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Sonia Verma
Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak-124001, Haryana, India.

Hitender Sharma
Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak-124001, Haryana, India.

Munish Garg
Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak-124001, Haryana, India.

Correspondence:
Sohail
Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak-124001, Haryana, India.

Phyllanthus Amarus: A Review

Sonia Verma, Hitender Sharma, Munish Garg

Abstract
Herbs have always formed an integral part of human health and are used in the treatment of several human diseases. One of such species which have wide patronage of use is *Phyllanthus amarus*. This herb is in traditional medicine for more than 3,000 years. The plant has also served as lead for several experimental investigations that explored its phytochemical constituents and pharmacological uses. Present paper compiles traditional uses, phytoconstituents and pharmacological properties of *Phyllanthus amarus*.

Keywords: *Phyllanthus amarus*, traditional uses, chemical constituents, pharmacological properties.

1. Introduction
Phyllanthus amarus is a plant of the family Euphorbiaceae and has about approximately 800 species which are found in tropical and subtropical countries of the world [1, 2]. The name '*Phyllanthus*' means "leaf and flower" and named so because of its appearance where flower, fruit and leaf appears fused [3]. *Phyllanthus amarus* is a branching annual glabrous herb which is 30-60 cm high and have slender, leaf-bearing branchlets, distichous leaves which are subsessile elliptic-oblong, obtuse, rounded base. Flowers are yellowish, whitish or greenish, auxillary, males flowers in groups of 1-3 whereas females are solitary. Fruits are depressed-globose like smooth capsules present underneath the branches and seeds are trigonous, pale brown with longitudinal parallel ribs on the back [4].
The plant has been found in Philippine, Cuba, Nigeria and among others. In India, *Phyllanthus amarus* is widely distributed as a weed in cultivated and waste lands [5].

2. Traditional Uses
Phyllanthus amarus herb has found its traditional usefulness in several health problems such as diarrhoea, dysentery, dropsy, jaundice, intermittent fevers, urinogenital disorders, scabies and wounds. Further, these are used in the treatment of kidney problems, urinary bladder disturbances, pain, gonorrhea, diabetes and chronic dysentery. Topically, it is used for several skin problems ranging from skin ulcers, sores, swelling and itchiness, wounds, bruises, scabies, ulcers and sores, edematous swellings, tubercular ulcers, ringworm, scabby and crusty lesions. Its effect in excretory system is due to its antiurolithic property and is used in the treatment of kidney/gallstones, other kidney related problems, appendix inflammation and prostate problems [6-8]. Because of its efficacy in the field of gastro-intestinal disorders it is used in the treatment of disorders like dyspepsia, colic, diarrhea, constipation and dysentery. The herb has found use in several female problems such as in leucorrhoea, menorrhagia and mammary abscess and can act as galactagogue. The young shoots of plant are administered in the form of an infusion for the treatment of chronic dysentery. Fresh leaf paste has wound healing capacity and used to cure white spots on skin & jaundice. The stem juice is also used as wound healers. The whole plant extract is used in urinary problems & swelling of liver. The root extract is used to cure stomach pain. The flower paste of plant is applied externally as antidote against snake bite [9-12].

3. Phytochemical Studies
Phyllanthus amarus have numerous phytocompounds such as alkaloids, flavonoids, tannins, lignins, polyphenolic compounds and tetracyclic triterpenoids. Several phytoconstituents isolated from this plant are enlisted in Table 1.

4. Pharmacological Activity
4.1 Anticancer activity
The aqueous extract of *Phyllanthus amarus* demonstrates potent anticancer activity against 20-metylcholanthrene (20-MC) induced sarcoma development. The aqueous extract inhibits DNA

topoisomerase II of mutant cell cultures and inhibited cell cycle regulatory enzyme cdc 25 tyrosine phosphatase of *Saccharomyces cerevisiae*. The anticarcinogenic and anti-tumour activity of *Phyllanthus amarus* proposed to be inhibition of metabolic activation of carcinogen as well as the inhibition of cell cycle regulators responsible for cancerous growth and DNA repair [23].

