International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

A Review On: Phytoconstituents, Traditional and Medicinal Uses of Phyllantus Amarus

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ABSTRACT:
Throughout history, nature has served as a rich source of numerous medicinal substances to treat a wide range of diseases and health conditions. The primary reason behind the observed therapeutic or pharmacological effects lies in the presence of bioactive compounds and secondary metabolites within these natural sources.

INTRODUCTION:
Throughout history, nature has served as a rich source of numerous medicinal substances to treat a wide range of diseases and health conditions. The primary reason behind the observed therapeutic or pharmacological effects lies in the presence of bioactive compounds and secondary metabolites within these natural sources. Another contributing factor to their success is the structural diversity they offer. These plants can be utilized in their natural form, with crude extracts or essential oils, or they can be processed using various extraction techniques and solvents [1,2]. Every part of the plant, whether it be the leaves, stems, buds, flowers, fruits, bark, pulp, or even the peel, has therapeutic effectiveness. They are readily available and affordable for people from all walks of life [3].
As chemical-based or synthetic drugs are increasingly being associated with safety concerns and reported side effects, the utilization of plants as crude drugs in various forms becomes especially crucial. Establishing quality control standards and standardization procedures for each plant under investigation becomes essential. This ensures accurate plant identification, preserves authenticity, and maintains therapeutic efficacy. Such standardization efforts play a crucial role in upholding the quality, safety, and effectiveness of these medicinal plants [4], while also preventing intentional or unintentional adulteration or substitution [5]. Medicinal plants, whether in the form of pure compounds or standardized extracts, offer abundant opportunities for new drug development due to their unparalleled chemical diversity. Given the rising demand for chemical diversity in drug screening programs and the pursuit of therapeutic drugs from natural sources, global interest in plant chemistry has surged. Research efforts focused on the extraction, isolation, identification, and biological examination of plant constituents have emerged as a prominent field of study. In response, pharmaceutical industries have begun incorporating crude extracts from medicinal plants in their drug manufacturing processes [6].

PHARMACOGNOSTICAL STUDIES:
PHYLLANTUS AMARUS
Phyllanthus amarus, a member of the Euphorbiaceae family, comprises approximately 800 species that inhabit tropical and subtropical regions across the globe [7,8]. Its name, "Phyllanthus," alludes to its unique appearance, where the flower, fruit, and leaf seem fused [9]. Phyllanthus amarus is a slender, branchy, glabrous herb that reaches heights of 30-60 cm, featuring slender, leaf-bearing branchlets and elliptic-oblong, obtuse leaves with a rounded base arranged distichously. The flowers are typically

yellowish, whitish, or greenish, appearing in auxiliary clusters of 1-3 for male flowers and solitary for female ones. The fruits are smooth, depressed-globose capsules located underneath the branches, with seeds characterized by longitudinal parallel ribs on the back and a pale brown color [10]. In India, Phyllanthus amarus is widely distributed as a weed in both cultivated and waste lands [11]. Within the Phyllanthus genus, one can observe all three major growth habits, including trees, shrubs, and herbs, with southern India identified as a genetic hotspot for Phyllanthus species [12]. Phyllanthus amarus, also known as Bhumi amla, belongs to a substantial family of upright or prostrate herbs or shrubs, often containing milky acrid juice [13]. In Unani literature, it is referred to as 'Bhuti,' signifying Bhum Amlak, which translates to Amla of the Land [14]. This plant plays a significant role in the development of green medicines, which are considered safer and more dependable than costly synthetic drugs, free from adverse effects. In Ayurveda, it goes by Sanskrit names like Bhoomy aamlakee, Taamalakee, and Bhoodha tree [15]. Its uses are gaining prominence due to its novel antiviral activity against hepatitis B virus and various other biological activities, such as the treatment of kidney and gallbladder stones, colds, flu, tuberculosis, and liver diseases [16].

COMMON NAMES:

This plant is also known by different common names in the different areas by local people.

