

Genus Phyllanthus: Traditional uses and biological activities

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ABSTRACT

Medicinal plants represent essential elements of traditional medicine. They have been used to treat various ailments. *Phyllanthus* (Euphorbiaceae) is a large genus, 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.

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

Running title : Overview of the genus *Phyllanthus*

INTRODUCTION

Medicinal plants have been used as medicinal and nutritional agents in many countries (Okiki et al., 2022). The effectiveness of these plants may not be due to single ingredient, but to the combination of the plant components (Akhtar and Gayathri, 2015). *Phyllanthus* (Euphorbiaceae) is a large genus, distributed in tropical and subtropical regions (Mao et al., 2016). The genus comprises about 1000 species (Sarin et al., 2014), including trees, shrubs. The genus rarely includes herbs (Basavaraju and Gunashree, 2022). The name *Phyllanthus* means "leaves and flowers" because the flower, as well as the fruit, seems to become one with the leaf (Khabiya et al., 2019). Many *Phyllanthus* species are

considered as important medicinal and ornamental plants (Sarg et al., 2011). Different parts of those plants have been scientifically proven to exert medicinal values (Sibiya et al., 2020). *Phyllanthus* has recently been the focus of numerous studies, due to its many medicinal properties in folk medicine, wide distribution, and numerous secondary metabolites (Eldeen et al., 2011). It has been estimated that more than 500 chemical constituents have been obtained from species of this genus (Geethangili and Ding, 2018).

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.

Traditional uses of *Phyllanthus* plants

Treatment using medicinal plants is a part of traditional medicine. These treatments have been developed by the local people (Geetangili and Ding, 2018). 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 (Geetangili and Ding, 2018). The WHO confirmed that this medicine is important to meet the health requirements, mainly in the developing countries (Saini et al., 2022). In recent years, traditional medicine has greatly aided in the biosynthesis of *Phyllanthus* natural products (Sibiya et al., 2020).

The extracts prepared from various parts of *Phyllanthus* plants are used to treat cancer, wounds, urinary tract disorders, sexually transmitted diseases, hypertension, diabetes (Sarin et al., 2014), and chronic liver disease (Okiki et al., 2022). Ayurveda uses the most abundant species for their beneficial properties to treat genitourinary, respiratory and digestive disorders (Mao et al., 2016). The fruits of *P. emblica* are used in Ayurveda as medicinal agent against inflammation and jaundice, and serve as rasayana (Saini et al., 2022). Niruri (*P. niruri*) is an herb traditionally known in India for its medicinal effects in dysentery, hyperglycemia, irritating sores, jaundice, and liver disease (Bavarva and Narasimhacharya, 2007). Traditionally, *P. acidus* is used as a blood purifier (Jain and Singhai, 2011). *P. muellerianus* is used in Ghana and other areas of West Africa to control wounds, wound infections, pain, inflammation, fever and menstrual disorders (Boakye et al., 2016). *P. simplex* has traditionally been used to treat hepatitis, gonorrhoea, itching, diarrhoea, hyperglycemia, jaundice, pruritus, and inflammation (Chouhan and Singh, 2011).

Pharmacological properties of *Phyllanthus*

Hepatoprotective effect:

The hepatoprotective effect of the crude extracts of *Phyllanthus* species against liver damage has been well studied. Hepatotoxicity induced by CCl₄ in rats was prevented by pretreatment with leaf and fruit extracts of *P. niruri*, indicating the hepatoprotective activity of this plant (Harish and Shivanandappa, 2006). Treatment with *P. amarus* reduced the liver and kidney toxicity imposed by rifampicin and carbon tetrachloride CCl₄ in a dose-dependent manner (Ogunmoyole et al., 2020). Relatedly, oral administration of alcoholic extracts of *P. niruri* and *P. urinaria* provided hepatoprotection in rats with CCl₄-induced (chronic) liver injury (Prakash et al., 1995). 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 CCl₄-induced acute liver damage (Lee et al., 2006). The aqueous extract of *P. acidus* leaves prevented the toxicity of acetaminophen (APAP) and thioacetamide in rats (Jain and Singhai, 2011). 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 (Sarg et al., 2011).

The methanolic extracts of three *Phyllanthus* plants showed hepatoprotective effect against *tert*-butyl hydroperoxide induced toxicity in HepG2 cells, with EC₅₀ of 12 µg/ml for *P. polyphyllus*, 19 µg/ml for *P. emblica* and 28 µg/ml for *P. indofischeri* (Srirama et al., 2012). In general, many *Phyllanthus* species contain various compounds with hepatoprotective effect such as flavonoids, lignans and tannins (Sarg et al., 2011).