Table 1: Phytochemicals in *Phyllanthus amarus*

Alkaloids	**Isobubbialine and Epibubbialine** [13]
Tannins	Geraniin, corilagin, 1,6-digalloylglucopyranoside rutin , quercetin-3-*O*-glucopyranoside , Amarulone, Phyllanthusiin D & Amariin [14, 15].
Lignans	Niranthin, Nirtetralin, Phyltetralin, Hypophyllanthin, Phyllanthin, demethylenedioxy-niranthin, 5-demethoxy-niranthin, Isolintetralin [16, 17, 18, 19].
Ellagitannins	Amariin, 1-galloyl-2,3-dehydrohexahydroxydiphenyl (DHHDP)-glucose, Repandusinic acid, Geraniin, Corilagin, Phyllanthusiin D, and flavonoids namely rutin, and quercetin 3-O-glucoside, 1-O-galloyl-2,4-dehydrohexahydroxydiphenoyl-glucopyranose elaeocarpusin, repandusinic acid A and geraniinic acid [20, 21] .
Volatile oil	Linalool and Phytol [22].
Tritepene	(2Z, 6Z, 10Z, 14E 18E, 22E-farnesil farnesol) [19].

4.2 Antiamnesic Activity

Antiamnesic activity of aqueous extract of leaves and stems of *Phyllanthus amarus* were evaluated for nootropic effects and brain cholinesterase activity in male Swiss albino mice. Scopolamine and diazepam were used as standard drugs to produce amnesia and elevated plus maze and passive avoidance paradigm as models for evaluation of cognitive functions. The result reveals a dose dependent attenuation of diazepam and scopolamine induced amnesic deficits and reduction in brain cholinesterase activity. Since the reduction in cholinesterase in linked with increase acetylcholine concentration in brain which further is responsible for improving memory, provide a rationale to use this therapeutic potential in the management of patients with cognitive disorders [24].

4.3 Antioxidative Activity

The DPPH assay is used to determine antioxidant potential, which is based on the reduction of stable radical DPPH to yellow coloured diphenyl picryl hydrazine. Thus, the ability of the test samples to quench this radical is a measure of its antioxidative ability. *Phyllanthus amarus* have powerful antioxidant property which is evident from the present study in which phyllanthin and *Phyllanthus amarus* extract were evaluated. In the experiment, it was observed that the DPPH free radical scavenging activity was concentration dependent and reaches maximum at a concentration of 20 mol/ml for phyllanthin and 300 g/ml for *Phyllanthus amarus* extract. Further, since phyllanthin possess very high antioxidative property as evident by its low IC_{50} value of 7.4 mol/ml as compared to *Phyllanthus amarus* extracts suggest its contribution in antioxidative effects [7]. In another study, it has been found that boiled water extract of the fresh and dried *Phyllanthus amarus* plant had comparatively greater antioxidant activity than microwave assisted extraction method employed for the extraction [25].

4.4 Antinociceptive Activity

The hydroalcoholic extract of four *Phyllanthus* species namely *Phyllanthus amarus*, *Phyllanthus orbiculatus*, *Phyllanthus fraternus* and *Phyllanthus stipulatus* were given intraperitoneally and evaluated in acetic acid-induced writhing and formalin and capsaicin-induced licking effects. In acetic acid-induced writhing test it was found that all produced significant inhibition of acetic acid-induced abdominal constrictions, with mean ID_{50} values of 0.3, 1.8, 7.4 and 26.5 mg/kg for *Phyllanthus amarus*, *Phyllanthus orbiculatus*, *Phyllanthus fraternus* and *Phyllanthus stipulatus*, respectively. Similarly, in the formalin test, it was observed that the hydroalcoholic extract of four species produced graded inhibition against both phases of formalin-induced licking, inhibition in licking being more active in the late phase. Apart from the above models, hydroalcoholic extract of the species also elicited significant reduction in the capsaicin-induced neurogenic pain. It was also observed that hydroalcoholic extract of the *Phyllanthus* species was less potent and efficacious when given orally compared to intraperitoneal route [4].

