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Phyllanthus amarus Lin. Schum. & Thonn: A critical review on ethnobotanical, phytochemical and pharmacological potential

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Abstract
Phyllanthus amarus is a member of the family Euphorbiaceae. Carry me seeds, stone breaker, gala of wind, bhumi amla and jangli amli are some common name of this plant. Ethno-botanically and pharmacologically it is an important showing antidiabetic, antioxidant, anticancerous, anti-inflammatory, antivenom hepato protective properties because whole plant is rich store house of different types of phytochemicals such as rutin, quercetin, geraniin, phylanthin, hypothylanthin, norsecurinine etc. The plant is also useful to cure various types of diseases like diarrhoea, dysentery, dropsy, jaundice, intermitted fever, urinogenital and disorder. The object of this review is to compile all the informations related to ethnic, phytochemicals and pharmacological potential of *Phylanthus amarus* to highlight the medicinal possibilities of this plant.

Keywords: ethnobotany, phytochemistry, pharmacology, *Phyllanthus amarus*, phyllanthin

Introduction
In India, *Phyllanthus amarus* is extensively distributed as a weed in cultivated and waste lands. All three major habits i.e., trees, herbs and shrubs are notice amongst the *Phyllanthus* species. *Phyllanthus amarus* has a long history of usage by people, because of its rich and high medicinal values. The genus *Phyllanthus* is most important groups of plants traded as a natural herbal drug in India [1]. Carry me seed, stone-breaker, wind breaker, gulf leaf flower or gala of wind are the common name of *P. amarus* [2]. Ravikant *et al.*, suggested that the southern India is genetic hotspot of *Phyllanthus* species [3]. The genus *Phyllanthus* has 1000 species and spread over tropical and sub-tropical continents like America, Africa, Australia and Asia [4].
P.amarus is generally known as Bhumi amla, having an erect or straight stem, herbs or shrubs, usually with milky white thorn juice. In Unani literature, it is described by the name of 'Bhuti' which means Bhum Amlak - Amla of Land [5]. It plays an important role in the development of green drugs. The use of this drug is safer and more reliable than expensive synthetic drugs and has no side effects.
In folk medicine it is generally used to treat jaundice, diabetes, otitis, diarrhoea, swelling, skin ulcer, gastrointestinal disturbances and blocks DNA polymerase in the case of hepatitis B virus during reproduction [6].
In Ayurveda it is described by the Sanskrit name – Bhoomy aamlakee, Taamalakee and Bhoodha tree [7]. Bhumy aamalakee, It is most commonly used in the Indian Ayurvedic system of medicine in the problems of genitourinary system, liver, stomach ache, kidney and spleen. *P. amarus* is an important medicinal plant because of it's novel antiviral activity against hepatitis B virus and for some other biological activities such as gallbladder and kidney, stones, for cold, flu, tuberculosis, liver diseases, etc [8].

Scientific Classification

Table 1

Kingdom	Plantae
Division	Angiospermae
Class	Dicotyledoneae
Order	Tubiflorae
Family	Euphorbiaceae
Genus	Phyllanthus
Species	amarus

Vernacular Names
Phyllanthus amarus plant is known by many various vernacular names in the different areas by the local people (Table 1). It is generally called stone breaker, carry me seed, wind breaker, leaf flower or gale of wind. *Phyllanthus* means leaf and flower because of its appearance, where leaf, flower and fruit appear to be fused.

Table 2: Names Used Worldwide of *P. amarus* [7, 9].

S. no.	Language	Vernacular Names
1.	Hindi	Hindi Bhumi amla, Jangli amli
2.	English	Black catnip, Carry me seed, Child pick-a-back, Gale of wind, Gulf leaf flower, Hurricane weed, Shatterstone, Stone breaker
3.	Rajasthani	Gugario
4.	Sanskrit	Bhoomyaamlakee, Bhoodhatree, Tamalakee
5.	Bengali	Bhui amla
6.	Tamil	Keelanelli (Keezhanelli)
7.	Oriya	Bhuiaola
8.	Telugu	Nela urika

Botanical Characteristics

Phylanthus amarus is an annual herb, 10-60 cm tall and glabrous. Roots are stout and woody; stems are often branched at base and angular. Leaves are numerous, sub-sessile, distichous, stipulate and peripinnate with small leaflets are oblong, having name obscure and base rounded. Flowers are very minute, shortly pedicelled, numerous, axillary and yellowish. Fruit is capsule, minute, globose and dehiscent. Fruits are a unit depressed-globose like sleek capsules present underneath the branches and seeds are trigonous, pale brown with longitudinal parallel ribs on the back. Capsules stalked, one - two mm long, round, smooth, two mm wide with six seeds. The plant has explosive seed capsules that propel the seeds far from the plant [9].

