Zagazig Journal of Pharmaceutical Sciences

Journal homepage: https://zjps.journals.ekb.eg/

Print ISSN: 1110-5089 Online ISSN: 2356-9786

Genus Phyllanthus: Traditional uses and biological activities

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ARTICLE INFO

Article History:
Received: 17 June 2023
Accepted: 27 Sept 2023
Published online: 25 Dec 2023

Key words:
Medicinal plants,
Euphorbiaceae,
biological activities,
antioxidant,
antibacterial

ABSTRACT

Medicinal plants represent essential elements of traditional medicine. They have been used to treat various ailments. Phyllanthus (Euphorbiaceae) is a large genus that includes important medicinal plants. It has about 1000 plant species, comprising trees, shrubs and herbs. Phyllanthus species are known globally for their medicinal uses and are used in the treatment of many diseases. It has been estimated that more than 500 chemical constituents have been obtained from species of this genus. The medicinal value of different plant parts is proven scientifically. The extracts prepared from Phyllanthus plants displayed anti-cancer, anti-inflammatory, anti-diabetic, anti-oxidant, anti-bacterial, nephroprotective, hepatoprotective, immunomodulatory effects. Phyllanthus species have been the focus of many biological and phytochemical studies in recent years, due to their wide distribution. This review emphasizes the importance of Phyllanthus plants, showing their traditional uses and scientifically proven biological effects to open the door to take advantage of them in medicine and industry.

1. Introduction:

Medicinal plants have been used as medicinal and nutritional agents in many countries [1]. The effectiveness of these plants may not be due to single ingredient, but to the combination of the plant components [2]. *Phyllanthus* (Euphorbiaceae) is a large genus, distributed in tropical and subtropical regions [3]. The genus comprises about 1000 species [4], including trees, shrubs. The genus rarely includes herbs [5]. The name *Phyllanthus* means "leaves and flowers" because the flower, as well as the fruit, seems to become one with the leaf [6]. Many *Phyllanthus* species are considered as important medicinal and ornamental plants [7].

Different parts of those plants have been scientifically proven to exert medicinal values [8]. *Phyllanthus* has recently been the focus of numerous studies, due to its many medicinal properties in folk medicine, wide distribution, and numerous secondary metabolites [9]. It has been estimated that more than 500 chemical constituents have been obtained from species of this genus [10].

This review emphasizes the importance of *Phyllanthus* plants, showing their traditional uses and biological effects to open the door to take advantage of them in medicine and industry.

DOI: 10.21608/ZJPS.2023.210628.1047
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2. Traditional uses of *Phyllanthus* plants

Treatment using medicinal plants is a part of traditional medicine. These treatments have been developed by the local people [10]. Each country has its own history of these treatments, such as "Ayurvedic medicine" in Southeast Asia, "Unani medicine" in Arab countries in the middle east, as well as "Traditional Chinese Medicine" which originated from China [10]. The WHO confirmed that this medicine is important to meet the health requirements, mainly in the developing countries [11]. In recent years, traditional medicine has greatly aided in the biosynthesis of *Phyllanthus* natural products [8].

The extracts prepared from various parts of *Phyllanthus* plants are used to treat cancer, wounds, urinary tract disorders, sexually transmitted diseases, hypertension, diabetes [4], and chronic liver disease [1]. Ayurveda uses the most abundant species for their beneficial properties to treat genitourinary, respiratory and digestive disorders [3]. The fruits of *P. emblica* are used in Ayurveda as medicinal agent against inflammation and jaundice, and serve as rasayana [11]. Niruri (*P. niruri*) is an herb traditionally known in India for its medicinal effects in dysentery, hyperglycemia, irritating sores, jaundice, and liver disease [12]. Traditionally, *P. acidus* is used as a blood purifier [13]. *P. muellerianus* is used in Ghana and other areas of West Africa to control wounds, wound infections, pain, inflammation, fever and menstrual disorders [14]. *P. simplex* has traditionally been used to treat hepatitis, gonorrhea, itching, diarrhea, hyperglycemia, jaundice, pruritus, and inflammation [15].