Nephroprotective activity of *Phyllanthus*

Nephrotoxicity is a serious kidney problem caused by drugs or toxins (Moirangthem et al., 2017). Previous studies had showed that the methanolic leaves extract of *P. niruri* may help in reducing nephrotoxicity induced by gentamicin in rats (Reddy et al., 2015).

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 (Giribabu et al., 2017).

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 (Li et al., 2022).

Similarly, oral administration of *P. amarus* seed extract and methanolic leaves extract of *P. acidus* showed protection against gentamicin-induced renal damage (Bakhtiary et al., 2012). The ethanolic extract *P. emblica* showed protection against kidney damage induced by ethylene glycol and ammonium chloride in rats (Halim et al., 2019). The aqueous extract of *P. fraternus* showed protection against nephrotoxicity induced by cyclophosphamide in albino rats (Moirangthem et al., 2017).

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 (Ofokansi et al., 2018). The methanolic extract of *P. niruri* plant displayed immunomodulatory activity and modulated the innate and adaptive immunity (Eze et al., 2014). Aqueous extract of *P. niruri* induced macrophage proliferation and NO secretion

after *Streptococcus sanguinis* infection, indicating potential immunomodulatory activity (Hutomo et al., 2018). 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 (Sukmanadi et al., 2020).

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) (Ilangkovan et al., 2015). *P. acidus* extract showed an immunomodulatory property. The result was shown from the increase in total leukocyte count and leukocyte differential, antibody titer value (Nurfadhilah et al., 2022).

Anti-inflammatory

The anti-inflammatory properties of some *Phyllanthus* species have been well documented. In a rat model of carrageenan-induced acute inflammation, the 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 (Boakye et al., 2016). 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 (Oseni et al., 2013; Hossain et al., 2016; Mostofa et al., 2017; Asmilia et al., 2020). 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 (Li et al., 2022). 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 (Chouhan and Singh, 2011).

Standardized extracts of *P. amarus* attenuated tumor necrosis factor (TNF- α) secretion induced by LPS, and reduced the expression of endotoxin-induced nitric oxide synthase (iNOS) and COX-2 (Kierner et al., 2003). *P. amarus* has been shown to target the NF- κ B, MAPK and PI3K-Akt signaling pathways to exert its anti-inflammatory effects by downregulating the inflammatory response (Harikrishnan et al., 2018).

Lung diseases

Previous study demonstrated that the methanolic extract of *P. emblica* leaves can play an important role in the treatment of CCl₄-induced pulmonary damages instigated with CCl₄. 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 changes in Clara cell architecture was normalized by the co-administration of the extract (Tahir et al., 2016).

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-1 β /miR-i101/Lin28B pathway (Wang et al., 2017).

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 (Upadhyay et al., 2014). 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 (Eldeen et al., 2011). 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 (Upadhyay et al., 2014). The TPC in the ethanolic seed extract of *P. acidus* was found to be 3.19 mg of gallic acid equivalent/g (GAE/g) (Chigurupati, 2020). According to (Khabiya et al., 2019) 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 (Zain and Omar, 2018).

Table 1: Antioxidant activity of some *Phyllanthus* species

Species	extract/ plant part	Technique	Con	Results	Ref.
<i>P. fraternus</i>	Ethanol (Aerial part)	DPPH	500 µg/ml	radical scavenging capacity=94.59 ± 1.10	(Upadhyay et al., 2014)
		Lipid peroxidati on	4000 µg/ml	Percentage inhibition=96.55 ± 0.27	
<i>P. acidus</i>	Water (fruits)	DPPH	-	IC50= 26.06 µg/ml	(Andrianto et al., 2017)
	Ethanol (seed)	DPPH	-	IC50= 28.26 ± 0.39 µg/ml	(Chigurup ati, 2020)
ABTS		-	IC50= 23.44 ± 0.48 µg/ml		
<i>P. emblica</i>	Methanol (leaves)	DPPH	-	IC50 = 39.75 ± 2.12 µg/ml	(Tahir et al., 2016)
		Nitric oxide	-	EC 50 = 39.14 ± 2.31 µg/ml	
		Lipid peroxidati on	-	IC50 = 84.10 ± 3.04 µg/ml	
<i>P. niruri</i>	Methanol	DPPH	-	EC 50= 29.3 ± 0.01 µg/ml	(Zain and Omar, 2018)
	Methanol	ABTS	-	EC 50= 26.0 ± 0.02 µg/ml	
<i>P. tetrasaria</i>	Methanol	DPPH	-	EC 50= 13.8 ± 0.01 µg/ml	
	Methanol	ABTS	-	EC 50= 11.2 ± 0.01 µg/ml	
<i>P. debilis</i>	Methanol	DPPH	-	EC 50= 26.3 ± 0.01 µg/ml	(Zain and Omar, 2018)
	Methanol	ABTS	-	EC 50= 16.2 ± 0.03 µg/ml	
<i>P. muelleriana</i>	Aqueous (aerial parts)	DPPH	-	IC 50 = 0.12 µg/ml	(Boalaye et al., 2016)
<i>P. chamensis</i>	Aqueous (leaves and	DPPH	-	EC50= 0.03 mg/ml	(Muninda

Values are 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.