4.5 Antimicrobial activity

Antimicrobial activity of ethanol and water extracts of *Phyllanthus amarus* were evaluated against the test organisms *Salmonella typhi.* Ethanolic, cold water extract and hot water extract of *Phyllanthus amarus* were employed for antimicrobial evaluation by agar cup diffusion method which were compared against standard antibiotics that were evaluated by disk diffusion method. The result demonstrates ethanolic extract to be most potent against the test bacteria with diameter of 8.0 mm as growth inhibition zone. This study establishes one of the traditional uses of *Phyllanthus amarus* against typhoid fever [26]. In another study, hexane, petroleum ether, chloroform, acetone and methanol extract of Phyllanthus leaves were tested for antibacterial activity against *Pseudomonas aeruginosa*, *Klebsiella pneumonia, Proteus mirabilis*, *Streptococcus faecalis, Enterobacter species, Serratia marcescens, Staphylococcus aureus* and *Escherichia coli* by agar well diffusion method. The results demonstrated methanol extract of *Phyllanthus amarus* for highest inhibitory activity against above bacterial species [27]. Similarly, in another study antimicrobial potential of *Phyllanthus amarus* were investigated using agar well diffusion method for activity against several drug resistant pathogens such as *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus* and *Klebsiella Species*. The results revealed minimum inhibitory

concentration (MIC) of the ethanolic plant extracts on *Escherichia coli*, *Staphylococcus aureus, Pseudomona aeruginosa* and *Klebsiella Species* were at 10 mg/ml, 50 mg/ml, 150 mg/ml and 100 mg/ml while the minimum bactericidal concentration were at 50 mg/ml, 100 mg/ml, 150 mg/ml and 150 mg/ml respectively [10]. Further studies on hexane, chloroform, ethyl acetate, acetone and methanol extract of stem bark extracts of *Phyllanthus amarus* demonstrated the antimicrobial activity for all these extracts with a diameter that ranges between 11 mm 24 mm against *Streptococcus pyogenes, Staphylococcus aureus, Salmonella typhi, Escherichia coli, Candidas albican, Aspergillus flavus* [8]. The antimicrobial activity of the methanolic extract of *Phyllanthus amarus* as studied by agar dilution method and disc diffusion showed significant concentration-dependent antibacterial activity specifically for gram-negative microbes.

It was also observed that antibacterial action was mainly due to the isolated phyllanthin [1]. These studies signify the antimicrobial potential of *Phyllanthus amarus* and need of isolation of some potential phytoconstituents from this species.

4.6 Antileptospiral Activity

Leptospirosis is globally important disease found mainly wherever human come in contact with the urine of infected animals or urine contaminated environment. *Phyllanthus amarus* have been investigated for the antileptospiral activity by micro dilution tests and tube dilution technique. The results revealed the inhibitory action of methanolic and aqueous extract of whole plant of *Phyllanthus amarus* against leptospira [28].

4.7 Anticonvulsant Activity

Epilepsy is a major neurological disorder characterized by the occurrence of recurrent seizures. The two widely proposed mechanisms involve alterations in the voltage-dependent ion channels such as reduction in inhibitory GABA-mediated drive or increase in excitatory glutamate mediated inputs. This chronic progressive CNS disorder affects a large population of the world. In search of herbal treatment, aqueous and ethanolic extract of *Phyllanthus amarus* were evaluated for anticonvulsant effect using pentylenetetrazole (PTZ) and maximal electroshock-induced seizures (MES) in swiss albino rats. The result showed ethanolic and aqueous extract of leaves and stem of *Phyllanthus amarus* significantly effective in abolishing hind limb extension induced by MES as well as PTZ induced seizures [29].

