Review Article

Stonebreaker activity review of seed-under-leaf, *Phyllanthus niruri*

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Phyllanthus niruri (Family: Phyllanthaceae) known as a seed-under-leaf, is one of the traditional medicinal plants. It is widely used in anti-nephrolithiasis and anti-urolithiasis or stone removal treatment since it is able to modify the structure, shape, and texture of the stone to a smoother and probably more fragile form, which could contribute to the elimination and dissolution of stone. Further, it has been shown to possess anticancer, antidiabetic, anti-hepatotoxic, anti-hypertensive, anti-inflammatory, antimicrobial, and antioxidant properties. Its phytochemical substances are alkaloids, coumarins, flavonoids, saponins, tannins, and terpenoids. The other important constituents are astragalin, geranin, hypophyllanthin, nirtetralin, phyllanthenol, phyllanthin, phyllochrysine, phyltetralin, and quercetin, and all of these contribute to its remedial properties. This is a brief overview of the stonebreaker activity of *P. niruri* to further provide an up-to-date review showing its importance.

Keywords: Herb, *Phyllanthus niruri*, Plant, Seed-under-leaf, Stonebreaker

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INTRODUCTION

The prevalence and incidence of stones, including nephrolithiasis and urolithiasis, are reported to be increasing globally. Romero et al. (2010) [1] reported these global increases are seen across age, race, sex, diet, and climate factors. National Health and Nutrition Examination Survey reported the prevalence of renal stones in US adults rose significantly from 5.2% in 1994 to 8.8% in 2012. Moreover, among men, the prevalence of stones was 10.6% compared with 7.1% among women s[2]. Patients with renal stones often have a benign course, but life-threatening complications like acute renal injury and infection can arise [3]. Moreover, the financial burden from medical expenditures and lost productivity is [4]. After accounting for increases in population and stone prevalence, obesity, diabetes, and population rates will contribute to an estimated $1.24 billion per year increase in the cost of renal stones by 2030 [5]. Even the advanced method and technology for stone removal or the treatment of stone is available, like open surgery, nephrostomy [6], and shock wave lithotripsy [7], it has their own limitation involving highly invasive surgeries, a long in-hospital recovery period, several side effects as even periodical reoccurrence of stones in a few. The alternative system of medicine usually employs natural sources or green medicine or medicinal plants due to their safety, efficacy, cultural acceptability, and lesser side effects as compared to synthetic drugs [8,9]. The plant that find very useful in the treatment of stone for the example *Abutilon indicum* [10], *Ageratum conyzoides* [11], *Borhaavia diffusa* [12], *Capparis decidua* [13], *Cassia tora* [14], *Launaea*

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Figure 1. *Phyllanthus niruri* morphology (A) leave, stem and root; (B) flower; (C-D) seed.

procumbens [15], *Morus alba* [16], *Phyllanthus niruri* [17], *Solanum xanthocarpum* [18].

Phyllanthus niruri

Plant description

P. niruri is an erect annual herb, growing 40-70 cm in height and having to ascend herbaceous branching, it is quite glabrous and branching at the base (Figure 1). **Stem**: horizontal branches and height of 30-60 cm, 1-2.5 mm width. **Leaves**: numerous, small, green, subsessile, closely arranged, elliptic oblong-shaped, obtuse, having short petiole and stipules present, they are arranged alternatively on each side of the stem. **Flowers**: yellowish, small, numerous, axillary. They are unisexual, monoecious flowers, male flowers having 1-3 sessile stamens, and female flowers are solitary in nature. **Fruits**: very small, depressed globose, and moreover capsule is smooth, 2-3 mm in diameter. **Root**: branches and large [19].

Taxonomical classification

The taxonomy of *P. niruri* is in the Kingdom (Plantae); Subkingdom (Viridiplantae); Infrakingdom (Streptophyta); Superdivision (Embryophyta); Division (Tracheophyta); Subdivision (Spermatophytina); Class (Magnoliopsida); Superorder (Rosanae); Order (Malpighiales); Family (Phyllanthaceae); Genus (Phyllanthus); Species (*P. niruri*) [20]. The plant genus Phyllanthus is a large genus of the family Phyllanthaceae, which comprises over 800 species distributed in tropical and subtropical regions [21]. The genus name "Phyllanthus" means "leaf and flower" because the flower, as well as the fruit, seem to become one with the leaf [22].

