

Lipid lowering activity of *P. niruri* Linn extract in triton and cholesterol induced hyperlipidemia was examined in male adult rats and compared to that of gemfibrozil. The acute administration of triton caused remarkable increase in serum levels of total cholesterol by 134%, phospholipids by 90%, triglyceride by 52% and protein by 69%. Treatment with *P. niruri* Linn at the dose of 200 mg/kg significant reversal was noticed in total cholesterol by 29%, phospholipids by 26%, triglyceride by 24% and protein by 32% compared to control. In addition, the administration of cholesterol in rats increased their serum levels of total cholesterol, phospholipids, triglyceride and protein and also gave rise to the reduction of the level of serum lipids after administration of *P. niruri* Linn extract at a dose of 100 mg/kg (Khanna et al., 2002).

2.2.4. Anti-inflammatory activity

Acute anti-inflammatory activity of aqueous extract of *P. niruri* Linn (400 mg/kg and 800 mg/kg) was studied in rats by carrageenan induced paw oedema and cotton pallets were implanted in rats to evaluate the effect on chronic granuloma.

The results revealed a significant anti-inflammatory activity in carrageenan model ($p < 0.001$) and chronic granuloma models ($p < 0.001$) (Sathisha et al., 2009). Moreover, the anti-inflammatory effect of spray dried standardized powder of *P. niruri* Linn was observed in carrageenan-induced paw edema and thioglycolate-induced leukocyte migration in Swiss male mice. The spray dried powder at doses of 100, 200, 800 or 1600 mg/kg significantly inhibited carrageenan-induced paw edema compared to the positive control group (carageena-1% w/v, 50 µL). Also, the results of this study revealed the inhibition of leukocyte migration at doses of 100 or 200 mg/kg of spray dried powder compared to the positive control group (Porto et al., 2013).

A similar study reported the anti-inflammatory activity of the methanolic extract of *P. niruri* Linn leaves which was assessed while using the ibuprofen (20 mg/kg) as the standard drug in carrageenan induced paw oedema of Swiss albino rats. Methanolic extract of the plant leaves showed the reduction of 46.8%, 55.32% and 69.14% at doses of 100, 200 and 400 mg/kg, respectively (Mostofa et al., 2017).

2.2.5. Antioxidant activity

Free radicals are concerned in the development of a wide range of disorders in humans, such as cell death, heart diseases, cancer, inflammation, neural disorders, arthritis and ageing (Köse et al., 2015).

From a mechanistic point of view, different free radicals attack on membranes causing oxidation of lipids and loss of different enzymes activities. Antioxidants are a group of compounds which have the ability to stop or delay the process of oxidation by scavenging both radicals and related non-radical oxygen species (Damanhouri and Ahmed, 2014).

Plants are important sources of natural antioxidants. Some *in vitro* studies revealed that the aqueous and methanolic extracts of *P. niruri* Linn were potent inhibitors of microsomal lipid peroxidation induced by Fe^{2+} and ascorbate. Moreover, both leaf and fruit extracts showed antioxidant activity and inhibition of the superoxide *in vitro* denoted that the aqueous extract of the leaf and fruit were more potent than methanolic extracts. DPPH radical scavenging activity of all the extracts of *P. niruri* Linn exposed a very high potency (Harish and Shivanandappa, 2006).

In addition, an administration of *P. niruri* Linn leaf aqueous extract to diabetic rats displayed reduction of oxidative stress in kidney via prevention of the decrease in activity levels of endogenous antioxidant enzymes (Giribabu et al., 2014). It has also been documented that the flavanoids isolated from *P. niruri* Linn showed potential DPPH free radical scavenging activity and hydroxyl radical scavenging activity even at low concentrations (Jose et al., 2014).

2.2.6. Wound healing activity

Wound healing activity was evaluated in two models of male albino wistar rats with burn wound and dexamethasone suppressed the burn wound. The burn wounds were made on rats under ketamine (50 mg/kg, intramuscular) anesthesia by pouring hot molten wax (2 g at 80 °C) on the shaven skin of the animal through a cylinder of 300 mm^2 circular opening. In dexamethasone suppressed burn model, dexamethasone was administered (0.17 mg/kg, I.P.) and continued on subsequent days till the day of eschar falling. The parameters studied were the wound contraction and the period of epithelialization. It was found that oral and ointment preparation of *P. niruri* Linn did not show any significant effect in wound contraction and the period of epithelialization when compared to control group. However, both topical and oral administration of ethanolic extract of *P. niruri* Linn showed remarkable effectiveness to reverse the dexamethasone suppresses burn wound healing (Shanbhag et al., 2010).