Ethno-pharmacological Uses

Phylanthus amarus has wide range of medicinal properties and has a long history in the health care system. It an important folk medicine for treating kidney stone, gallbladder stone, diseases related to liver such as liver cancer and jaundice. In addition to these it also shows anti-inflammatory, anti-tumour, anti-nociceptive and anti-oxidant properties. Further it is also used in the treatment for diarrhoea, dysentery, dropsy, intermittent fevers, gonorrhea, diabetes and chronic infections, skin issues such as skin ulcers, sores, swelling and itchiness, wounds, scabies and tubercular ulcers, ringworm, scabby and crusty lesions. Fresh leaf paste has wound healing capability and used to cure white spots on skin. The stem juice is additionally used as wound healers. The entire plant extract is used in urinary issues and swelling of liver. The root extract is used to cure abdomen pain. The flower paste is applied outwardly as curative against snake bite [10].

Phyllanthus amarus herb has found its traditional uses in many health problems because of its efficacy in the field of gastrointestinal disorders. If the selection of plants is made on the grounds of their traditional use, the chance of research success is greater. This herb is in traditional medicine for more than 3000 years. Whole plant extract is used in urinary problems, liver disease, dyspepsia, anorexia, constipation and dysentery [11]. It is used in several female problems such as in leucorrhoea, menorrhagia and mammary abscess and can act as galactagogue. Fresh leaf paste has the capacity to cure white spots on skin, diabetes, and jaundice [12]. Treatment of malaria has been made by P. amarus entire plant extract. Gonorrhea and syphilis can be treated by a boiling of leaves, sugar and cumin seeds [13].

Phytochemical Profiling

The phytochemical research is play most important role in the development of green medicines, which are safer to use. Different types of phytochemicals have been extracted, isolated and detected from whole plant of *P. amarus* by using different techniques. This plant has various types of phytochemical constituents such as phyllanthin. Hypophyllanthin, alkaloids, flavonoids, tannins, lignans, polyphenolic compounds and tetracyclic triterpenoids. (Table2).

Table 3: Phytochemicals Profiling of *P. amarus*

S.No.	Class	Phytochemicals	References
1.	Alkaloids	Niranthin, nirtetralin	[14,15]
		Phyltetralin	[15]
		Heliobupthalmin lactone, virgatusin Isonirtetralin, lintetralin	[15]
		Isolintetralin, demethylenedioxy-niranthin, 5-demethoxy-niranthin	[16]
		Hinokinin	[17]
		Phyllanthin, hypophyllanthin	[14]
		Securinine, nor-securinine, epibubbialine, isobubbialine, dihydrosecurinine	[18]
2.	Flavonoids	Rutin	[19]
		Quercetin, kaempferol, astragalin, quercetin-3-O-glucoside, quercitrin.	[20,21]
3.	Tannins	Amarulone, geraniin, amariin, furosin, corilagin, melatonin, phyllanthusin D.	[20,22,23]
4.	Lignans	Phyllanthin, hypo-phyllanthin, 5- dimethoxy-niranthin, nirtetralin, phyltetralin, hinokinin, 4-(3,4- diethoxy-phenyl)-1-(7-methoxybenzo[1,3]dioxol-5-yl)-2,3-bismethoxy methyl-butan-1-ol	[6, 24]
5.	Sterols	Amarosterol A, amarosterol B.	[24]
6.	Triterpenes	Phenazine and phenazine derivatives, 2Z, 6Z, 10Z, 14E, 18E, 22E-farnesyl farnesol.	[25]
7.	Volatile Oils	Linalool, Phytol.	[26]

Pharmacological Potential

Researches on pharmacological potential of *P.amarus* have reported different types of pharmacological properties such as anti-microbial, anti-viral, anti-oxidant, anti-cancer, anti-inflammatory, anti-plasmodial, diuretic and hepto protective. All plants as a source of new drugs are still poorly explored and only a small percentage has been investigated phytochemically and their pharmacological properties (Table 3).