4.8 Antidiabetic Activity

Diabetes is a metabolic disorder of carbohydrate, fat and protein and is considered as the world's largest endocrine disease [30]. The antidiabetic potential of *Phyllanthus amarus* investigated in an experiment model where fasted rats were made diabetic by single intraperitoneal injection of 120 mg/kg of alloxan monohydrates and then two doses of the aqueous and hydroalcoholic extract of *Phyllanthus amarus* administered orally which were then compared with the normal control group that received distilled water only. After 15 days treatment the result demonstrates aqueous and hydroalcoholic extract of *Phyllanthus amarus* decrease the blood glucose level significantly. Serum analysis of the treated experimental animals showed an increase in insulin and reduction in the malondialdehyde concentration, therefore demonstrated the potential antidiabetic property of aqueous and hydroalcoholic extract of *Phyllanthus amarus* [31]. In another study the methanolic extract of *Phyllanthus amarus* was found to inhibit lipid perxidation & scavenge hydroxyl and superoxide radicals [32]. Since free radicals are linked with diabetes, therefore quenching of free radical could be one mechanism of action [40]. However, there is a need of further experimental studies in order to isolate chemical constituents and their mechanism of action.

4.9 Anti-Inflammatory Activity

The anti-inflammatory potential of *Phyllanthus amarus* was evaluated using different models such as rat Kupffer cells, macrophages RAW264.7, human whole blood and in mice. Two different extracts of *Phyllanthus amarus* (hexane and ethanol/water extracts) and their anti-inflammatory effect was evaluated against the lipopolysaccharide stimulated above mentioned test cells. In addition, anti-inflammatory effect was evaluated in mice that were treated with galactosamine/lipopolysaccharide for inducing acute toxic hepatitis. The evaluation parameters were production of nitrite, prostaglandin E_2 and cytokines that were measured by Griess assay, prostaglandin E_2 by radioimmunoassay and latter by enzyme-linked immunosorbent assay. The other inflammatory markers such as endotoxin-induced nitric oxide synthase (iNOS) and cyclooxygenase (COX-2) were determined by Western blot and activation of NF-κB and activator protein 1 (AP-1) by electrophoretic mobility shift assay (EMSA). The results revealed ethanol/water extracts and hexane extracts effective in inhibition of liopolysaccharide induced production of nitric oxide (NO) and prostaglandin E2 (PGE_2) in Kupffer cells and in macrophages RAW264.7. The extracts also attenuated the lipopolysaccharide induced secretion of tumor necrosis factor (TNF-α) in macrophages RAW264.7 as well as in human whole blood. Hexane and ethanol/water extracts of *Phyllanthus amarus* reduced expression of endotoxin-induced nitric oxide synthase iNOS and cyclooxygenase COX-2 and inhibited activation of nuclear factor NF-κB. *Phyllanthus amarus* also inhibited induction of interferon-γ (IFN-γ), interleukin (IL)-1β and interleukin (IL)-10 in human whole blood and reduced tumor necrosis factor (TNF-α) production *in-vivo* [33]. Further, experimental studies have been done to determine the chemical compounds responsible for the activity. In an attempt to test phytoconstituents and extracts of *Phyllanthus amarus* for anti-inflammatory effect, the purified lignans of *Phyllanthus amarus* and different extracts obtained from this plant were evaluated in carrageenan induced paw oedema and neutrophil influx model of inflammation. The result showed that hexane extract and the lignan-rich fraction, or lignans phyltetralin, nirtetralin and niranthin inhibited carrageenan-induced rat paw oedema, lower the increase of interleukin (IL)-1β tissue levels induced by carrageenan and inhibited neutrophil influx, bradykinin activating factor, platelet activating factor and endothelin-1-induced paw oedema. These results show that the hexane extract, the lignan-rich fraction and the lignans niranthin, phyltetralin and nirtetralin exhibited marked anti-inflammatory properties [34]. Another interesting study where anti-inflammatory effect of soft drink prepared from the leaf extract of *Phyllanthus amarus* was evaluated for its anti-inflammatory effect and the result revealed anti-inflammatory activity of soft drink similar to reference compound Ibuprofen [35]. All these studies acknowledge *Phyllanthus amarus* as potent anti-inflammatory plant and lignins as potent phyto-compounds.