Antibacterial activity

Pathogenic microorganisms develop resistance to conventional antibiotics, resulting in the need for alternative treatments (Okiki et al., 2022). Medicinal plants are rich in antimicrobial compounds and their use in medicine is beneficial because they have less side effects (Jahan and Akter, 2015).

The antimicrobial components of plants are

Species	Extract/ plant part	Micro-organisms	MIC values	Ref.
<i>P. acidularis</i>	EE/ leaves	<i>Stigella dysenteriae</i> (BMLRU1011)	31.3 mg/ml	(Islam et al., 2013)
		<i>Salmonella typhi</i> (BMLRU1009)	62.5 mg/ml	
		<i>Pseudomonas aeruginosa</i> (BMLRU1007)	15.6 mg/ml	
		<i>Stigella sonnei</i> (BMLRU1015)	31.3 mg/ml	
		<i>Sarcola lutea</i> (BMLRU1012)	31.3 mg/ml	
		<i>Bacillus megaterium</i> (BMLRU1010)	31.3 mg/ml	
		<i>Bacillus subtilis</i> (BMLRU1008)	62.5 mg/ml	
		<i>Staphylococcus aureus</i> (BMLRU1002)	15.6 mg/ml	
		<i>Bacillus cereus</i> (BMLRU1004)	31.3 mg/ml	
<i>P. amara</i>	ME/ leaves	<i>Staphylococcus aureus</i> (ATCC 25923)	25 mg/ml	(Okiki et al., 2022)
		<i>Escherichia coli</i> (ATCC 35218)	50 mg/ml	
		<i>Klebsiella pneumoniae</i> (ATCC 34089)	6.25 mg/ml	
		<i>Pseudomonas aeruginosa</i> (ATCC27833)	50 mg/ml	
		<i>Salmonella Typhi</i> (ATCC 22648)	12.5 mg/ml	
<i>P. sibiriana</i>	ME/ leaves	<i>Staphylococcus epidermidis</i> (MTCC 435)	31.25 µg/ml	(Na tara jan et al., 2014)
		<i>Streptococcus pneumoniae</i> (MTCC 655)	15.62 µg/ml	
		<i>Stigella flexneri</i> (MTCC 1457)	125 µg/ml	
		<i>Salmonella typhisuarian</i> (MTCC 98)	500 µg/ml	
		<i>Pseudomonas aeruginosa</i> (MTCC 741)	250 µg/ml	
		<i>Klebsiella pneumoniae</i> (MTCC 109)	500 µg/ml	
<i>P. tetrasaria</i>	ME/ WP	<i>Bacillus licheniformis</i> (ATCC12759)	154 µg/ml	(EIddeen et al., 2011)
		<i>Bacillus spizizenii</i> (ATCC6633)	79 µg/ml	
		<i>Staphylococcus aureus</i> (ATCC12600)	39 µg/ml	
		<i>Escherichia coli</i> (ATCC 25922)	185 µg/ml	
		<i>Klebsiella pneumoniae</i> (ATCC13883)	156 µg/ml	

secondary metabolites that inhibit bacterial growth, bacterial adhesion, exopolysaccharide synthesis, DNA gyrase, plasma membrane function and energy metabolism (Natarajan et al., 2014). 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

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.

Antidiabetic activity

Diabetes is a common disease 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 (Akhtar and Gayathri, 2015). Herbal preparations and herbs are used more widely to treat and control diabetes mellitus instead of modern hypoglycemic drugs (Bashir et al., 2018).

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 (Garg et al., 2008; Shetti and Kaliwal, 2015). Another *in vivo* study indicated that ethanolic fruit extract of *P. emblica* had significant hypoglycemic activity and can improve insulin resistance by enhanced insulin sensitivity in the peripheral tissues (Bashir et al., 2018).

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 (Shetti et al., 2012).

