Journal of
Medicinal Plants and Herbs

Review Article Open Access

Phyllanthus Muellerianus, (Kuntze) Eccell. Review of the Ethnomedical Uses, Phytochemistry and Pharmacological Activities

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Received Date: April 12, 2023 **Accepted Date:** May 12, 2023 **Published Date:** May 15, 2023

Citation: Martha Nneoma Ofokansi, Peter Achunike Akah, Juliet Ogochukwu Omewu (2023) Phyllanthus Muellerianus, (Kuntze) Eccell.: Review of the Ethnomedical Uses, Phytochemistry and Pharmacological Activities. J Med Plant Herbs 2: 1-12

Abstract

Herbal products have been used over the decades in the management and treatment of some health challenges and diseased conditions. Phyllanthus muellerianus (Kuntze) Excell (Phyllanthaceae), a popular member of genus Phyllanthus is native to Africa and most tropical and subtropical countries. The readily availability and cultural heritage of this plant across generations may account for its wide use as traditional medicine. The plant is reported to possess many beneficial pharmacological activities such as anti-inflammatory, anti-nociceptive, antibacterial, antioxidant, anticancer, hypocholestrolemic and immunomodulatory activities. The purpose of this review is to provide updated and comprehensive literature data on the traditional uses, phytochemistry and pharmacological activities of Phyllanthus muellerianus so as to expose its numerous therapeutic potentials and possible future research opportunities.

Keywords: Phyllanthus Muellerianus; Folkloric uses; Pharmacological activities; Phytochemistry

Introduction

The Phyllanthaceae family is the second-most species-rich segregate from Euphorbiaceae sensu lato that is recognized [1]. Currently, it is comprised of 2000 species [2,3]. The relationships and circumscriptions of the genera has been the focus of extensive discussion. Revised classification of different tribes of Phyllanthaceae [4,5-7] was done after the previous study on the phylogenetic which elucidated their numerous structures [5,8,9]. The genus Phyllanthus muellerianus (Kuntze) Exell (Euphobiaceae) is widely distributed in the tropical region of West Africa. It is a small plant that grows throughout the season with canopy-forming leaves. It has fruits that are copious panicles of small red, shining berries that eventually turn black.

The relationship between genus Phyllanthus L. and other members of pantropical family Phyllanthaceae was confirmed by the similarities in their nuclear DNA sequenced data collected from previous studies [8-10]. Species in this genus vary widely, and are distributed in southern Nigeria and the tropical regions of the world [8,11]. They are monoecious plant with simple alternate leaves and very small diclinous flowers that cluster in cup-shaped structures. The fruit is a lobed-capsule extending from the cup and commonly the long stalk pendant. Phyllantus muellerianus is a woody climber, up to 12 m tall and sometimes arborescent. It has spines, with copious inflorescences of minute greenish flowers, and small berry-like red fruit [12,13]. The purpose of this review is to provide comprehensive information on the phytochemistry, traditional uses and pharmacological activities of Phyllanthus muellerianus in order to explore its therapeutic potentials, highlight the lacunae in the present knowledge and also evaluate future research opportunities.

Figure 1: Phyllanthus muellerianus (Kuntze) Excell (Phyllanthanceae)

Photograph by: Marco Schmidt; African plants - A Photo Guide

Chemical Constituents

Detailed phytochemical properties of P. muellerianus are necessary to understand its pharmacological activities, mechanisms of action and also for quality control purposes. Chemical investigations of this specie have led to the identification and isolation of several groups of chemical constituents. More than 510 compounds were isolated from Phyllanthus [14] and comprised mostly of triterpenoids [15], flavones [16], tannins [17,18] and lignans [19] Basic phytochemical groups have been isolated and reported from muellerianus species (Table 1). These isolated compounds exhibit various functions and are considered to exert different pharmacological activities. The proximate analysis of P.muellerianus leaf [20] indicated that it is enriched with fibre, fat, proteins, carbohydrates, ash and moisture contents making the leaf a source of food supplement in developing countries. The high fibre content makes it a good hypocholesterolaemic agent for people with cholesterol related problems [21]. Flavonoids have been reported to be

synthesized by plants in response to microbial infection and have been shown to have antibacterial activities [22-24]. The terpenoids are established as anti-inflamatory agent as well as analgesic agent [25,26]. Gallate is an antioxidant used in fatty food preservation [27]. Other properties conferred on this plant by the presence of these compounds include sweetening property, immune modulation, regulation of cell proliferation, neutral sterol metabolism and energy boosting property [20].