Table 4: Pharmacological potential of major phytochemicals of *P. amarus*:

S. No.	Class	Phytoconstituents	Pharmacological effect	Reference
1.	Flavonoid	Rutin	Radioprotective Anti-oxidant	[19] [21]
		Quercetin-3-O-glucoside	Anti-oxidant	[22]
2.	Tannins	Geraniin	Anti-viral Radioprotective Hepatoprotective	[27] [29]
		Amariin	Anti-oxidant Radioprotective Hepatoprotective	[21] [21] [28]
		Repandusinic acid A	Anti-oxidant Radioprotective	[22] [19]
		Corilagin	Anti-oxidant Radioprotective Anti-viral	[19] [28]

		Phyllanthusiin A, B, C, D	Anti-oxidant radioprotective	[21] [19]
3.	Alkaloids	Norsecurinine	Anti-fungal	[30]
4.	Volatile Oils	Linalool, phytol	Anti-microbial	[31]
5.	Polyphenol		Anti-cancer	[32]
6.	Lignans	Phyllanthin	Hepatoprotective Anti-cancer, anti-tumour Anti- bacterial Antiamnestic Anti-aging Anti-oxidant Anti-inflammatory, anti-apoptotic	[33] [34] [19] [21] [17] [27]
		Hypophyllanthin	Anti-tumor, anticancer	[34]
		Niranthin	Antitumor Antiviral Anti-inflammatory	[18] [27] [15]
		Phyltetralin	Anti-inflammatory	[15]
		Nirtetralin	Anti-inflammatory Anti-viral Reverses multidrug resistance	[15] [27] [23]
		Hinokinin	Anti-viral	[27]

Anti-diabetic Activity

Oral administration of ethanolic leaf extract (400 mg/kg body weight) for 45 days resulted in vital decline in blood glucose and increase in the activity of glucokinase in the liver of diabetic mice [35]. The methanolic extract of *P. amarus* was found to reduce the blood sugar in alloxan diabetic rats by 6 percent at a dose level of 200 mg/kg body weight and 18.7 percent reduction in blood sugar [36]. Anti-diabetic impact of an aqueous and hydroalcoholic extract of P. amarus used in African nation for treating diabetes and many other diseases. Two doses (500 and 1000 mg/kg) of the each extracts were administered orally to diabetic rats. Consequently, liquid and hydroalcoholic extract of *P. amarus* decreases significantly blood sugar level after fifteen days of administration [37].

Anti-oxidant Activity

The anti-oxidant activity of a number of the principal constituents, particularly amariin, repandusinic acid, geraniin, 1-galloyl-2,3- dehydrohexahydroxydiphenyl (DHHDP)-glucose, corilagin, phyllanthusiin D, rutin and quercetin 3-O-glucoside were examined for his ability to scavenge free radicals in a range of systems together with DPPH, 2,2-azobis3-ethylbenzthiazoline-6-sulfonic acid (ABTS)/ ferrylmyoglobin, ferric (metal) reducing anti-oxidant power (FRAP) and pulse radiolysis. *P. amarus* extracts seem to act as an *in vivo* natural anti-oxidant and an effective gastro-protective agent that's as effective as cimetidine. Extract of *P. amarus* may also offer protection against toxic effects of alcohol to the liver [38]. Phyllanthin, one of the active lignin present in *P. amarus* was isolated from the aerial components, by colloid column chromatography using gradient extraction with hexane-ethyl acetate solvent mixture. Methanolic extract of *P. amarus* was found to own potential anti-oxidant activity because it might inhibit lipid peroxidation and scavenge hydroxyl and superoxide radicals *in vitro.* The amount required for 50 percent inhibition of lipid peroxide formation was 104 µg/ml and also the concentrations required to scavenge hydroxyl and superoxide radicals were 117 and 19 mg/ml respectively [36].

Anti-viral Activity

An aqueous extract of *P. niruri* inhibits endogenous DNA polymerase of hepatitis B virus (HBV) and binds to the surface antigen of hepatitis B virus in vitro and in vivo. The extract also inhibits woodchuck hepatitis B virus (WHV) DNA polymerase and bids to the surfsce antigen of WHV in vitro [39]. *In-vitro* culture of hairy roots of *P. amarus* induced by genus *Agrobacterium rhizogenes* was shown to possess eighty five percent inhibition (in contrast to fifteen % in the control) in binding of serum Hepatitis B surface antigen (HBsAg) to its antibody (anti-HBs) after 24 h of incubation with Hbs Ag-positive sera in-vitro at 37 °C [40]. Study on 25 compounds isolated from *P. amarus*, *P. multiflorus*, *P. tenellus* and *P. virgatus* found that niranthin, nirtetralin, hinokinin and geraniin at the non-cytotoxic concentration of fifty µm, suppressed effectively each HBsAg and hepatitis B effective antigen (HbeAg) expression, of these, niranthin showed the most effective anti HBsAg activity, whereas the for most potent anti-HBeAg activity was determined with hinokinin [41].