Phytochemicals in *P. urinaria* have also been shown to be effective as an alternative to the Metformin drug in the treatment of diabetes (Akhtar and Gayathri, 2015). In addition, the alcoholic extract of *P. niruri* showed antidiabetic activity in normal, insulin-dependent diabetes mellitus (Bavarva and Narasimhacharya, 2007).

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 (Okoli et al., 2010).

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 (Okoli et al., 2011).

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 (Pammi and Giri, 2021).

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 $\mu\text{g/ml}$ for Acetone and hydroethanolic extracts, respectively (Grauzdytė et al., 2018). The ethanol extract of *P. niruri* had a potential cytotoxic effect towards human leukemic cells MOLT-4 cells

($\text{IC}_{50} = 97.06 \pm 18.29 \mu\text{g/ml}$). 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 (Puspita and Alhebshi, 2019).

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 $\mu\text{g/ml}$. The extract also reduced the adhesion and migration of the carcinoma cells (Lee et al., 2011).

Previous study showed that the bark extract of *P. emblica* had cytotoxic effect (IC_{50} of 52.2 $\mu\text{g/ml}$) and induces apoptosis of the KKU-452 CCA cell line. The extract also inhibited cell migration at 25 and 50 $\mu\text{g/ml}$ by 42.8 and 32.9%, respectively (Samatiwat et al., 2021).

Similarly, Previous investigation revealed that *P. reticulatus* leaf extracts have anti-proliferative, apoptotic and antimigratory activities against liver cancer cell line (HepG2) (Deivayanai et al., 2019). However, preliminary in vitro data are insufficient and unreliable, as all experiments are performed in an environment other than the human body (Tang and Sekaran, 2011).

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 $\mu\text{g/ml}$, 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 $\mu\text{g/ml}$, respectively.

The study suggested that *P. pectinatus* may be useful in the discovery of anticancer drug (Ramasamy et al., 2011).

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 (Bello and Ibaba, 2020).

Ethanolic extracts of *P. fraternus* have been shown to have anticoagulant effects. The extract increased clotting time and bleeding time in rabbits –in vitro- (Koffuor and Amoateng, 2011). It was suggested that the alkaloid extract of *P. amarus* had significant activity against plasmodium (Uzuegbu et al., 2022). The methanolic extract of *P. reticulatus* leaves exhibited anti-diarrhoeal properties in several experimental animals with diarrhea (Nesa et al., 2014).

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.

REFERENCES

Akhtar, MN., Gayathri, M. (2015) Analysis of anti-diabetic properties of *Phyllanthus urinaria* by docking studies. Der Pharm Lettre, 7(12):132–7.
Andrianto, D., Widiyanti, W., and Bintang, M. (2017) Antioxidant and Cytotoxic Activity

of *Phyllanthus acidus* Fruit Extracts. IOP Conf Ser Earth Environ Sci. 58:1–5.
Asmilia, N., Sutriana, A., Aliza, D., and Sudril, N. (2020) Anti-inflammatory Activity of Ethanol Extract from Malacca Leaves (*Phyllanthus emblica*) in Carrageenan Induced Male Mice. E3S Web Conf. 151(01066):1–3.
Bakhtariy, SA., Iqbal, MM., and Ibrahim, Md. (2012) Hepatoprotective and nephroprotective activity of *Phyllanthus amarus* Schum & Thonn. seed extract. Ann Phytomedicine. 1(2):97–104.
Basavaraju, M., and Gunashree, B. S. (2022) *Phyllanthus Niruri* L: A Holistic Medicinal Plant with Modern Therapeutics. Med Plants. 1–13.
Bashir, A., Mushtaq, A., and Mehboob, T. (2018) Evaluation of Antioxidant and Antidiabetic Activity of *Phyllanthus emblica* (Fruit). Biologia (Bratisl). 64(1):85–91.
Bavarva, JH., and Narasimhacharya, AVR.L. (2007) Comparative Antidiabetic, Hypolipidemic, and Antioxidant Properties of *Phyllanthus niruri* . in Normal and Diabetic Rats. Pharm Biol. 45(7):569–74.
Bello, M., and Ibaba, H. (2020) Effect of Crude Ethanolic Leaf Extract of *Phyllanthus amarus* and Highly Active Antiretroviral Therapy (Tenofovir-Lamivudine Combination) in Wistar Rats. Direct Res J Heal Pharmacol. 8:52–64.
Boakye, YD., Agyare, C., and Dapaah, SO. (2016) In vitro and in vivo antioxidant properties of *Phyllanthus muellerianus* and its major constituent, geraniin. Oxid Antioxid Med Sci. 5(2):70–78.
Boakye, YD., Agyare, C., Kofi, W., Abotsi, M., Ayande, PG., Ossei, P., et al. (2016) Anti-inflammatory activity of aqueous leaf extract of *Phyllanthus muellerianus* (Kuntze) Exell. and its major constituent, geraniin. J Ethnopharmacol. 1–25.