It is commonly called as Bhumi amla , carry me seed, stone breaker, wind breaker, leaf flower or gale of wind[17].

Hindi - Bhumi amla, Jangli amli

English - Black catnip, Carry me seed, Child pick-a-back, Gale of wind,

Gulf leaf flower, Hurricane weed, Shatterstone, Stone breaker.

Tamil - Keelanelli (Keezhanelli)

Bengali - Bhui amla

Rajasthani - Gugario

Oriya - Bhuiaola

Telugu - Nela urika

Kannada - Nela-nelli, Kirunelli

Malayalam - Kilanelli

Sanskrit - Bhoomyaamlakee, Bhoodhatree, Tamalakee-

French - Poudre de plomb (ivory coast)

America - Yerbade la nina , Chanca piedra , Hurricane weed

Spanish - Yerba magica [15,18].

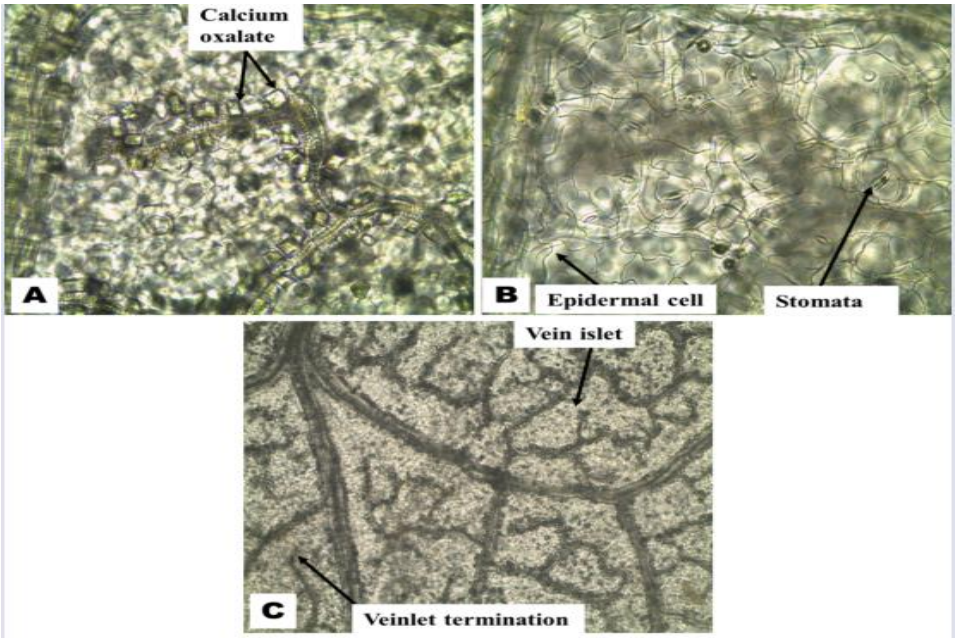
MICROSCOPIC CHARACTERISTICS:

Phyllanthus amarus is a yearly herb with a branching growth pattern, lacking hair on its surface, and typically attains a height within the range of 30 to 60 centimeters. It possesses slender branchlets that bear leaves arranged alternately in two vertical rows. These leaves have an elliptic-oblong shape with blunt tips and a rounded base. The flowers grow from the leaf axils and exhibit colors that can vary from yellowish to whitish or greenish. Male flowers tend to cluster in groups of 1 to 3, while female flowers are solitary. The fruits resemble smooth, depressed-globose capsules located beneath the branches, and the seeds are three-sided (trigonous), pale brown, with longitudinal parallel ribs on their back [19]. Furthermore, the plant produces capsules on stalks, measuring 1 to 2 millimeters in length and having a round, smooth appearance that is 2 millimeters wide, each containing six seeds. One notable feature is the plant's ability to expel its seeds a certain distance away from itself due to its explosive seed capsules. These seeds take on a triangular shape, are light brown, approximately 1 millimeter in length, and possess 5 to 6 ribs on their backs.[20].