Table 1: The compounds isolated from Phyllanthus muellerianus

Number	Compounds	References
1.	(E)-Geranyl acetone	[25]
2.	(E)-α-Ionone	[25]
3.	(E)-β-Ionone	[25]
4.	1-Hexadecene	[25]
5.	1-Octadecene	[25]
6.	1-Tetradecene	[25]
7.	1β,22β-Dihydroxyfriedelin	[15]
8.	22β-Hydroxyfriedel-1-ene	[15]
9.	3,5-Dicaffeoylquinic acid	[28,29]
10.	3-Friedelanone	[29,30]
11.	4-Terpineol	[25]
12.	Acorenone	[25]
13.	Alkaloids	[30-32]
14.	Anthraquinones	[30-32]
15.	Astragalin	[29,33]
16.	Bis(2-ethylicosyl)phthalate	[30]
17.	Bis(2-ethyloctyl)phthalate	[30]
18.	Caffeic acid	[29,33]
19.	Caffeoylmalic acid	[29,33]
20.	Cardiac glycosides	[28]
21.	Caryophyllene oxided	[25]
22.	Chlorogenic acid	[29,33]
23.	Citronellal	[25]
24.	Citronellol	[25]
25.	Corilagin	[29,33]
26.	E-caryophyillene	[25]
27.	E-isoelemicin	[25]
28.	Flavonoids	[30-32]
29.	Furosin	[27]
30.	Gallic acid	[29,33]
31.	Geraniin	[29,33,35]
32.	Geraniol	[25]

33.	Hexahydrofarnesyl acetoned	[25]
34.	Humulene epoxide II	[25]
35.	Inremedeol	[25]
36.	Isocaryophyllened	[25]
37.	Isoquercitrin	[29,33]
38.	Lignans	30-32
39.	Limonened	[25]
40.	Linalool	[25]
41.	Methyl gallate	[33]
42.	Mustakone	[25]
43.	neo-Intermedeol	[25]
44.	Neophytadiene I	[25]
45.	n-Heptadecane	[25]
46.	n-Pentadecane	[25]
47.	Pentadecanald	[25]
48.	Phenols	[34]
49.	Phenylethyl alcohol	[25]
50.	Quercitrin	[29,33]
51.	Sabinene	[25]
52.	Saponins	[30-32]
53.	Spathulenol	[25]
54.	Tannins	[30-32]
55.	Tetradecanal	[25]
56.	Tetradecanoic acid	[25]
57.	Thujopsan-2-α-ol	[25]
58.	Triterpenes	[34]
59.	α-cadinol	[25]
60.	α-Copaene	[25]
61.	α-Humulene	[25]
62.	β-Caryophyllene	[25]
63.	γ-Eudesmol	[25]
64.	δ-Cadinene	[25]
65.	β-Sitosterol	[30]
66.	3-O-Methylellagic acid 3'-O-α-L-rhamnopyronoside	[36]
67.	1-O-galloyl-6-O-luteoyl-α-D-glucopyranoside	[36]

Ethnopharmacological Uses

Available literatures have provided information on the traditional uses of P. muellerianus in the treatment of different ailments in different parts of the world. The most widespread uses are in wound healing, menstrual disorder, dysentry and pain as well as kidney disorders. It has also been used against skin infections, intestinal worms and eye infections. Table 2 presents various documented ethnobotanical uses of P. muellerianus in different parts of the

world.

In Guinea, the leaves are boiled with palm fruits and administered to women undergoing labor. The root is cooked with maize meal in Ghana for treating chronic dysentery and in Togo, Côte d'Ivoire, and Zambia, both the roots and leaves are boiled for treatment of eruptive fever in children [37]. The fresh juice of the plant is used in southern part of Nigeria and Sierra Leone to treat skin and eye infections [37,38], as well as bronchitis, relieving urethral discharge and wound healing [37].