- Chigurupati, S. (2020) Antioxidant and antidiabetic properties of *Phyllanthus acidus* (L.) Skeels ethanolic seed extract. *Int Food Res J.* 27(4):775–782.
- Chouhan, HS., and Singh, SK. (2011) Phytochemical analysis, antioxidant and anti-inflammatory activities of *Phyllanthus simplex*. *J Ethnopharmacol.* 137:1337–1344.
- Deivayanai, M., Vadivelu, J., and Vadivazhagi, MK. (2019) Anticancer activity of *Phyllanthus reticulatus* ethanolic and chloroform extracts against liver cancer cell lines. *A J Compos Theory.* XII(X):292–302.
- Eldeen, IMS., Seow, E., Abdullah, R., and Sulaiman, SF. (2011) In vitro antibacterial, antioxidant, total phenolic contents and anti-HIV-1 reverse transcriptase activities of extracts of seven *Phyllanthus* sp. *South African J Bot.* 77:75–9.
- Eze, CO., Nworu, CS., Esimone, CO., and Okore, VC. (2014) Immunomodulatory activities of methanol extract of the whole aerial part of *Phyllanthus niruri* L. *J Pharmacogn Phyther.* 6(4):41–46.
- Garg, M., Dhar VJ., and Kalia AN. (2008) Antidiabetic and antioxidant potential of *Phyllanthus fraternus* in alloxan induced diabetic animals. *Pharmacogn Mag.* 4(14):138–143.
- Geethangili, M., and Ding, S., (2018) A Review of the Phytochemistry and Pharmacology of *Phyllanthus urinaria* L., *Front Pharmacol.* 9:1–20.
- Giribabu, N., Karim, K., Kilari, E., and Salleh, N. (2017) *Phyllanthus niruri* leaves aqueous extract improves kidney functions, ameliorates kidney oxidative stress, inflammation, fibrosis and apoptosis and enhances kidney cell proliferation in adult male rats with diabetes mellitus, *J Ethnopharmacol.* 205:123-137.
- Grauzdytė, D., Pukalskas, A., Viranaicken, W., Kalamouni, C., and Venskutonis, P. (2018) Protective effects of *Phyllanthus phillyreifolius* extracts against hydrogen peroxide induced oxidative stress in HEK293 cells. *Plosone.* 1–15.
- Halim, P., Girsang, E., Nasution, AN., Lister, IE., and Lie, S. (2019) Nephroprotective Effect of Ethanolic Extract of Balakka (*Phyllanthus emblica* L.) on Rats Induced Ethylene Glycol and Ammonium Chloride. *Indones J Pharm Clin Res.* 02(2):36–42.
- Harikrishnan, H., Jantan, I., Haque, M., and Kumolosasi, E. (2018) Anti-inflammatory effects of *Phyllanthus amarus* Schum. & Thonn. through inhibition of NF- κ B, MAPK, and PI3K-Akt signaling pathways in LPS-induced human macrophages. *BMC Complement Altern Med.* 18(224):1–13.
- Harish R., and Shivanandappa T. (2006) Antioxidant activity and hepatoprotective potential of *Phyllanthus niruri*, *Food Chem.* 95(2):180-185.
- Hossain, S., Akter, S., Begum, Y., Bulbul, J. (2016) Analgesic and Anti-inflammatory Activities of Ethanolic Leaf Extract of *Phyllanthus acidus* L. on Swiss Albino Mice. *European J Med Plants.* 13(1):1–10.
- Hutomo, S., Putri, DU., Suryanto, YI., and Susilowati, H. (2018) Potential immunomodulatory activity of *Phyllanthus niruri* aqueous extract on macrophage infected with *Streptococcus sanguinis*. *Dent J.* 51(3):124–128.
- Ilangkovan, M., Jantan, I., Mesaik, M., Bukhari, S. (2015) Immunosuppressive effects of the standardized extract of *Phyllanthus amarus* on cellular immune responses in Wistar-Kyoto rats. *Drug Des Devel Ther.* 9:4917–30.