MICROSCOPIC CHARACTERSTIC:

The leaves were examined at a microscopic level in accordance with the established procedures outlined in the WHO guidelines on Quality Control Methods for Herbal Materials from 2011. Small sections measuring 4 square millimeters (4 mm^2) were obtained from the fully developed leaf blades. These sections were subjected to approximately two hours of boiling in a chloral hydrate solution. Subsequently, the prepared samples were placed in glycerin and covered with a glass cover slip. The examination of these slides was carried out using a LECIAD light microscope, with observations made at both low power (×10) and high power (×40) magnifications.

The mounted samples were scrutinized for the presence of calcium oxalate crystals, and observations were made regarding stomata and trichomes. Various quantitative parameters, including the count of vein islets, veinlet termination numbers, stomatal count, and stomatal index, were determined. To achieve this, each of these parameters was counted across ten different fields of view, and the values were calculated per square millimeter of the leaf's surface [21]



Parameter	*P. amarus*
Stomatal Number	5 ± 2.8
Epidermal Cell Number	35 ± 2.0
Vein islet Number	10 ± 1.7
Veinlet termination number	6 ± 1.9
The stomatal index [stomata per square mm of epidermis]	12.5 ± 2.1

PHYTOCHEMICAL SCREENING:

Standard protocols were employed to perform chemical analyses on both methanolic extracts and powdered samples in order to ascertain their constituents. These procedures, described by experts such as Trease and Evans in 1989, Harborne in 1998, Sofowara in 1993, and Odebedy and Sofowara in 1978, relied on characteristic changes in color.

To illustrate, the presence of tannins was confirmed when the sample exhibited a brownish-green coloration upon the addition of three drops of ferric chloride. Flavonoids were established to be present when a yellow coloration appeared and then disappeared upon the sequential introduction of 5ml of dilute ammonia solution and concentrated sulfuric acid to a portion of the extract. The confirmation of steroids involved a change in color from violet to blue when 2ml of acetic anhydride and 2ml of sulfuric acid were added to 0.5g of plant extract.

Terpenoids were verified through the development of a reddish-brown coloration at the interface when 2ml of chloroform and 3ml to 5ml of the extract were combined with concentrated sulfuric acid. Saponins were identified in the plant by a frothing test. Cardiac glycosides were confirmed by the appearance of a brown ring at the interface when 2ml of glacial acetic acid containing 1 drop of ferric chloride solution and 1ml of concentrated sulfuric acid were introduced. Alkaloids' presence was affirmed using Dragendorff reagent, which produced a reddish-brown precipitate upon interaction with the sample.[22].

Phytochemicals	***P.amarus***
Alkaloids	+
Flavonoids	+
Terpenoids	+
Saponins	+
Tannins	+
steroid	+
Resins	-
Cardiac glycosides	+

+ = present
- = absent

CHEMICAL CONSTITUENTS:

Phyllanthus amarus, also known as "bhumi amla" or "stonebreaker," is a plant that is used in traditional medicine for its potential medicinal properties. It contains various chemical constituents, including:

1. Alkaloids: Phyllanthus amarus contains alkaloids like phyllanthine and hypophyllanthine, which are believed to have therapeutic effects.

2. Flavonoids: These are a group of polyphenolic compounds with antioxidant properties. Flavonoids found in Phyllanthus amarus include quercetin, kaempferol, and rutin.
3. Lignans: The plant contains lignans such as phyllanthin and hypophyllanthin, which are believed to have hepatoprotective (liver-protecting) properties.
4. Tannins: Tannins are polyphenolic compounds that may contribute to the plant's antioxidant and anti-inflammatory properties.
5. Essential Oils: Phyllanthus amarus may contain essential oils that contribute to its aroma and potential medicinal properties.
6. Terpenoids: Some terpenoids may also be present in Phyllanthus amarus, contributing to its chemical composition.