3. Pharmacological properties of *Phyllanthus*

3.1 Hepatoprotective effect:

The hepatoprotective effect of the crude extracts of *Phyllanthus* species against liver damage has been well studied. Hepatotoxicity induced by CCl_4 in rats was prevented by pretreatment with leaf and fruit extracts of *P. niruri*, indicating the hepatoprotective activity of this plant [16]. Treatment with *P. amarus* reduced the liver and kidney toxicity imposed by rifampicin and carbon tetrachloride CCl_4 in a dose-dependent manner [17]. Relatedly, oral administration of alcoholic extracts of *P. niruri* and *P. urinaria* provided hepatoprotection in rats with CCl_4-induced (chronic) liver injury [18]. Oral administration of the methanolic extracts of *P. acidus* and *P. urinaria* reduced the increase in ALT and AST levels, and also elevated the activity of liver reduced glutathione peroxidase and reduced liver infiltration and necrosis in rats with CCl_4- induced acute liver damage [19]. The aqueous extract of *P. acidus* leaves prevented the toxicity of acetaminophen (APAP) and thioacetamide in rats [13]. Previous study revealed that alcoholic extracts of the aerial parts and roots of *P. atropurpureus* had antihepatotoxic properties, similar to silymarin. Both of them improved the SGPT and SGOT levels [7].

The methanolic extracts of three *Phyllanthus* plants showed hepatoprotective effect against *tert*-butyl hydroperoxide induced toxicity in HepG2 cells, with EC_{50} of 12 µg/ml for *P. polyphyllus*, 19 µg/ml for *P. emblica* and 28 µg/ml for *P. indofischeri* [2o]. In general, many *Phyllanthus* species contain various compounds with hepatoprotective effect such as flavonoids, lignans and tannins [7].

3.2 Nephroprotective activity of *Phyllanthus*

Nephrotoxicity is a serious kidney problem caused by drugs or toxins [21]. Previous studies had showed that the methanolic leaves extract of *P. niruri* may help in reducing nephrotoxicity induced by gentamicin in rats [22].

In another study, the aqueous leaves extract of *P. niruri* helped to keep kidney function near to normal and prevent histopathological changes by ameliorating fibrosis, inflammation, oxidative stress and apoptosis while enhancing proliferation of the kidney in diabetes mellitus [23].

Ellagic acid, an ingredient in *P. niruri*, has been reported to be responsible for protective effect of the plant against renal damage induced by calcium oxalate [24].

Similarly, oral administration of *P. amarus* seed extract and methanolic leaves extract of *P. acidus* showed protection against gentamycin-induced renal

damage [25]. The ethanolic extract *P. emblica* showed protection against kidney damage induced by ethylene glycol and ammonium chloride in rats [26]. The aqueous extract of *P. fraternus* showed protection against nephrotoxicity induced by cyclophosphamide in albino rats [21].

3.3 Immunomodulatory activity

In previous study, *P. muellerianus* methanolic leaf extract exhibited both immune-boosting and immunosuppressing actions. In cyclophosphamide-induced myelosuppression, the extract caused a decrease in total leukocytes count and a decrease in lymphocyte proliferation and an increase in neutrophil proliferation [27]. The methanolic extract of *P. niruri* plant displayed immunomodulatory activity and modulated the innate and adaptive immunity [28]. Aqueous extract of *P. niruri* induced macrophage proliferation and NO secretion after *Streptococcus sanguinis* infection, indicating potential immunomodulatory activity [29]. Catechin and quercetin in *P. niruri* can inhibit the expression of TNF-α, IL- 1, IL-6, and iNOS thereby inhibiting the excessive inflammation process and playing an immunomodulatory role [30].