- Islam, M., Akhtar, M., Sharmin, SA., Rahman, A., Rahman, M., Khalekuzzaman, M., Anisuzzaman, M., and Alam M. (2013) Antibacterial potential of leaf extracts from *Phyllanthus reticulatus* Poir. Int J Pharm Res Dev. 5(04):88–95.
- Jahan, N., and Akter, S. (2015) Assessment of the antimicrobial activity of the ethanolic extract of *Phyllanthus emblica* in combination with different classes of antibiotics against single and multi- drug resistant strains. J Pharmacogn Phytochem. 4(4):142–55.
- Jain, NK., and Singhai, AK. (2011) Protective effects of *Phyllanthus acidus* (L.) Skeels leaf extracts on acetaminophen and thioacetamide induced hepatic injuries in Wistar rats. Asian Pac J Trop Med. 470–474.
- Khabiya, R., Choudhary, G., and Gn, D. (2019) Spectrophotometric Determination of Total Phenolic Content for Standardization of Various *Phyllanthus* Species. Asian J Pharm Clin Res. 12(8):297–301.
- Kiemer, AK., Hartung, T., Huber, C., and Vollmar, AM. (2003) *Phyllanthus amarus* has anti-inflammatory potential by inhibition of iNOS, COX-2, and cytokines via the NF- κ B pathway. J Hepatol. 38:289–297.
- Koffuor, GA., and Amoateng, P. (2011) Antioxidant and Anticoagulant Properties of *Phyllanthus fraternus* GL Webster (Family: Euphorbiaceae), J Pharmacol Toxicol, 6(7):624-636.
- Lee, C., Peng, W., Cheng, H., Chen, F., Lai, M., and Chiu, T. (2006) Hepatoprotective Effect of *Phyllanthus* in Taiwan on Acute Liver Damage Induced by Carbon Tetrachloride, Am J Chin Med, 34(3):471-482.
- Lee, SH., Jaganath, IB., Wang, SM., and Sekaran, SD. (2011) Antimetastatic Effects of *Phyllanthus* on Human Lung (A549) and Breast (MCF-7) Cancer Cell Lines. Plos One. 6(6):1–14.
- Li, P., Wang, C., Lu, W., Song, T., and Wang, C. (2022) Antioxidant, Anti-Inflammatory Activities, and Neuroprotective Behaviors of *Phyllanthus emblica* L. Fruit Extracts. Agriculture. 12, 588.:1–12.
- Li, M., Liu, L., Zhou, Q., Huang, L., Shi, Y., Hou, J., Lu, H., Yu, B., and Chen, W. (2022) *Phyllanthus Niruri* L. Exerts Protective Effects Against the Calcium Oxalate-Induced Renal Injury via Ellagic Acid. Front Pharmacol. 13:1–12.
- Mao, X., Wu, L., Guo, H., Chen, W., Cui, Y., Qi, Q., Li, S., Liang, W., Yang, G., et al. (2016) The Genus *Phyllanthus*: An Ethnopharmacological, Phytochemical, and Pharmacological Review. Evidence-Based Complement Altern Med. ID 7584952:1–37.
- Menéndez-perdomo, I., Wong-guerra, M., Fuentes-león, F., Carrazana, E., Casadelvalle, I., Vidal, A., and Sánchez-Lamar, A. (2017) Antioxidant, photoprotective and antimutagenic properties of *Phyllanthus* spp. from Cuban flora. J Pharm Pharmacogn Res. 5(4):251–61.
- Moirangthem, RS., Gunindro, N., Takhellambam, DS., Khurajam, SD., Meena, N., and Rita, S. (2017) Protective effect of *Phyllanthus fraternus* against cyclophosphamide- induced nephrotoxicity in rats. Int J Basic Clin Pharmacol. 6(4):984–9.
- Mostofa, R., Ahmed, S., Begum, M., Rahman, M., Begum, T., Ahmed, SU., et al. (2017) Evaluation of anti-inflammatory and gastric anti-ulcer activity of *Phyllanthus niruri* L. (Euphorbiaceae) leaves in experimental rats. BMC Complement Altern Med. 17(267):1–10.
- Natarajan, D., Srinivasan, R., and Shivakumar, MS. (2014) *Phyllanthus wightianus* Müll.