Alkaloids, flavonoids, hydrolysable tannins (Ellagitannins), major lignans, polyphenols, triterpenes, sterols, and volatile oil are among P. amarus's secondary metabolites. Lignans (phyllanthin, hypophyllanthin, nirurin niranthin, phyltetralin, niranthine, nirtetralin, etc.) are the primary active ingredients of P. amarus.

S. No.	Secondary metabolites		Phyto-constituents	References
1	Lignans		Phyllanthin, hypophyllanthin, niranthin, phyltetralin, nirtetralin, isonirtetralin, hinokinin	Morton (1981), Sharma et al. (1993), Chevallier (2000), Srivastava et al. (2008), Kassuya et al. (2006), Huang et al. (2003), Singh et al. (2009)
			Lintetralin, isolintetralin, demethylenedioxy-niranthin, 5-demethoxy-niranthin	Maciel et al. (2007)
			(3-(3,4-dimethoxy-benzyl)-4-(7-methoxy-benzo[1,3]dioxol-5-yl-methyl)-dihydrofuran-2-one, 4-(3,4-dimethoxy-phenyl)-1-(7-methoxy-benzo[1,3]dioxol-5-yl)-2,3-bis-methoxymethyl-butan-1-ol	Singh et al. (2009)
2	Flavonoids		Rutin, astragalin, kaempferol, quercetin-3-O-glucoside, quercetin, quercitrin	Morton (1981), Foo and Wong (1992), Foo (1993a, 1995), Londhe (2008)
3	Hydrolysable tannin (Ellagitannins)	Tannin precursors	Gallic acid, ellagic acid, gallocatechin	Foo (1993a, 1995)
		Simple tannins	1,6-digalloylglucopyranose, 4-O-galloylquinic acid	Foo (1993a, 1995)
		Complex tannins	Geraniin, amariin, furosin, geraniinic acid B, amariinic acid, amarulone, repandusinic acid A, corilagin, isocorilagin, elaeocarpusin, phyllanthusiin A, B, C and D, melatonin	Foo and Wong (1992), Foo (1993a, 1995)
4	Alkaloids		Securinine, dihydrosecurinine, tetrahydrosecurinine, securinol, phyllanthine, allo-securine, nor-securinine, epibubbialine, isobubbialine	Houghton et al. (1996), Kassuya et al. (2006)
			4-methoxy-nor-securinine, 4-methoxy dihydrosecurinine, 4-methoxytetrahydrosecurinine, 4 hydrosecurinine	Foo and Wong (1992)
			Phenazine and phenazine derivatives	Foo (1993a)
5	Triterpenes		2Z, 6Z, 10Z, 14E, 18E, 22E-farnesylfarnesol	Maciel et al. (2007)
			Lupeol, phyllanthenol, phyllanthenone, phyllantheol, Oleanolic acid, ursolic acid	Foo and Wong (1992)
6	Sterols		Amarosterol A, amarosterol B	Ahmad and Alam (2003)
7	Volatile oil		Linalool, phytol	Moronkola et al. (2009)

TRADTIONAL USE:

The traditional applications of the Phyllanthus amarus herb encompass a wide array of health issues, including diarrhea, dysentery, dropsy, jaundice, intermittent fevers, urinogenital disorders, scabies, and

wounds. Additionally, it is utilized in the management of kidney problems, urinary bladder disturbances, pain, gonorrhea, diabetes, and chronic dysentery. When applied topically, it addresses various skin problems, such as ulcers, sores, swelling, itching, wounds, bruises, scabies, ulcers, edematous swellings, tubercular ulcers, ringworm, and scabby, crusty lesions.