P. amarus exerted a potent immunosuppressive effect, through many immunomodulatory mechanisms. Rats treated with *P. amarus* exhibited a dose-dependent inhibition of lipopolysaccharide-stimulated B-cell proliferation and concanavalin A–stimulated T-cell proliferation, and decreased expression of CD4+ and CD8+ in splenocytes and in serum cytokines of T helper (Th1) (IL-2 and IFN-γ) and Th2 (IL-4) [31]. *P. acidus* extract showed an immunomodulatory property. The result was shown from the increase in total leukocyte count and leukocyte differential, antibody titer value [32].

3.4 Anti-inflammatory

The anti-inflammatory properties of some *Phyllanthus* species have been well documented. In a rat model of carrageenan-induced acute inflammation. Treatment with aqueous leaf extract of *P. muellerianus* reduced the maximal swelling attained from the inflamed control response. In the chronic inflammation caused by the adjuvant, *P. muellerianus* treatment reduced the total limb swelling over 16 days in the polyarthritic stage [14]. Using carrageenan induced edema test, *P. acidus* leaves extract, methanolic extract of *P. niruri*, the whole plant aqueous extract of *P. fraternus*, ethanolic extract of malacca leaves (*P. emblica*) showed anti-inflammatory properties [33,34,35,36]. In another study, *P. emblica* fruit extract showed dose-dependent inhibition of nitric oxide in lipopolysaccharide stimulated RAW264.7 cells and significantly high cyclooxygenase)COX-2) inhibition [24]. The ethanol extract of *P. simplex* plant significantly inhibited NO production in isolated rat peritoneal macrophages. It also has a significant effect in inhibition of paw edema induced by carragennan and granuloma formation induced by cotton pellet [15].

Standardized extracts of *P. amarus* attenuated tumor necrosis factor (TNF-a) secretion induced by LPS, and reduced the expression of endotoxin-induced nitric oxide synthase (iNOS) and COX-2 [37]. *P. amarus* has been shown to target the NF-κB, MAPK and PI3K-Akt signaling pathways to exert its anti-inflammatory effects by downregulating the inflammatory response [38].

3.5 Lung diseases

Previous study demonstrated that the methanolic extract of *P. emblica* leaves can play an important role in the treatment of CCl_4-induced pulmonary damages instigated with CCl_4. Administration of methanolic extract of *P. emblica* leaves resulted in a dose-dependent reduction in the oxidative injuries in rats. Histopathological damages such as damaged alveoli, infiltration of macrophages and and changes in Clara cell architecture was normalized by the co-administration of the extract [39].

In previous study, the aqueous fruit extract of *P. emblica* protected the lung from inflammatory damage. The authors also concluded that the extract can prevent precancerous lung lesions by regulating the IL-1β/miR-i101/Lin28B pathway [40].

3.6 Antioxidant activity

The antioxidant capacity of *Phyllanthus* species was extensively studied (table 1). Phenolic compounds

have the best antioxidant effect -among natural antioxidants- due to their ability to quench oxygen-derived free radicals by donating a hydrogen atom or electron to a free radical [41]. Total phenolic content (TPC) of different extracts of *Phyllanthus* species was determined.

TPC was found to be (207 and 205 mg/GAE/g) for *P. myrtifolius* and *P. urinaria*, respectively [9]. It has also been indicated that TPC in the ethanolic aerial parts extract of *P. fraternus* is about 230.85 ± 0.59 mg/g GAE [41]. The TPC in the ethanolic seed extract of *P. acidus* was found to be 3.19 mg of gallic acid equivalent/g (GAE/g) [42]. According to [6] TPC in methanolic extracts of different *Phyllanthus* species (*P. reticulatus, P. virgatus, P. acidus, P. virosus, P. amarus, P. emblica, P. fraternus, P. maderaspatensis, P. urinaria*) ranged from 41.801 to 87.542 mg/g of the dry weight of extract (GAE/g). The TPC of the methanolic whole plant extracts of *P. niruri, P. debilis* and *P. urinaria* were found to be (197.09 ± 0.03, 159.13 ± 0.02, 308.71 ± 0.04) mg GAE/g DW, respectively [43].

