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Recent Advances in Pharmacological and Phytochemistry Studies on *Phyllanthus amarus*

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Abstract

The use of medicinal plants for the treatment of various diseases has been increased due to minimum side effect compared to synthetic drug. Further the herbal products are considered as safe drugs. *Phyllanthus amarus* claimed tribal people for remedy of different diseases namely diarrhoea, dysentery, dropsy, jaundice, intermittent fevers, kidney problems, urinary bladder disturbances, pain, gonorrhea, diabetes, urogenital disorders, chronic dysentery, skin ulcers, sores, swelling, itchiness, tubercular ulcers, ringworm, scabies and wounds. *Phyllanthus amarus* contains isobubbialine, epibubbialine, securinine, nor-securinine, dihydrosecurinine, geraniin, corilagin, 1,6-digalloylglucopyranoside rutin , quercetin3-O-glucopyranoside, amarulone, niranthin, nirtetralin, phyltetralin, hypophyllanthin, phyllanthin, hypo-phyllanthin, demethylenedioxy-niranthin, kaempferol, astragalin, etc chemical constituents in its different parts. The extract of *Phyllanthus amarus* retains multiple pharmacological activities such as Anticarcinogenic, Antiproliferative, Gastroprotective, Cardioprotective, Antileptospiral, Antibacterial, Antidiabetic, Antiviral, Antivenom, Antiinflammatory etc. We planned to illustrate the recent studies appeared in Phytochemisty and Pharmacological activities of *Phyllanthus amarus* in order to highlight its multi-activity properties.

1 Introduction

Medicinal plants may be defined as those plants that are commonly used in treating and preventing specific ailments and that are generally considered to be harmful to humans. From thousands of year plants have been an important source of medicine and plays a key role in world health. It is estimated that approximately one quarter of prescribed drugs are plant extracts or active ingredients obtained from plant sources. World Health Organization estimates that about 80% of these people rely almost exclusively on traditional medicine for their primary healthcare needs. Medicinal plants are the "backbone" of traditional medicine, which means more than 3.3 billion people in the less developed countries utilize medicinal plants on a regular basis[1].

Medicinal plants not used only for the treatment of diseases but also as potential material for maintaining good health and conditions. The reasons for this is because of their better cultural acceptability, better compatibility and adaptability with the human body and pose lesser side effects. Medicinal plant contains chemical compounds that dictate their therapeutic potency. Researchers have shown that different plants contain different bioactive components at different concentrations. The higher the amount of the important phytochemical in medicinal plants, the greater therapeutic potency or medicinal importance of the plants[1,2].

Phyllanthus is one of the ancient medicinal plants cultivated for its highly priced fruits and other parts. The genus Phyllanthus belongs to family Euphorbiaceae, is one of the largest genera of flowering plants consists of about 800 species which are distributed in a wide range of habitats exhibiting relatively wider range of habits such as annual or biennial herbs, shrubs and trees throughout the tropical and subtropical regions of both the hemispheres.

The name 'Phyllanthus' means "leaf and flower" and named so because of its appearance where flower, fruit and leaf appears fused[3]. Different species of Phyllanthus are considered to be very effective and rich in biochemical compounds used in health care, food and cosmetic industry. Numerous phytochemical and bioactivity studies have been carried out on Phyllanthus species, resulting in the isolation and identification of various compounds (alkaloids, coumarins, flavonoids, lignans, and terpenes). The major lignans of the genus namely, phyllanthin and hypophyllanthin, have been shown to be antihepatotoxic against carbon tetrachloride and galactosamine induced hepatotoxicity.

Phyllanthus amarus commonly known as Bhumi amla, is upright or prostrate herbs or shrubs, often with milky acrid juice. In Unani literature, it is described by the name of 'Bhuti' which means Bhum Amlak - Amla of Land. *Phyllanthus amarus* has been found throughout the tropics and sub- tropics such as West Africa (including Nigeria and Ghana), Europe, Asia (including China, Pakistan, India and Malaysia Indian ocean), central and south America.

In India, it is widely distributed as a weed in cultivated and waste lands. It is an annual herb grows to a height 6 inches to15 inches. Stem is angular with numerous distichous, elliptic oblong leaves. 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[4-6].