Phyllanthus amarus's impact on the excretory system is attributed to its antiurolithic properties, making it beneficial in treating kidney and gallstones, other kidney-related issues, appendix inflammation, and prostate problems. [23-25]

Given its efficacy in gastrointestinal disorders, it is employed for conditions like dyspepsia, colic, diarrhea, constipation, and dysentery. The herb also finds use in addressing female concerns such as leucorrhoea, menorrhagia, and mammary abscesses, while also serving as a galactagogue. For the treatment of chronic dysentery, the infusion of young plant shoots is administered. Fresh leaf paste is known for its wound-healing capabilities and is used to remedy white spots on the skin and jaundice. Stem juice is another application for wound healing. The entire plant extract is used to manage urinary problems and liver swelling. Root extract is employed to alleviate stomach pain, and the flower paste is applied externally as an antidote for snake bites. [26-29]

MEDICINAL AND PHARMACOLOGICAL USES:

1. Anticancer activity:

The aqueous extract of Phyllanthus amarus demonstrates strong anti-cancer effects in the context of sarcoma development induced by 20-methylcholanthrene (20-MC). This extract effectively hinders the activity of DNA topoisomerase II in mutant cell cultures and also acts as an inhibitor for the cell cycle regulatory enzyme cdc 25 tyrosine phosphatase in Saccharomyces cerevisiae. The proposed mechanisms behind Phyllanthus amarus' anticarcinogenic and anti-tumor properties involve its ability to block the metabolic activation of carcinogens and impede the cell cycle regulators responsible for cancerous growth and DNA repair.[30]

2. Antiamnesic Activity:

The potential of the aqueous extract from the leaves and stems of Phyllanthus amarus to counteract memory impairment was investigated in male Swiss albino mice, focusing on its nootropic effects and its impact on brain cholinesterase activity. In this study, amnesia was induced using scopolamine and diazepam as standard drugs, and cognitive function was assessed using the elevated plus maze and passive avoidance paradigm.

The findings indicate that the aqueous extract demonstrated a dose-dependent reduction in the memory deficits induced by diazepam and scopolamine, along with a decrease in brain cholinesterase activity. This reduction in cholinesterase activity is associated with an increase in acetylcholine concentration in the brain, which is known to enhance memory. These results suggest a rationale for considering this therapeutic potential in the management of patients with cognitive disorders. [31]

3. Antioxidative Activity:

The DPPH assay is employed to assess antioxidant capacity by gauging the reduction of the stable radical DPPH to a yellow-colored compound called diphenyl picryl hydrazine. Consequently, the ability of the test samples to neutralize this radical is indicative of their antioxidative potential. The potent antioxidant characteristics of Phyllanthus amarus are evident in our current investigation, which evaluated both phyllanthin and Phyllanthus amarus extract. The results showed that the scavenging of DPPH free radicals is concentration-dependent, reaching its peak at a concentration of 20 mol/ml for phyllanthin and

300 g/ml for the Phyllanthus amarus extract the remarkable antioxidative capacity of phyllanthin is highlighted by its low IC50 value of 7.4 mol/ml in comparison to Phyllanthus amarus extracts. This underscores the significant role of phyllanthin in producing antioxidative effects.

In a separate study, it was observed that boiled water extracts of both fresh and dried Phyllanthus amarus plants exhibited notably higher antioxidant activity when compared to the microwave-assisted extraction method used for extraction. [32]