***Table 1**: Antioxidant activity of some Phyllanthus species*

Species	extract/ plant part	Technique	Conc.	Results	Ref.
P. fraternus	Ethanol (Aerial part)	DPPH	500 µg/ml	radical scavenging 1.10±capacity=94.59	[41]
		Lipid peroxidation	4000 µg/ml	Percentage 96.55 =inhibition 0.27±	
P. acidus	Water (fruits)	DPPH	-	IC50= 26.06 µg/ml	[44]
	Ethanol (seed)	DPPH	-	IC50= 28.26 ± 0.39 µg/ml	[42]
		ABTS	-	IC50= 23.44 ± 0.48 µg/ml	
P. emblica	Methanol (leaves)	DPPH	-	IC50 = 39.73 ± 2.12 µg/ml	[39]
		Nitric oxide	-	IC50 = 39.14 ± 2.31 µg/ml	
		Lipid peroxidation	-	IC50 = 84.10 ± 3.04 µg/ml	
P. niruri	Methanol	DPPH	-	EC50= 29.3 ± 0.01 µg/ml	[43]
	Methanol	ABTS	-	26.0 ± 0.02 EC50= µg/ml	
P. urinaria	Methanol	DPPH	-	EC50= 15.8 ± 0.01 µg/ml	
	Methanol	ABTS	-	11.2 ± 0.01 EC50= µg/ml	
P. debilis	Methanol	DPPH	-	EC50= 26.3 ± 0.01 µg/ml	
	Methanol	ABTS	-	16.2 ± 0.03 EC50= µg/ml	
P. muellerianus	Aqueous (aerial parts)	DPPH	-	IC50 = 0.12 µg/ml	[45]
P. chamaecristoides	Aqueous (leaves and stems)	DPPH	-	EC50= 0.03 mg/ml	[46]

P. microdictyus		DPPH	-	EC50= 1.16 mg/ml	
P. williamioides		DPPH	-	EC50= 0.15 mg/ml	
P. amarus	Ethanolic (leaves)	DPPH	-	IC50 = 38.38 mg/ml	[47]
		FRAP	-	IC50 = 29.31 mg/ml	
		TBARS	-	IC50 = 29.34 mg/ml	

Values represent mean ± standard deviation. DPPH: 2,2-diphenyl-1-picrylhydrazyl, FRAP: Ferric reducing antioxidant power, ABTS: 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid), TBARS: Thiobarbituric acid reactive substances, Con: concentration.

3.7 Antibacterial activity

Pathogenic microorganisms develop resistance to conventional antibiotics, resulting in the need for alternative treatments [1]. Medicinal plants are rich in antimicrobial compounds and their use in medicine is beneficial because they have less side effects [48].

The antimicrobial components of plants are secondary metabolites that inhibit bacterial growth, bacterial adhesion, exopolysaccharide synthesis, DNA gyrase, plasma membrane function and energy metabolism [49]. The antimicrobial activity of some species of the genus *Phyllanthus* against many bacterial strains such as *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Shigella flexneri*, *Salmonella typhimurium*, *Pseudomonas aeruginosa*, are presented in table 2.

***Table 2**: Antibacterial activity of some Phyllanthus species*

Species	Extract/ plant part	Micro-organisms	MIC values	Ref.
P. reticulatus	EE / leaves	*Shigella dysenteria* (BMLRU1011)	31.3 mg/ml	[50]
		Salmonella typhi (BMLRU1009)	62.5 mg/ml	
		Pseudomonas aeruginosa (BMLRU1007)	15.6 mg/ml	
		Shigella sonnei (BMLRU1015)	31.3 mg/ml	
		Sarcina lutea (BMLRU1012)	31.3 mg/ml	
		Bacillus megaterium (BMLRU1010)	31.3 mg/ml	
		Bacillus subtilis (BMLRU1008)	62.5 mg/ml	
		Staphylococcus aureus (BMLRU1002)	15.6 mg/ml	
		Bacillus cereus (BMLRU1004)	31.3 mg/ml	
		Staphylococcus-ß-haemolytica (BMLRU1006)	62.5 mg/ml	
P. amarus	ME/ leaves	*Staphylococcus aureus* (ATCC 25923)	25 mg/ml	[1]
		Escherichia coli (ATCC 35218)	50 mg/ml	
		Klebsiella pneumoniae (ATCC 34089)	6.25 mg/ml	
		Pseudomonas aeruginosa (ATCC27853)	50 mg/ml	
		Salmonella Typhi (ATCC 22648)	12.5 mg/ml	
P. wightianus	ME/ leaves	*Staphylococcus epidermidis* (MTCC 435)	31.25 µg/ml	[49]
		Streptococcus pneumoniae (MTCC 655)	15.62 µg/ml	
		Shigella flexneri (MTCC 1457)	125 µg/ml	
		Salmonella typhimurium (MTCC 98)	500 µg/ml	