Phyllanthus amarus herb has a number of traditional uses such as diarrhoea, dysentery, dropsy, jaundice, intermittent fevers, kidney problems, urinary bladder disturbances, pain, gonorrhea, diabetes, urogenital disorders, chronic dysentery, skin ulcers, sores, swelling, itchiness, tubercular ulcers, ringworm, scabies and wounds. It is also used in cough, asthma, other bronchial infections, kidney related problems, appendix inflammation and prostate problems. Because of its efficacy in the field of gastro-intestinal disorders it is used in the treatment of disorders like dyspepsia, colic, constipation and dysentery. The herb has found to be effective in several female problems such as in leucorrhoea, menorrhagia and mammary abscess and can act as galactagogue[7-9].

Hence it will be worthy to review on *Phyllanthus amarus* and produce data mainly on the pharmacological activities and chemical constituents of the plant to the scientists.

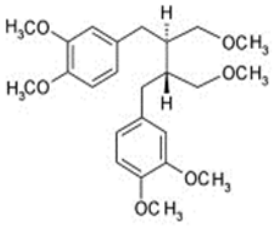
2 Phytochemistry of *Phyllanthus amarus*

Phyllanthus amarus have numerous phytochemical constituents such as alkaloids, phenols, tannins, and flavonoids, terpenoids, steroids, saponins, carbohydrates etc displayed in table 1 & Fig 1.

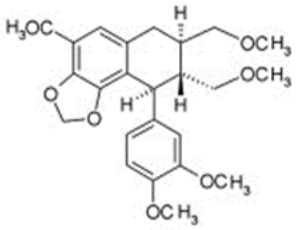
Table 1: Phytochemicals in *Phyllanthus amarus*

Bioactive compounds	Phytochemicals	References
Alkaloids	Isobubbialine, Epibubbialine, Securinine, nor-securinine, dihydrosecurinine	[10]Houghton *et al.;* [11]Kassuya *et al.*
Tannins	Geraniin, corilagin, 1,6-digalloylglucopyranoside rutin , quercetin3-O-glucopyranoside , Amarulone, Phyllanthusiin D & Amariin, Furosin, corilagin, melatonin, phyllanthus D (ellagitannin)	[12]Foo *et al.*
Lignans	Niranthin, Nirtetralin, Phyltetralin, Hypophyllanthin, Phyllanthin, hypo-phyllanthin, demethylenedioxy-niranthin, 5-demethoxy-niranthin, Isolintetralin, hinokinin, 4-(3,4-dimethoxy-phenyl)-1-(7-methoxy benzo[1,3]dioxol-5-yl)-2,3-bismethoxymethyl-butan-1-ol, nirphyllin (3,3',5,9,9'-pentamethoxy-4-hydroxy4', 5 '-methylenedioxylignan) and phyllnirurin (3,4-methylenedioxy-5 '-methoxy-9'-hydroxy-4',7- epoxy-8,3'-neolignan), cubebin dimethyl ether and urinatetralin	[13]Leite *et al.;* [14]Maciel *et al.;* [15]Singh B *et al.;* [16]Elfahmi *et al.*
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-Ogalloyl-2,4-dehydrohexahydroxydiphenoyl-glucopyranose elaeocarpusin, repandusinic acid A and geraniinic acid	[17]Londhe *et al.*
Volatile oil	Linalool and Phytol	[18]Moronkola *et al.*
Triterpenes	Phenazine and phenazine derivatives, 2Z, 6Z, 10Z, 14E 18E, 22E-farnesil farnesol	[14]Maciel *et al.;* [19]Foo *et al.*
Sterols	Amarosterol A, amarosterol B	[20]Ahmad *et al.*
Flavonoid	Quercetin, kaempferol, astragalin, quercetin-3-O-glucoside, quercitrin , gallic acid, (-)-epicatechin, (+)-gallocatechin, (-)-epigallocatechin, (-)-epicatechin 3-O-gallate and (-)-epigallocatechin 3-O-gallate	[19,]Foo *et al.;* [21]Foo *et al.;* [22]Ishimaru *et al.*

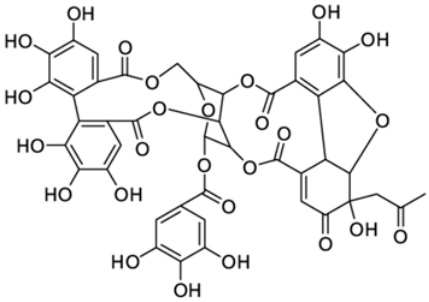
Also mineral elements such as iron manganese, magnesium, zinc, calcium, potassium, phosphorus, copper and chromium were found in appreciable amount, with calcium present in the highest concentration.