Nomenclature

P. niruri is a medicinal herb found mainly in rainforests of tropical areas throughout the world, including India, China, and Southeast Asia [23]. The vernacular name of *P. niruri* is also known as seed under leaf or stone breaker (English), noar (Bemgali), quebra pedra, arranca pedra (Brazil), ye xia zhu, be bei cai, xiao fan hun (Chinese), quinine creole (French), bhuiaonla, chalmeri, harfarauri (Hindi), arinelli, kizhanelli, nellipuli (Malayalam), rayavali, bhuiavli (Marathi), quebra pedra (Portuguese), ajata, amala, sukshmadala, vituntika (Sanskrit), chanca piedra, quinine criolla (Spanish), sampa-sampalukan (tagalog), keezha nelli (Tamil), nela usiri, ratsavusirike (Telugu), de sampablo (Thai) and bhui amla (Vietnam) [19,24].

Phytochemical substances

P. niruri contained active phytochemical substances as follows: (1) Flavonoids including geranin, rutin, quercetin, quercitrin, astragalin, and catechin [25-29]; (2) Terpenes and terpenoids including limonene, cymene, phyllanthenol, and lupeol; (3) Coumarins including ellagic acid and methyl brevifolincarboxylate; (4) Tannins including repandusinic acid, geraniin, hypophyllanthin,

phyllanthin, phyltetralin and corilagin [30-32]; (5) Lignans [33,34]; (6) Saponins [35]; (7) Alkaloids [36].

Traditional uses

From review literatures that regarding the traditional uses or phytochemical properties of *P. niruri* are shown in Table 1.

Phytochemical properties
Hair growth promoting activity [37]
Anti-allergic activity [32]
Anticancer activity [38-40]
Antidiabetic activity [41,42]
Anti-hepatitis B [43-45]
Anti-inflammation [46]
Anti-lipidemia activity [47,48]
Antimicrobial activity [49-52]
Antioxidant activity [53-56]
Anti-parasitic activity [57,58]
Antihyperuricemic activity [59,60]
Cardioprotective activity [61]
Hepatoprotective activity [62-68]
Nephrolithiasis treatment [69,70]
Neuroprotective activity [71]
Urolithiasis treatment [72]

Stonebreaker activity

The Spanish name of this plant, *chanca piedra*, means "stone breaker" or "shatter stone" because it effectively uses the generation of people to eliminate gallstones and kidney stones. In Brazil, this plant is known as *quebra pedra* or *arranca pedra* which also mean to "break stone" [73]. The present review is to introduce *P. niruri* as a medicinal plant by highlighting its traditional applications in stonebreaker activity.

In vitro study

Barros et al. (2003) [74] evaluated the effect of an aqueous extract *P. niruri* on calcium oxalate crystallization in vitro. Calcium oxalate precipitation was induced by the addition of 0.1 M sodium oxalate to unfiltered urine sample from Wistar rats and human urine in the presence or absence of *P. niruri* extract in a dose 0.25 mg/ml of urine. They observed that the presence of *P. niruri* extract did not inhibit calcium oxalate precipitation, but the crystals were significantly smaller than those in the urine samples without *P. niruri*. Moreover, they observed that after 24 hours, the precipitated crystals formed large agglomerates in untreated urine, but the crystals remained dispersed in urine with *P. niruri*. Those authors concluded that *P. niruri* did not decrease the number of crystals but induced a marked reduction of particle size and crystal aggregation. Khare et al. (2014) [17] reported the aqueous extract of *P. niruri* could dissolve 56.8% calcium oxalate crystals when compared with cystone, the standard drug, which could dissolve 58.4% crystals in vitro study. Moreover, the aqueous extract of this plant could also inhibit up to 53.09% aggregation of calcium oxalate crystals compared to the cystone with 76.54%. Similarly, Agarwal and Varma (2014) [75] reported that the maximum inhibition was 61.97% of the aqueous extract of *P. niruri* on calcium oxalate crystallization in vitro.