Table 2: Ethnomedicinal uses of Phyllantus muellerinus

Indication	Parts	Region	References
Wound healing	Aerial parts	Ghana	[33,38,39]
	Stem bark	Cameroun	[34]
	Leaves	Nigeria, Sierra leone, Cameroun	[31,33]
	Twigs	Ghana	[38]
	Leaves and stem bark	Nigeria	[32]
Menstural disorder	Leaves	Nigeria	[31,,33]
		Ghana, Cameroun and Sierra leone	[31,33]
	Twigs	Ghana	[39]
Tetanus	Stem bark	Cameroun	[34]
Pain	Oil and LeafTwig	NigeriaGhana	[25,40][39,41]
Jaundice	Twig and shoot	Nigeria	[28]
Paralysis	Twig	Ghana	[39]
Epilepsy	Twig	Ghana	[41]
Dysentry	Leaf	Nigeria	[42,43]
	Root	Ghana	[26,37]
Constipation	Leaf	Nigeria	[43]
Fever	Leaf	Côte d'Ivoire, Zimbabwe, Nigeria	[38,44]
	Root	Nigeria	[44]
Malaria	Whole plant	Africa	[45]
Skin infection	Leaf	Sierra leone, Ghana, Nigeria, Cameroun	[28,31]
Bronchitis	Leaf	India	[46]
Urethral discharge	Leaf	India	[46]
Sinusitis	Leaf	Cameroun	[17,18]

Pharmacological Activities

P. muellerianus posseses numerous pharmacological properties. It has complex chemistry with molecules of therapeutic importance. Extracts of the leaf of P. muellerianus are nontoxic to tested living organs [45,47]. The neuro- and hepatoprotective potentials of the leaf extract have been reported [48,49]. Several pharmacological studies have been carried out to investigate its acclaimed uses in wound healing, management of pain and inflammation; antioxidant, immunomodulatory and other pharmacological properties.

The information on this species was collected via electrionic search engines (using Pubmed, SciFinder, Google Scholar and Web of Science) and articles published in peer-reviewed journals. Some of the pharmacological investigations on P. muellarianus are summarized thus;

Antimicrobial

The leaf and stem bark of P. muellerianus have demonstrated antimicrobial activity against different pathogenic strains [32,50]. The methanol and ethyl acetate stem bark extracts have been reported to exhibit potent antibacterial activity [41,51]. The antimicrobial activity of *the* stem bark essential oil against *Clostridium sporogenes* and *Streptococcus pyogenes* has been documented [38]. The effects of the aqueous leaf extracts against S. aureus, S. pyogenes, P. aeruginosa, E. coli and C. albicans was attributed to the geraniin content [26]. Two studies [52,53] reported that the methanol leaf extract and chromatographic fractions exerted antimicrobial action against P. aeruginosa, P. mirabilis and E. faecalis while synergestic effect against P. aeruginosa was observed through combination of ciprofloxacin and the extract.

Klebsiella granulomatis, a human pathogenic bacterium was inhibited by the volatile oil from the leaf [49]. Other human pathogenic bacteria such as Escherichia coli, Staphylococcus aureas, and Salmonella typhi [54] and other bacteria like Bacillus cereus and Klebsiella pneumonia [55] have been reported to be sensitive to the leaf extracts.

Anti-inflamatory and Anti-nociceptive

The aqueous leaf extract of *P. muellerianus* and the major isolate, geraniin have demonstrated anti-inflammatory activity [26[. The essential oil from the leaf was reported to exhibit both anti-inflammatory and anti-nociceptive activities by suppressing the production of pro-inflammatory mediators and depressing the central nociceptors respectively. A significant anti-nociceptive activity of the aqueous extract of the aerial parts of Phyllanthus muellerianus against chemical (acetic acid and formalin)-induced nociception in mice is also documented [56].