4.10 Antifertility Activity

Phyllanthus amarus possess antifertility activity. This activity was shown in the experimental study where alcoholic extract of *Phyllanthus amarus* brought changes in 3-beta and 17-beta hydroxyl steroid dehydrogenase (HSDs) levels, thereby effecting

hormonal conversions in the female mice that confirmed by observation of no pregnancy in cohabited normal females and male mice [36].

4.11 Nephroprotective and cardioprotective activity
Nephroprotective and cardioprotective effect of *Phyllanthus amarus* is evident from the study in which methanol extract of *Phyllanthus amarus* leaves caused a significant dose dependent decrease in the levels of total cholesterol, urea, total protein, uric acid, and prostatic, alkaline and acid phosphatases, aspartate transaminase (AST) and alanine transaminase (ALT) [37]. Since increase in these enzymes is related to hepatic and heart disorders therefore their reduction shows that the leaves of *Phyllanthus amarus* have hepato protective, nephroprotective and cardioprotective properties.

4.12 Hepatoprotective effect
Hepatoprotective effects of aqueous extract from *Phyllanthus amarus* on ethanol-induced rat hepatic injury were studied in *in vitro* study where *Phyllanthus amarus* increases the percentage 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) reduction assay and decreased the release of aspartate transaminase (AST) and alanine transaminase (ALT) in rat primary cultured hepatocytes treated with ethanol. The results reveal that treatment of rats with *Phyllanthus amarus* extract orally brought cell recovery in ethanol-induced liver injury by bringing the levels of aspartate transaminase (AST), alanine transaminase (ALT), high-sensitivity human thyroglobulin (HTG) and Tumor necrosis factor (TNF-α) to normal. Histopathological study confirmed the beneficial effect of *Phyllanthus amarus* with its potential antioxidant activity [38].

4.13 Antiviral activity
Phyllanthus amarus possess antifungal, antiviral and anticancerous properties [4]. Further, evaluation of antiviral activity of *Phyllanthus* species were evident from experiment study where aqueous extract of *Phyllanthus amarus* along with other species of *Phyllanthus* genus were evaluated against Herpes Simplex Virus type-1 and Herpes Simplex Virus type-2 in vero cells by quantitative polymerase chain reaction. Western blot and 2D-gel electrophoresis were used to study protein expressions of treated and untreated infected vero cells. *Phyllanthus amarus* along with *Phyllanthus urinaria* demonstrate the strongest antiviral activity against Herpes Simplex Virus type-1 and Herpes Simplex Virus type-2 which is proposed to its action in the early stage of infection and replication [39].

4.14 Haematological Properties
Phyllanthus amarus has been found to produce some haematological changes in experimental studies. When albino rats were treated with the *Phyllanthus amarus* aqueous extract prepared from the whole plant, dose dependent decrease in erythrocyte sedimentation rate (ESR) and packed cell volume (PCV) was observed. Circulating leucocytes and neutrophils count were significantly increased in rats treated with 100 mg/kg of aqueous extract of *Phyllanthus amarus* as evident by total and different count studies of blood of experimental animals. In addition quantitative analysis of alanine aminotransferases (ALT) and aspartate aminotransferases (AST) gave significantly higher values of alanine aminotransferases (ALT) in treated rats. Author has suggested immunostimulant potential of plant [5, 41].

5. Conclusion
Phyllanthus amarus herb is widely used Tropical countries including India. It has significant traditional uses, some of them have been experimentally established and an attempt has been made to isolate potential chemical constituents and their mechanism of action. Present review had compiled the traditional uses, pharmacological properties and chemical constituents present, which can be useful information for further study on this plant.

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