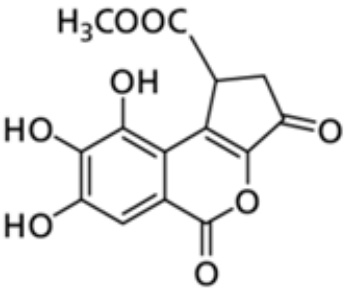
Phyllanthin



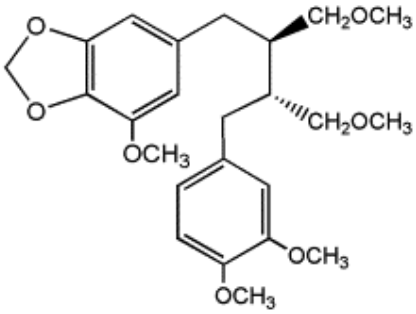
Hypophyllanthin



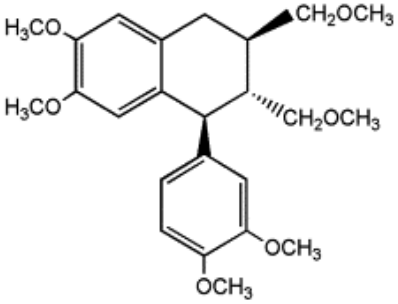
Phyllanthus D (ellagitannin)