In vivo study

Freitas et al. (2002) [76] studied the effect of 42 days of chronic oral administration of 1.25 mg/ml/day *P. niruri* in adult male Wistar rats that induced urolithiasis by the introduction of a calcium oxalate crystal into the bladder. They reported that treatment with *P. niruri* strongly inhibited the growth of the matrix calculus and reduced the number of stone satellites (0.028 g) compared with the control group (0.174 g). Barros et al. (2006) [72] evaluated the effect of 30 days chronic oral administration of 5 mg/rat/ day of *P. niruri* on the performed calculus induced by introduction of a calcium oxalate seed into the bladder of male Wistar rats. They reported that *P. niruri* reduced the number and the weight of calculi compared with the untreated group. Calculi from *the P. niruri treated group had a smoother, homogeneous surface than* the spicule shape of calculi found in the untreated group. Singh et al. (2014) [77] evaluated the effect of 30 days of chronic oral administration of 150 mg/kg of *P. niruri* in ethylene glycol-induced urolithiasis in Wistar rats. Oxalate and calcium excretions significantly increased in hyperoxaluric rats as compared to control rats. The *P. niruri* treatment also significantly reduced the level of malondialdehyde and improved the activity of antioxidant enzymes, followed by a reduction of blood urea nitrogen, urea and serum creatinine. Histological analysis indicated that the *P. niruri* treatment also inhibited calcium oxalate crystal deposition and renal cell damage.

Clinical study

Nishiura et al. (2004) [78] studied the effects of *P. niruri* on the chemical promoters and inhibitors of stone formation in known calcium stone-forming patients.

Sixty-nine patients (38±8 years old) were randomized to take either 450 mg capsules three times daily of *P. niruri* (n=33) or placebo (n=36) for 3 months. They found that there was no significant difference in urinary levels of measured metabolites calcium, uric acid, citrate, oxalate, and magnesium among all patients. However, *P. niruri* significantly reduced the mean urinary calcium in hypercalciuric patients. Micali et al. (2006) [79] studied the effect of *P. niruri* on 150 patients who had extracorporeal shock wave lithotripsy. Seventy-eight patients received *P. niruri* for 3 months or more after this lithotripsy, while 72 received none. Those with lower pole stones who received this plant had fewer recurrent lithigenesis over 6 months than those who did not use this plant. Stones in mid or upper-pole did not show significant recurrence rate changes compared with the control group.

Phytochemical study

Grases et al. (2009) [80] evaluated the antilithiasic activity of a traditional Mallorcan herbal extract and antioxidant flavonoids, catechin, and epicatechin in Wistar rats with ethylene glycol induced calcium oxalate lithiasis. These flavonoids showed the ability to prevent the development of papillary and intratubular calcification in the kidney. Among the phytochemical substances in *P. niruri*, triterpenes have been found to inhibit the per-oxidative changes and cytotoxicity induced by calcium oxalate [81] as well as to reduce excretion of stone-forming constituents such as calcium, oxalate, and uric acid [82].

Antilithiasic study in other Phyllanthus spp.

Woottisin et al. (2011) [83] evaluated the effect of 28 days chronic oral administration of 3.5 mg daily of *P. amarus* in glycolate diet induced hyperoxaluria in Wistar rats. The P. amarus group revealed less calcium oxalate crystal deposition in the kidney. Moreover, the stone breaker was also reported in *P. tenellus* [84]; *P. emblica* [85].

CONCLUSION

In conclusion, even in the gallbladder, kidney, or urinary system, stone formation is a complex process that results from several events, including supersaturation, stone growth, aggregation, and retention within the tissue or organ [8]. This plant has proved to have the capacity to interfere with many stages of stone formation, reducing crystals aggregation [74], modifying their structure, shape, and composition [72,76], and altering the interaction of the crystals with tubular cells leading to reduced subsequent endocytosis [70], as well as showed great potential to dissolve the existing stone crystal [17]. The current reviews summarized here suggest that *P. niruri* may have therapeutic potential for stonebreakers since it is able to modify the shape and texture of calculi to a smoother and probably more fragile form, which could contribute to the elimination and dissolution of calculi.

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