4. Anti-Inflammatory Activity:

The anti-inflammatory potential of Phyllanthus amarus was assessed using various models, including rat Kupffer cells, macrophages RAW264.7, human whole blood, and mice. Two different extracts of Phyllanthus amarus (hexane and ethanol/water extracts) were evaluated for their anti-inflammatory effects on cells stimulated with lipopolysaccharide. Additionally, the anti-inflammatory impact was tested in mice with acute toxic hepatitis induced by galactosamine/lipopolysaccharide. The evaluation parameters included the measurement of nitrite, prostaglandin E2, and cytokines using various assays such as the Griess assay, radioimmunoassay for prostaglandin E2, and enzyme-linked immunosorbent assay for cytokines. Other inflammatory markers, like endotoxin-induced nitric oxide synthase (iNOS) and cyclooxygenase (COX-2), were assessed via Western blot, while the activation of NF-κB and activator protein 1 (AP-1) was determined using electrophoretic mobility shift assay (EMSA).The results demonstrated that both the ethanol/water extracts and hexane extracts effectively inhibited the lipopolysaccharide-induced production of nitric oxide (NO) and prostaglandin E2 (PGE2) in Kupffer cells and macrophages RAW264.7. These extracts also mitigated the lipopolysaccharide-induced secretion of tumor necrosis factor (TNF-α) in macrophages RAW264.7 and human whole blood. [33] Furthermore, Phyllanthus amarus extracts reduced the expression of endotoxin-induced nitric oxide synthase iNOS and cyclooxygenase COX-2, while inhibiting the activation of nuclear factor NF-κB. Phyllanthus amarus also hindered the induction of interferon-γ (IFN-γ), interleukin (IL)-1β, and interleukin (IL)-10 in human whole blood, and decreased tumor necrosis factor (TNF-α) production in vivo.Moreover, experiments were conducted to identify the chemical compounds responsible for these anti-inflammatory effects. In tests evaluating the anti-inflammatory properties of purified lignans from Phyllanthus amarus and various plant extracts, it was found that the hexane extract and the lignan-rich fraction, including lignans such as niranthin, phyltetralin, and nirtetralin, exhibited notable anti-inflammatory characteristics. [34]They inhibited carrageenan-induced rat paw edema, reduced the increase in interleukin (IL)-1β tissue levels induced by carrageenan, and inhibited neutrophil influx, bradykinin activating factor, platelet-activating factor, and endothelin-1-induced paw edema.Additionally, an intriguing study explored the anti-inflammatory effects of a soft drink made from the leaf extract of Phyllanthus amarus and found that it exhibited anti-inflammatory activity similar to the reference compound Ibuprofen. Collectively, these studies confirm Phyllanthus amarus as a potent anti-inflammatory plant and highlight lignans as potent phyto-compounds with anti-inflammatory properties.[35]

5. AntiDiabetic Activity:

Diabetes is a metabolic disorder affecting the processing of carbohydrates, fats, and proteins and stands as one of the most widespread endocrine diseases globally. To investigate the potential of Phyllanthus amarus as an antidiabetic agent, an experimental model was employed. Fasted rats were induced with diabetes through a single intraperitoneal injection of 120 mg/kg of alloxan monohydrate. Subsequently, they were administered two doses of aqueous and hydroalcoholic extracts of Phyllanthus amarus orally, and their outcomes were compared to a normal control group that received distilled water only. After a 15-

day treatment period, the results showed a significant decrease in blood glucose levels due to the aqueous and hydroalcoholic extracts of Phyllanthus amarus. Serum analysis of the treated experimental animals indicated an increase in insulin levels and a reduction in malondialdehyde concentration, providing evidence of the potential antidiabetic properties of these extract. [36] In another study, the methanolic extract of Phyllanthus amarus was observed to inhibit lipid peroxidation and scavenge hydroxyl and superoxide radicals.[37] Considering the association between free radicals and diabetes, this suggests that one potential mechanism of action may involve the scavenging of free radicals. [38] Nevertheless, further experimental investigations are needed to isolate the specific chemical constituents and elucidate their mechanisms of action.

6. Anticonvulsant Activity:

Epilepsy stands as a prominent neurological condition characterized by the occurrence of recurring seizures. The two most widely proposed mechanisms involve changes in voltage-dependent ion channels, such as a decrease in inhibitory GABA-mediated activity or an increase in excitatory glutamate-mediated signals. This chronic and progressive disorder of the central nervous system affects a substantial portion of the global population. In the pursuit of herbal remedies, the anticonvulsant potential of aqueous and ethanolic extracts of Phyllanthus amarus was examined using pentylenetetrazole (PTZ) and maximal electroshock-induced seizures (MES) in Swiss albino rats. The results revealed that both the ethanolic and aqueous extracts from the leaves and stems of Phyllanthus amarus were notably effective in preventing hind limb extension induced by MES and seizures induced by PTZ.[39]

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