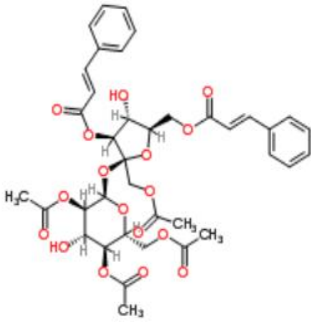
Methyl brevifolincarboxylate



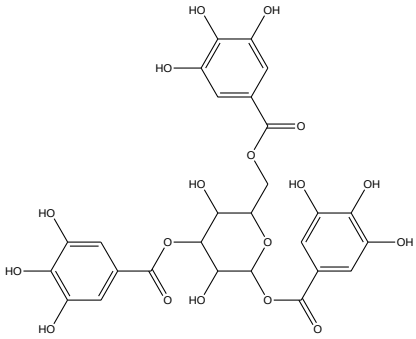
Niranthin



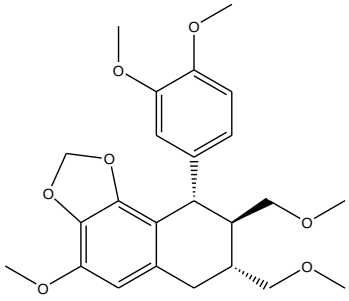
Phyltetralin



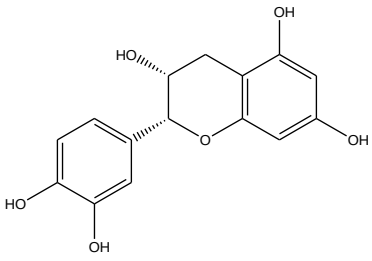
Niruriside



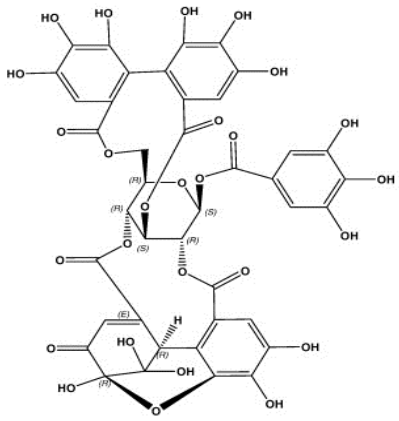
Corilagin



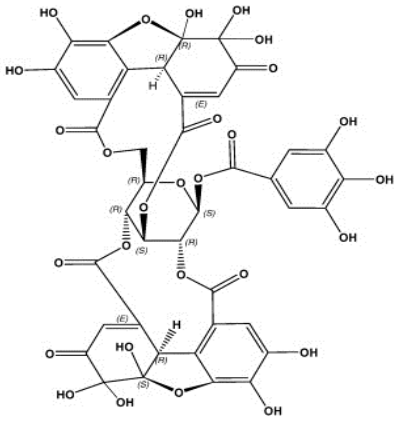
Isolintetralin



Epicatechin



Geraniin



Amariin

Fig 1: Chemical Structure of some active constituents presents in *Phyllanthus amarus*

3 Pharmacological activities of *Phyllanthus amarus*

The *Phyllanthus amarus* has pharmacological activities such as anti-diabetic, antitumor, immunomodulation, antifungal, antibacterial and anti-inflammation activities and antioxidant effects[24] (Table 2).

Table 2: Pharmacological activities of various parts of *Phyllanthus amarus*

Part used	Pharmacological activity	Findings of effectiveness	References
Leaves	Anticarcinogenic & anti-tumour activity	Inhibition of metabolic activation of carcinogen as well as the inhibition of cell cycle regulators responsible for cancerous growth and DNA repair	[25]Rajeshkumar *et al.*
Roots	Antiproliferative activity	Induction of apoptosis mediated by increased intracellular reactive oxygen species in conjunction with decreased mitochondrial membrane potential in the MCF-7 cells through	[26]Abhyankar *et al.*
Whole plant	Anti-cancer Activity	Decline Cr(VI)-induced cytotoxicity in MDA-MB-435S human breast carcinoma cells with an increase in extract dosage	[27]Guha *et al.*
Whole plant	Antimetastatic effects	Inducing apoptosis in conjunction, with more than 3-fold increase of caspases-3 and -7, the presence of DNA-fragmentation and terminal deoxynucleotidyl transferase mediated dUTP nick end labeling assay (TUNEL)-positive cells	[28]Lee *et al.*
Aerial parts	Anti-oxidant activity	Different drying treatments led to a significant reduction in antioxidant properties of *P. amarus* methanol extracts	[29]Lim *et al.*
Aerial parts	Gastroprotective, & antioxidant activities	Effective gastro-protective agent that is as effective as cimetidine against toxic effects of alcohol on an absolute ethanol-induced ulcer in albino rats	[30]Shokunbi *et al.*
Leaves	Anti-oxidant activity	Phyllanthin effectively alleviated the changes induced by CCl_4-induced toxicity in HepG2 cell line in a concentration-dependent manner by reducing oxidative stress	[31]Krithika *et al.*
Callus	Anti-oxidant activity	Methanol extract of *Phyllanthus amarus* contains the highest amount of phenolic compounds and exhibits the greatest antioxidant activity in comparison to other extracts	[32]Sen *et al.*
Whole plant	Cardioprotective effect	Showed protection from HF-diet induced increase in stress markers (LPO and PO), decreased non-enzymatic (GSH and Vit-C) and enzymatic (GR, GPx, GST, SOD, and CAT) antioxidants in	[33]Putakala *et al.*