		Pseudomonas aeruginosa (MTCC 741)	250 µg/ml	
		Klebsiella pneumoniae (MTCC 109)	500 µg/ml	
P. urinaria	ME/ WP	*Bacillus licheniformis* (ATCC12759)	154 µg/ml	[9]
		Bacillus spizizenii (ATCC6633)	79 µg/ml	
		Staphylococcus aureus (ATCC12600)	39 µg/ml	
		Escherichia coli (ATCC25922)	185 µg/ml	
		Klebsiella pneumoniae (ATCC13883)	156 µg/ml	
		Pseudomonas stutzeri (ATCC17588)	117 µg/ml	
P. myrtifolius	ME/ WP	*Bacillus licheniformis* (ATCC12759)	75 µg/ml	
		Bacillus spizizenii (ATCC6633)	20 µg/ml	
		Staphylococcus aureus (ATCC12600)	40 µg/ml	
		Escherichia coli (ATCC25922)	306 µg/ml	
		Klebsiella pneumoniae (ATCC13883)	178 µg/ml	
		Pseudomonas stutzeri (ATCC17588)	78 µg/ml	
P. maderaspatensis	EE/Sh	*Salmonella typhimurium* (MTCC98)	625 µg/ml	[51]
		Staphylococcus aureus (MTCC 737)	625 µg/ml	
		Pseudomonas aeruginosa (MTTC 1688)	312 µg/ml	
		Klbsiella pneumoniae (MTCC 109)	312 µg/ml	

AE: Aqueous extract, EE: ethanolic extract, PEE: petroleum ether extract, CE: chloroform extract, ME: methanolic extract, WP: whole plant, Sh: shoot, ATCC: American Type Culture Collection.

3.8 Antidiabetic activity

Diabetes is a common disease that affects many people in several countries. There is interest in finding and discovering new antidiabetic drugs with high safety, due to the many toxicities of hypoglycemic drugs [2]. Herbal preparations and herbs are used more widely to treat and control diabetes mellitus instead of modern hypoglycemic drugs [52].

Using alloxan-induced diabetic model, previous investigations revealed that the ethanolic extracts of *P. fraternus* whole plant and *P. amarus* leaf have antidiabetic effect and significantly improved blood glucose levels [53,54]. Another *in vivo* study indicated that ethanolic fruit extract of *P. emblica* had significant hypoglycemic activity and can imporve insulin resistance by enhanced insulin sensitivity in the peripheral tissues [52].

Likewise, previous research has shown that oral administration of ethanolic leaf extract of *P. amarus* for 45 days caused a decrease in blood glucose level, an improvement in body weight in diabetic mice, a decrease in glucose-6-phosphatase and fructose-1-6-disphosphatase activities in liver, and significant increase in the activity of glucokinase in liver of diabetic mice compared with that of diabetic control [55].

Phytochemicals in *P. urinaria* have also been shown to be effective as an alternative to the Metformin drug in the treatment of diabetes [2]. In addition, the alcoholic extract of *P. niruri* showed antidiabetic activity in normal, insulin- dependent diabetes mellitus [12].

Relatedly, oral administration of methanolic extract of *P. niruri* aerial parts significantly reduced blood glucose levels, triglycerides and total cholesterol levels in diabetic and normoglycaemic rats [56].