- Arg.: A Potential Source for Natural Antimicrobial Agents. *Biomed Res Int.* 1–10.
- Nesa, L., Islam, R., Ripa, F., mamum, A., Kadir S. (2014) Antidiabetic and antidiarrheal effects of the methanolic extract of *Phyllanthus reticulatus* leaves in mice. *Asian Pacific J Reprod.* 3(2):121–127.
- Nurfadhilah, D., Yuandani, Y., Anjelisa, P., and Hasibuan, Z. (2022) Immunomodulatory Effects of Cermay Leaves (*Phyllanthus acidus* (L.) Skeels) Ethanol Extract on Normal Male Rats and Cyclophosphamide Induction. *Sci Found SPIROSKI, Skopje, Repub Maced.* 10(A):782–787.
- Ofokansi, MN., Nworu, CS., Akunne, TC., Agbo, MO., and Akah, PA. (2018) Immunomodulatory Effects of *Phyllanthus muellerianus*: A Mechanistic Approach. *J Clin Cell Immunol.* 9(5):1–7.
- Ogunmoyole, T., Awodooju, M., Idowu, S., and Daramola, O. (2020) *Phyllanthus amarus* extract restored deranged biochemical parameters in rat model of hepatotoxicity and nephrotoxicity, *Heliyon.* 6:1-9.
- Okiki, PA., Egbebi, A., Akharaiyi, FC., Adewole, E., Asoso, SO. (2022) Drug properties and antimicrobial evaluations of extracts from *Phyllanthus amarus*. *J Microbiol Exp Res.* 10(1):10–16.
- Okoli, CO., Ibiam, AF., Ezike, AC., Akah, PA., and Okoye, TC. (2010) Evaluation of antidiabetic potentials of *Phyllanthus niruri* in alloxan diabetic rats. *African J Biotechnol.* 9(2):248–259.
- Okoli, CO., Obidike, IC., Ezike, AC., Akah, PA., and Salawu, OA. (2011) Studies on the Possible mechanisms of antidiabetic activity of extract of aerial parts of *Phyllanthus niruri*, *Pharm Biol,* 49(3):248-255.
- Oseni, L., Amiteye, D., Antwi, S., Tandoh, M., and Aryitey, G. (2013) Preliminary in vivo evaluation of anti-inflammatory activities of aqueous and ethanolic whole plant extracts of *Phyllanthus fraternus* on Carrageenan-induced Paw Oedema in Sprague-Dawley Rats. *J Appl Pharm Sci.* 3(03):62–65.
- Pammi, S., and Giri, A. (2021) In vitro cytotoxic activity of *Phyllanthus amarus* Schum. & Thonn. *World J Biol Pharm Heal Sci.* 6(2):34–42.
- Prakash, A., Satyan, K., Wahi, S., and Singh, R. (1995) Comparative Hepatoprotective activity of three *Phyllanthus* Species, *P. urinaria*, *P. niruri* and *P. simplex*, on Carbon Tetrachloride Induced Liver Injury in The Rat, *Phyther Res,* 9(8):594-596.
- Puspita, N., and Alhebshi, H. (2019) The effect of *Phyllanthus niruri* L extracts on human leukemic cell proliferation and apoptosis induction. *Indones J Pharm.* 30(4):1–12.
- Ramasamy, S., Wahab, N., Abidin, N., and Manickam, S. (2011) Cytotoxicity evaluation of five selected Malaysian *Phyllanthaceae* species on various human cancer cell lines, *5(11):2267-2273.*
- Rani, SS., and Raju, RRV. (2014) Antimicrobial Studies of *Phyllanthus maderaspatensis* and *Celosia argentea*. *Int J Eng Sci.* 3(3):35–38.
- Reddy, GS., Raparla, LP., Reddy, GR., and Charan, DV. (2015) Evaluation of Nephroprotective Activity of the Methanolic Extract of *Phyllanthus niruri* (Family-Euphorbiaceae). *Int J Pharm Phytopharm Res.* 4(5):276–280.
- Saini, R., Sharma, N., Oladeji, O., Sourirajan, A., Dev, K., Zengin, G., et al., (2022) Traditional uses, bioactive composition, pharmacology, and toxicology of *Phyllanthus emblica* fruits: A comprehensive review, *J Ethnopharmacol.* 282:1-6.
- Samatiwat, P., Chankhonkaen, P., Jaisin, Y., Ratanachamnong, P., Niwaspragrit, C., Rungsiwiwut, R., and Dhorranintra, B.