Anti-cancerious Activity

An aqueous extract of *P. amarus* was shown to be capable of inducing programmed cell death (apoptosis) in conjunction with its anti-metastastic action, with over 3-fold increase of caspases-3 and -7, the presence of DNA-fragmentation and terminal deoxynucleotidyl transferase enzyme mediated dUTP nick end labeling assay (TUNEL)-positive cells. The flexibility of *P. amarus* to exert anti-metastatic activity is generally associated to the presence of polyphenol compounds in its extracts [32].

Antimicrobial Activity

Methanolic extrct of P.amarus showed antimicrobial activity against all Gram+ and Gram – bacteria responsible for common infections of skin, urinary and gastro intestinal tracts [42]. Pre inoculation treatment showed bigger effectivity than post-inoculation in inhibiting powdery mildew development on pea plants in a glasshouse. Most inhibition occurred at 2000 µg/mL [30]. Antimicrobials of plant origin have an extremely large therapeutical potential. They are effective in the treatment of infectious diseases, while simultaneously alleviating many of the side effects that are often connected with artificial antimicrobials [43].

Anti-inflammatory Activity

The effects of alcohol extract of *P. amarus* on completely different phases of inflammation were examined and

investigations were performed victimization completely various phlogistic agents-induced paw edema, carrageenan-induced air-pouch inflammation and cotton pellet granuloma in rats. The extract considerably inhibited serotonin, carrageenan, bradykinin and prostaglandin E1-induced paw edema, but failed to inhibit the histamine-induced paw edema. The extract substantially decreased the formation of granuloma tissue in chronic inflammation model [44]. *P. amarus* plant product ethanol, liquid and hexane extracts showed an inhibition of LPS-induced production of NO and PGE2. The extracts additionally attenuated the LPS induced secretion of tumor necrosis factor (TNF). Each extracts reduced expression of iNOS and Cyclooxygenase-2 and stifled activation of NF-κB, ut not of AP-1. *P. amarus* stifled induction of interleukin (IL)-1β, IL-10, and interferon-γ in human blood and reduced TNF-α production in-vivo [45].

Anti-venom Activity

The combination of the extract of *P. amarus* and *Andrographis paniculata* plant possess potent venom neutralizing capability and used for therapeutic function in case of snake bite. Di-herbal plant extracts effectively neutralized the cobra snake venom induced lethal activity. About 0.24 mg of di-herbal plant extract is fully able to neutralize the lethal activity of 2 LD50 of genus N. naja venom [46].

Fertility Effect

Fertility in Male

Leaf extract of *P.amarus* increases the level of testosterone but has little or no effect on the levels of Leutinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) [47]. This increase could also be responsible for the sweetening of fertility as a result of the optimum level of androgenic hormone (Testosterone) is needed for normal sex drive in adult male and increase in spermatozoa, hence rise in male fertility [48]. Traditional practitioners also claim to boost the fertility in men.

Anti-fertility in Female

An alcoholic extract of the whole plant of P.amarus dose of 100mg/ kg weight was given orally to cyclic adult mice for 30 days and it was observed that no vital changes were seen in absolute body, organ weights and even in general metabolic status. Cohabited females with normal male mice were unable to become pregnant as their cyclicity was affected [49]. On the other hand, an abortion of some pregnant female mice has reported. Some experiments were designed to check the impact of liquid extract of *P. amarus* (AEPA) leaves on implantation and pregnancy. AEPA reduced the time frame for implantation within the treated rats and caused abortion of pregnant rats. Though the liquid extract of *P. amarus* reduces the time frame for implantation, its abortifacient impact doesn't support the normal claim that it will treat sterility [50].

Conclusion

Phyllanthus amarus belongs to family Euphorbiaceae. It is a small herb having wide range of medicinal properties therefore extensively used across the word. Each country has their own traditional use of *P. amarus* but the way of curing disease is almost common everywhere. Extracts of this plant is used as medicine to treat bronchitis, anaemia, asthma, urinary disorders and leprosy. P.amarus is rich store house of several bioactive compounds such as lignans, phyllanthin, hypothyllanthin, flavonoids, alkaloids, tannins, glycosides, ellagitannins, triterpines, phenyl propanoids, steroids, ricinolic acid, niruricide etc. P.amarus is used in folk mecicine for treating of kidney stone, gallbladder stone, diseases related to liver such as liver cancer and jaundice. In addition to these it also shows anti- inflammatory, anti-tumour, anti-nociceptive and anti-oxidant properties. Further it is also used in the treatment for diarrhoea, dysentery, dropsy, intermittent fevers, gonorrhea, diabetes and chronic infections, skin issues such as skin ulcers, sores, swelling and itchiness, wounds, scabies and tubercular ulcers, ringworm, scabby and crusty lesions. P. amarus is very important medicinal plant therefore, it marketed by prominent companies and recommended in daily used medicine as chyawanprash and its powder.

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