It has been suggested that the hypoglycemic properties of the aerial parts of *P. niruri* may be due to inhibition of glucose absorption and improvement of glucose storage [57].

3.9 Cytotoxic activities

Cytotoxic activity of *P. amarus* leaf extract was tested against HCT 15 and T47D cell lines. The results showed that the inhibitory effect on HCT 15 cell line was greater than T47D. Growth inhibition increased from 8.86% to 87%, and from 8.39 % to 86.01%, for the HCT 15 and T47D cell lines, respectively, with the increasing concentration [58].

Acetone and hydroethanolic extracts of aerial parts of *P. phillyreifolius* exhibited low levels of cytotoxicity against HEK293 cell line, reducing cell viability to 50% at concentrations of 489 and 387 µg/ml for Acetone and hydroethanolic extracts, respectively [59]. The ethanol extract of *P.*

niruri had a potential cytotoxic effect towards human leukemic cells MOLT-4 cells (IC_{50}= 97.06±18.29 µg/ml). It was found that p53 expression was increased after MOLT-4 treatment with methanolic extract, suggesting that p53 induction may play a role in cell apoptosis [60].

Previous research revealed that methanolic extracts of several *Phyllanthus* species (*P. amarus, P. watsonii*, *P. niruri*, and *P. urinaria*) can inhibit the growth of lung (A549) and breast (MCF-7) carcinoma cells with IC_{50} values of 50–180 µg/ml. The extract also reduced the adhesion and migration of the carcinoma cells [61].

Previous study showed that the bark extract of *P. emblica* had cytotoxic effect (IC_{50} of 52.2 µg/ml) and induces apoptosis of the KKU-452 CCA cell line. The extract also inhibited cell migration at 25 and 50 µg/ml by 42.8 and 32.9%, respectively [62].

Similarly, Previous investigation revealed that *P. reticulatus* leaf extracts have anti-proliferative, apoptotic and antimigratory activities against liver cancer cell line (HepG2) [63]. However, preliminary in vitro data are insufficient and unreliable, as all experiments are performed in an environment other than the human body [64].

The cytotoxic activity of crude methanol, hexane and ethyl acetate extracts of *P. niruri* (aerial parts), *P. pectinatus* (leaves and fruits) and *P. acidus* (leaves) was evaluated with an in vitro growth inhibition assay system against four human cancer cell lines, breast cancer cell line (MCF7), epidermal carcinoma of cervix cell line (CaSki), ovarian cancer cell line (SKOV3) and colon cancer cell line (HT29). The results showed that methanolic and ethyl acetate extracts of *P. pectinatus* leaves were active against SKOV3 cell with an IC_{50} value of 4.8 and 5.8 µg/ml, respectively. The ethyl acetate extract of *P. pectinatus* fruits was active against MCF7 and CaSki cells, with an IC_{50} values of 18.1 and 19.4 µg/ml, respectively. The study suggested that *P. pectinatus* may be useful in the discovery of anticancer drug [65].

3.10 Other biological activities:

Previous study revealed that ethanolic extract of *P. amarus* leaves can reverse the deleterious effects of prolonged highly active antiretroviral therapy administration on the experimental rats [47].

Ethanolic extracts of *P. fraternus* have been shown to have anticoagulant effects. The extract increased clotting time and bleeding time in rabbits –in vitro- [66]. It was suggested that the alkaloid extract of *P. amarus* had significant activity against plasmodium [67]. The methanolic extract of *P. reticulates* leaves exhibited anti-diarrhoeal properties in several experimental animals with diarrhea [68].

4. Conclusion

In this work, *Phyllanthus* species were reviewed for their biological activities and traditional uses. These species have been shown to have many biological activities, so they represent valuable natural sources in the pharmaceutical industry. More research is needed to explore the exact mechanisms of these biological activities and identify the active ingredients responsible for them.

Conflict of interest statement

Authors declare that there is no conflict of interest.

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