- (2021) Anticancer Activity of the Bark Extract of *Phyllanthus emblica* on Cholangiocarcinoma In Vitro, J Basic and Appl Pharmacol, 1(1):60-71.
- Sarg, T., Ghani, AA., Zayed, R., and El-sayed, M. (2011) Antihepatotoxic Activity of *Phyllanthus atropurpureus* Cultivated in Egypt. Verlag der Zeitschrift für Naturforschung, 66 c:447–452.
- Sarin, B., Verma, N., Martín, JP., and Mohanty, A. (2014) An Overview of Important Ethnomedicinal Herbs of *Phyllanthus* Species: Present Status and Future Prospects. Sci World J. 1–12.
- Shetti, A., and Kaliwal, BB. (2015) Hypoglycemic activity of ethanolic leaf extract of *Phyllanthus amarus* in alloxan induced diabetic mice. Eur J Exp Biol. 5(1):26–29.
- Shetti, AA., Sanakal, RD., and Kaliwal, BB. (2012) Antidiabetic effect of ethanolic leaf extract of *Phyllanthus amarus* in alloxan induced diabetic mice. Asian J Plant Sci Res. 2(1):11–15.
- Sibiya, AM., Ramya, AK., and Vaseeharan, B. (2020) Bioactive Molecules from *Phyllanthus Niruri* and Investigating their effects against Diabetes. MedDocs eBooks. 1–7.
- Srirama, R., Deepak, H B., Senthilkumar, U., Ravikanth, G., Gurumurthy, BR., Shivanna, M B, Chandrasekaran, C V, Agarwal, A, and Shaanker, R. (2012) Hepatoprotective Activity of Indian *Phyllanthus*, Pharm Biol, 50(8):948-953.
- Sukmanadi, M., Koestanti, E., and Ananda, AT. (2020) In Silico Study: *Phyllanthus Niruri* L. as Immunomodulator Against Covid-19. Indian J Forensic Med Toxicol. 14(4):3156–3161.
- Tahir, I., Khan, MR., Shah, NA., and Aftab, M. (2016) Evaluation of phytochemicals, antioxidant activity and amelioration of pulmonary fibrosis with *Phyllanthus emblica* leaves. BMC Complement Altern Med. 16(406):1–12.
- Tang, Y., and Sekaran, SD. (2011) Evaluation of *Phyllanthus*, for Its Anti-Cancer Properties. 305–320.
- Upadhyay, R., Chaurasia, JK., Tiwari, KN., and Singh, K. (2014) Antioxidant Property of Aerial Parts and Root of *Phyllanthus fraternus* Webster, an Important Medicinal Plant. Sci World J. 1-7.
- Uzuegbu, UE., Onyesom, I., Opajobi, AO., and Elu, C. (2022) Evaluation of erythrocyte viability, antioxidant capacity and antiplasmodial activity induced by alkaloid extract of *Phyllanthus amarus*. J Herbmec Pharmacol. 11(4):554–561.
- Wang, C., Yuan, J., Wang, C., Yang, N., Chen, J., Liu, D., et al. (2017) Anti-inflammatory Effects of *Phyllanthus emblica* L on Benzopyrene-Induced Precancerous Lung Lesion by Regulating the IL-1 β / miR-101 / Lin28B Signaling Pathway. Integr Cancer Ther. 16(4):505 –515.
- Zain, S., and Omar, W. (2018) Antioxidant Activity, Total Phenolic Content and Total Flavonoid Content of Water and Methanol Extracts of *Phyllanthus* species from Malaysia. Pharmacogn J. 10(4):677–681.

الجنس *Phyllanthus*: الاستخدامات الشعبية والفعاليات الحيوية

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الملخص

تمثل النباتات الطبية عناصراً أساسية في الطب التقليدي، وتم استخدامها لعلاج أمراض مختلفة. يعد جنس *Phyllanthus* التابع للفصيلة الفرّيبونِيَّة (Euphorbiaceae) من أهم النباتات الطبية، يضم الجنس حوالي 1000 نوع، بما في ذلك الشجيرات والأشجار والأعشاب النادرة. تُعرف أنواع جنس *Phyllanthus* في جميع أنحاء العالم بأهميتها الطبية وتستخدم لعلاج أمراض مختلفة، وقد أثبتت علمياً الأهمية الطبية لأجزاء نباتية مختلفة من أنواع الجنس. أظهرت المستخلصات النباتية المحضرة من أنواع جنس تأثيرات مفيدة في علاج داء السرطان، السكري، كمضاد التهاب، مضاد أكسدة، حماية الكلى، حماية الكبد، تأثيرات معدلة للمناعة، وغيرها. أصبحت الخصائص الدوائية لأنواع جنس *Phyllanthus* مؤخراً نقطة محورية للعديد من الدراسات نظراً لاستخداماتها العلاجية الواسعة في الطب الشعبي وانتشارها الواسع بالإضافة إلى مستقلباتها الثانوية المتنوعة. تسلط هذه المراجعة الضوء على أهمية جنس *Phyllanthus*، وتلخص بعض الفعاليات البيولوجية لأنواع الجنس، لفتح المجال للاستفادة من هذه الأنواع في المجالات الطبية والصناعية.

الكلمات المفتاحية: نباتات طبية، الفصيلة الفرّيبونِيَّة، فعاليات حيوية، مضاد أكسدة، مضاد جرثومي.