Antioxidant

Evidence has been provided suggesting that P. muellerianus could stimulate the production of super oxide dismutase, catalase and ascorbate peroxidase which are antioxidant coding genes acting against reactive oxygen species causing delay in wound healing [39]. Similar in-vitro antioxidant activity of P.muellerianus has been reported by other workers [20,28,57]. Compared to the methanol extract, the aqueous leaf extract contains high hydroxyl radical scavenging and free radical scavenging (DPPH) antioxidant activity, while ferric reducing antioxidant was more in the methanol extract. The hydromethanolic extract of P.-muellerianus appeared to possess a high antioxidant activity compared to other Phyllanthus species [58]. The antioxidant property of the plants was attributed to the presence of flavonoids acting as free radical scavenger and also aids in inhibition of lipid peroxidation hence relaxation of vascular system thereby preventing artherosclerosis [59]. Previous study [38] attributed the antioxidant activity to its geraniin constituent. The geranin is a strong antioxidant and it is used in treatment of chronic wound [56]. It has been suggested [60-62] that P. muellerianus would be of great health benefits due to its antioxidant properties.

Antianemic

Aqueous root extract of P. muellerianus was demonstrated efficacious against anemia in rats, exhibiting a dose dependent effect [63,64]. A study [65] also revealed that the root extract could be used for recovery of damaged blood tissue in fish because of its haematopoietic effects. The leucopoietic effect of the methanol leaf extract of the plant in immunocompromised rats is also reported [66].

Hypocholestrolemic and cardioprotective effects

Reduction and normalization of the glucose level in streptozotocin induced diabetic rat by aqueous leaf extract of P. muellerianus has been reported [67]. The study also reported the normalization of total cholesterol levels, LDL-cholesterol and triglycerides with significant increase in HDL-cholesterol. P. muellerianus has been used to treat atrial fibrillation due to congenital heart defects because of the presence of cardiac glycosides [68]. Saponins present in this plant expressed several benefits such as; inhibition of growth of cancerous cells and as hypocholesterolemic agent [69].

Immunomodulatory

The methanol extract and ethylacetate fraction of P. muellerianus exhibited significant effects on leucopoiesis in cyclophosphamide-induced immunosuppressed rats [66]. There was an inhibition and stimulation of delayed

type-hypersensitivity reaction against sheep red blood cells in mice with the ethyl acetate fraction evoking the highest inhibition and stimulation at highest and lowest dose respectively [66]. Thus, it is suggested that P. muellerianus may be useful as an immunosuppressive agent at high doses for unwanted immune (eg allergic and inflammatory reactions) reactions and immune booster at low doses in the cases of impaired immunity.

Neuropharmacological

A recent study [70] has shown that the methanol leaf extract of P. muellerianus elicited sedative, anticovulsants and anxiolytic activities. According to the report, the ethyl acetate fraction produced anxiolytic and anticonvulsant activities but devoid of sedative effect as is the case with many currently available anxiolytic and anticonvulsant agents [70].

Antimalarial

In vitro antiplasmodial studies [45] has shown that the ethanol leaf extracts of P. muellerianus exhibited potent inhibitory activity against chloroquine-resistant FcB1 strain of *Plasmodium falciparum.* The result showed a high selectivity for the parasite hence, its potential benefit in the treatment of resistant falciparum malaria.

Anticancer activity

The anti-proliferative and pro-apoptotic activities of P. muellerianus has been illustrated [57] and the study indicated that the plants expressed anti-proliferative property against human prostate cancer PC-3 cells through modulation of the calcium channels making it a good therapeutic agent for the treatment of prostate cancer.

Conclusion

The healing properties of Phyllanthus muellerianus have been used for decades in traditional medicine. Current studies have illustrated different pharmacological activities which are also in line with their ethnopharmacological uses. The numerous studies conducted on Phyllanthus muellerianus, portray a plant with a lot of promising prospects. Extensive research has been done on the antimicrobial, anti-inflammatory as well as the antioxidant activity but there are other less putative effects especially in cancer treatment that have not been explored, hence there is need for more studies with a view of uncovering its therapeutic benefits.

Conflict of Interest

The authors declare no conflict of interest

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