2.2.7. Action on kidney stones

P. niruri Linn is known as stone crusher due to its impact on urinary tract (Micali et al., 2006) and interferes with stone formation at many stages. The calcium oxalate (CaOx) crystals is the main constituent of human urinary stones and can stick to the lining of the urinary tract and may cause cell damage. The toxicity of CaOx is inhibited by the triterpenes of *P. niruri* Linn and also inhibits the markers of crystal deposition in the urinary system (Boim et al., 2010). The water extract of *P. niruri* Linn has ability to modify the shape and texture of the calculi to a smoother and probably more fragile form, which could contribute to elimination or dissolution of the calculi (Barros et al., 2006).

2.2.8. Immunomodulatory activity

It has been shown that aqueous extracts of *P. niruri* Linn are capable of potentiating macrophage responses to *Streptococcus sanguinis* infection through inducing proliferation and nitric oxide production in dose and time dependent ways. Accordingly, the highest effect was observed at concentration of 400 µg/mL at 48 hours (Hutomo et al., 2018).

A similar research designed to evaluate the immunomodulatory activity of the flavonoids isolated from *P. niruri* Linn at various concentrations on normal lymphocytes by using MTT assay. The compound exhibited higher growth stimulation even at low concentrations (Jose et al., 2014).

Immunomodulatory activity of methanolic and ethanolic extracts of *P. niruri* Linn was detected by nitrobluetetrazolium assay which revealed that the ethanolic extract of *P. niruri* Linn stimulates the neutrophils provoking phagocytic activity to significant degree of 67.91, 61.25 and 6.02 at concentrations of 1000 µg/mL, 500 µg/mL and 100 µg/mL ($p < 0.05$) (Shilpa et al., 2018).

2.2.9. Anti-diabetic activity

The hypoglycemic activities of methanolic extract (200 and 400 mg/kg) from the aerial parts of of *P. niruri* Linn

was evaluated in normal and alloxan diabetic rats. The results obtained in this study revealed that the methanolic extract significantly reduced ($p < 0.05$) fasting blood glucose in dose related manner and suppressed the post prandial rise in blood glucose after a heavy glucose meal in normoglycemic rats (Okoli et al., 2010).

2.2.10. Anticancer activities

A research was established to assess the anti-tumor activity of a hydro-alcoholic extract of the whole plant of *P. niruri* Linn in 7-9 weeks old male Swiss albino rats. In this study, skin carcinogenesis was induced by a single topical application on two stage process of 7,12-dimethylbenz (a) anthracene (DMBA) and two weeks later repeated application of croton oil (1.0% in acetone/ three times a week) till the end of the experiment (16 weeks).
The extract of *P. niruri* Linn was administered (100 mg/kg) at seven days before and seven days after DMBA application and at the starting from the croton oil application. The reported results revealed that the initial phase of pappilomagenesis caused significant reduction in tumor incidence, tumor yield, tumor burden and cumulative number of pappilomas as compared to carcinogen-treated controls (Sharma et al., 2009).
Colorectal carcinoma (HT29) and human hepatocellular carcinoma (HepG2) cells were treated with spray dried extracts of *P. niruri* Linn with cisplatin at different concentrations (0.5 mg/mL and 1 mg/mL) for 4 and 24 h. The obtained results revealed that the spray died extract of *P. niruri* Linn had significantly different cytotoxic effects on HT29 and HepG2 cells when compared to control cells. This study also exhibited that the spray dried extract of *P. niruri* Linn is selectively toxic against two cancer cell lines. Additionally, when combined with cisplatin, it induces a synergistic increase in the cell death of both HT29 and HepG2 cells (De AraújoJúnior et al., 2012).

4. Concluding remarks

P. niruri Linn is an important medicinal herb mentioned in Ayurveda system of medicine. Some of its medicinal uses have been proven in experimental models which suggest that the plant possesses various pharmacological activities.
Regarding a number of published reports, *P. niruri* Linn shows potent pharmacological actions against hepatitis B virus, liver carcinoma, kidney stones and HIV. These findings may lead to further development of novel pharmaceutical preparations from *P. niruri* Linn in the future.

Conflict of interest

The authors declare that there is no conflict of interest.

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