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-
Phyllanthus niruri Linn can be known as one of the commonly used herbs in Ayurveda system of medicine particularly 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, litholysis 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; Jantat 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, acuminate and often cordate 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 hepatotoxicity model of mice caused by CCl4. The decreasing levels of sera 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 (ID50) 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...
Botanical classification

|-----------------|--------------------------|----------------------|---------------------|---------------------|-------------------|-----------------|

<table>
<thead>
<tr>
<th>Country</th>
<th>Vernacular names</th>
<th>Plant Names</th>
</tr>
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<tbody>
<tr>
<td>Sri Lanka</td>
<td>Sinhala: Ela Pitawakka, Bimnelli</td>
<td>Tamil: Kulhainelli</td>
</tr>
<tr>
<td>India</td>
<td>Sanskrit: Bhoomyamalaki, Tamalaki, Bhudhatri, Bahuphala, Bahupathra</td>
<td>Hindi: Chalmeri, Harfarauri, Bhuiaonla</td>
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<tr>
<td>Bangladesh</td>
<td>Bhui amla</td>
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</tr>
<tr>
<td>Brazil</td>
<td>Shka-ninn-du, erva pombinha</td>
<td></td>
</tr>
<tr>
<td>Colombia</td>
<td>Holy Friday</td>
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</tr>
<tr>
<td>Fiji</td>
<td>Chanca Piedra</td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>Viemes santo</td>
<td></td>
</tr>
<tr>
<td>Phillipians</td>
<td>Santa Maria, San Pedro, Herb of San Pablo, Sampasampalkan</td>
<td></td>
</tr>
<tr>
<td>Thailand</td>
<td>Yerba, De sanpablo</td>
<td></td>
</tr>
<tr>
<td>West India</td>
<td>Cane peas senna, chick weed, gale-wind grass, Hurricane weed, Jar amLa</td>
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</table>

Table 1

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

<table>
<thead>
<tr>
<th>Class</th>
<th>Compound</th>
<th>Action</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flavanoids</td>
<td>Rutin</td>
<td>Antioxidant</td>
<td>Gao et al., 2003</td>
</tr>
<tr>
<td>Flavanoids</td>
<td>Quercetin</td>
<td>Strengthen and modulate the permeability of the walls of blood vessels</td>
<td>Gupta et al., 1984</td>
</tr>
<tr>
<td>Flavanoids</td>
<td>Quercitrin</td>
<td>Anti-leishmanial Anti-nociceptive Anti-inflammatory</td>
<td>Rusmana et al., 2017</td>
</tr>
<tr>
<td></td>
<td>Astragalin</td>
<td>Diuretic Immunomodulatory</td>
<td>Kale et al., 2001</td>
</tr>
<tr>
<td></td>
<td>Catechin</td>
<td>Suppressed the growth of human colon and hepatic epithelial cancer cells</td>
<td>Useto et al., 2001</td>
</tr>
<tr>
<td></td>
<td>Niruriflavone</td>
<td>Antioxidant</td>
<td>Than et al., 2006</td>
</tr>
<tr>
<td>Terpenes</td>
<td>Limonene</td>
<td>Anticancer activity on liver tumor cells</td>
<td>Mills et al., 1995</td>
</tr>
<tr>
<td></td>
<td>p-Cymene</td>
<td>Antioxidant</td>
<td>Tomaino et al., 2005</td>
</tr>
<tr>
<td></td>
<td>Lupeol</td>
<td>Anti-inflammatory Inhibit CaOx crystal aggregation</td>
<td>Geeta and Varalakshmi, 2001; Malini et al., 2000</td>
</tr>
<tr>
<td>Coumarins</td>
<td>Ellagic acid</td>
<td>Anticancer</td>
<td>Whitley et al., 2003</td>
</tr>
<tr>
<td>Coumarins</td>
<td>Methyl brevifolinicarboxylate</td>
<td>Vasorelaxant effect</td>
<td>Lizuka and Nagai, 2006</td>
</tr>
<tr>
<td>Lignans</td>
<td>Phyllanthin</td>
<td>Hepatoprotective</td>
<td>Dnyaneshwar et al., 2014</td>
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<tr>
<td>Lignans</td>
<td>hypophyllanthin</td>
<td>Anti-genotoxic Inactivation of hepatitis B virus</td>
<td>Venkateswaran et al., 1987</td>
</tr>
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Table 2 Continued

<table>
<thead>
<tr>
<th>Class</th>
<th>Compound</th>
<th>Action</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tannins</td>
<td>Repandusinic acid</td>
<td>Inhibited HIV-1-RT</td>
<td>Xu et al., 2000</td>
</tr>
<tr>
<td></td>
<td>Geraniin</td>
<td>Anti-nociceptive</td>
<td>Ueno, et al., 1988</td>
</tr>
<tr>
<td>Saponins</td>
<td>Crude Saponins</td>
<td>Antifungal</td>
<td>Ajibade et al., 2018</td>
</tr>
<tr>
<td>Alkaloids</td>
<td>Norsecurinine</td>
<td>Antimalarial</td>
<td>Weenen et al., 1990</td>
</tr>
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</table>

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 (carrageena-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 edema 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 (Damanhour 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 Fe²⁺ 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 methano-lic 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 flavonoids 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, intra-muscular) anesthesia by pouring hot molten wax (2 g at 80 °C) on the shaven skin of the animal through a cylinder of 300 mm² 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 nitroblue tetrazolium 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 *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-di-methylbenz (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 papillomagenesis caused significant reduction in tumor incidence, tumor yield, tumor burden and cumulative number of papillomas 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 dried 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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An insight into the modulatory effects and mechanisms of actions of *Phyllanthus* species and their bioactive metabolites on the immune system. Front. Pharmacol. 10(878).