		the heart and aorta and also reduced fat deposition and necrosis	
Whole plant	Antileptospiral activity	Showed inhibitory action of methanol and aqueous extract against leptospira	[34]Chandan *et al.*
Leaves	Antibacterial & antidiabetic activities	The MIC and MBC further confirmed the potency of the aqueous extract on selected bacteria *In vitro* antidiabetic evaluation showed a concentration dependent activity	[35]Ukwubile *et al.*
Leaves	Anti-diabetic Activity	Reduce the blood sugar in alloxan diabetic rats by 6% at a dose level of 200 mg/kg body weight and 18.7% reduction in blood sugar.	[36]Raphael *et al.*
Leaves	Anti-diabetic Activity	Oral administration of ethanolic leaves extract for 45 days resulted in significant decline in blood glucose and increase in the activity of glucokinase in the liver of diabetic mice	[37]Shetti *et al.*
Whole plant	Antifungal activity	Nor-securinine, an alkaloid isolated from *Phyllanthus amarus* was effective against most of the fungi	[38]Sahni *et al.*
Leaves	Antimicrobial & antifungal activities	The dichloromethane fraction had activity against all the test organisms with MIC at 100 µg/ml	[39]Okwute *et al.*
Aerial parts	Antibacterial & antioxidant	Showed inhibitory activities against four of the five *E. coli* isolates due to antioxidant property	[40]Eldeen *et al.*
Roots	Anti-viral Activity	Possess 85% inhibition in binding of Hepatitis B Surface Antigen (HBsAg) to its antibody (anti-HBs) after 24 h of incubation with HbsAg-positive sera *in-vitro* at 37 °C.	[41]Bhattacharyya *et al.*
Aerial parts	Anti-viral Activity	Aqueous extract showed partial antiviral activity against white spot syndrome virus in shrimp at the concentration of 150 mg/kg of animal body weight for 30 days	[42]Balasubramanian *et al.*
Roots and Leaves	Anti-viral Activity	Root extract showed significant inhibition of HCV-NS3 protease enzyme; whereas leaves extract showed considerable inhibition of NS5B in the *in- vitro* assays against HCV	[43]Ravikumar *et al.*
Aerial parts	Antivenom activity	Di-herbal plant extracts *(P. amarus* & *A. paniculata)* effectively neutralized the cobra venom induced lethal activity	[44]Sornakumar *et al.*
Leaves	Fertility Effect	Causes an increase in the level of testosterone but has little or no effect on the levels of leutinizing hormone and follicle stimulating hormone	[45]Obianime *et al.*
Whole plant	Contraceptive effects	The results revealed no significant change in absolute body and organ weights and even in general metabolic status Cohabited females with normal male mice were unable to become pregnant as their cyclicity was affected	[46]Rao *et al.*
Whole plants	Anti-inflammatory Activity	Significantly inhibited the production of pro-inflammatory mediators (TNF-α, IL-1β, PGE_2) and COX-2 protein expression in LPS-induced U937 human macrophages Extract also down regulated the expression of upstream signaling molecules, TLR4 and MyD88, which play major role in activation of NF-κB, MAPK and PI3K-Akt signaling pathways.	[47]Hemavathy *et al.*
Whole plant	Anti-inflammatory Activity	Showed an inhibition of LPS-induced production of NO and PGE2	[48]Kiemer *et al.*

		It also attenuated the LPS-induced secretion of Tumor necrosis factor (TNF) and reduced expression of iNOS and COX-2 and inhibited activation of NF-κB *Extract* inhibited induction of interleukin (IL)-1β, IL-10, and interferon-γ in human whole blood and reduced TNF-α production *in-vivo*	
Whole plant	Anti-inflammatory Activity	Methanol extract significantly inhibited carrageenan, bradykinin, serotonin and prostaglandin E1-induced paw edema, but failed to inhibit the histamine-induced paw edema It significantly decreased the formation of granuloma tissue in chronic inflammation model	[49]Mahat *et al.*
Leaves and stem	Anticonvulsant activity	Significantly effective in abolishing hind limb extension induced by maximal electroshock-induced seizures as well as pentylenetetrazole induced seizures	[50]Manikkoth *et al.*
Whole plant	Diuretic effect	After 24 h, Extract at 10 mg/kg increased significantly UVE, Na^+ (43 mEq) and Cl^- (97 mEq) urinary excretions without promoting kaliuresis. In rats pretreated with indomethacin, the urinary excretion and the natriuretic response of EFPA were significantly reduced	[51]Yao *et al.*

4 Conclusion

Presently the use of medicinal plants increased considerably globally due to lesser side effects. The studies explored *Phyllanthus amarus* is one of the utmost needed medicinal plants for the treatment of different diseases.

Phyllanthus amarus are rich in secondary metabolite and are the key factors for various pharmacological activities. The present information concerning *Phyllanthus amarus* may serve as the baseline data to impose to do widespread studies for the innovative of novel active compounds and promote evaluation for their pharmacological activities.

5 Conflict of interests

None

6 Author's contributions

MG and JSV collected the data and drafted the manuscript. Both authors have read and approved the final manuscript.

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