

Review Article

Agelathus dodoneifolius (African Mistletoe): A Review

Assoc. Prof. Modupe Iretiola Builders*

Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, Bingham University, Karu, Nasarawa State

***Corresponding Author**

Assoc. Prof. Modupe Iretiola Builders

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Abstract: *Agelanthus dodoneifolius* DC Danser synonym to *Tapinanthus dodoneifolius*, (family Loranthaceae) popularly called African mistletoe is a hemi-plant parasite used ethnomedicinally as a remedy for various diseases affecting humans and animals that include stomach ache, diarrhoea, dysentery, wound and cancer by the Hausa and the Fulani tribes of Northern Nigeria. Ailments such as circulatory and respiratory diseases, malaria, diabetes, hypertension and sterility have been treated using different parts of the plants. Phytochemicals such as alkaloids, flavonoids, tannins, anthraquinones cardiac glycosides, saponins, glycosides, sterols, resins, volatile oil, terpenes and phenols have been reported in the plant. This review covers its phytochemistry and pharmacology.

Keywords: *Agelanthus dodoneifolius*, African mistletoe, Phytochemistry, Pharmacology, Toxicology.

INTRODUCTION

Agelathus dodoneifolius belongs to the family Loranthaceae (mistletoes) which is a parasitic plant widely known for its destructive nature to the host plants which they parasitized [1]. *A. dodoneifolius*, also named African mistletoe is a common shrub that is largely distributed throughout Africa including Nigeria [2]. *A. dodoneifolius* is an evergreen, perennial plant species that form a dark green to yellowish-green, drooping bush that can reach 0.6-0.9m long on the branch of a host tree. It has thickly crowded, forking branches and round, jointed stems, the opposite, oval, lance shaped with leathery leaves of about 5cm long [3].

A. dodoneifolius belongs to the genus *Agelathus*, largest genus of the Afrotropical Loranthaceae containing some 61 species, but there are two well recognized species besides African mistletoe; *Agelanthus braunneus* and *Agelanthus heteromorphus* [4]. *Agelanthus dodoneifolius* (DC) is a parasitic plant that is found growing on the branches or aerial parts of the host plants usually tree indigenous trees tree crops of economic importance such as citrus plants like orange (*Citrus* sp.), guava (*Psidium guajava*), *Vitellaria paradoxa* (Sheer butter), *Anacardium occidentale* (cashew), *Mangifera indica* (mango), *Annona squamosa* (sugar apple), *Azadirachta indica* (Neem), *Acacia nilotica*, *Mangifera indica*, *Phyllanthus niruri*, *Parkia biglobosa* and *Ziziphus spina-christi* [1].

Agelathus as a parasite

African mistletoe (*A. dodoneifolius*) is a partial parasite or a “hemiparasite” that grows on the branches of trunk of trees and produces haustoria that penetrate into the tree and take up nutrients [5]. The parasitic plant (African mistletoe) can simultaneously parasitize many host species because different host species supply a parasite with different resources, a mixture of host and parasite may be superior to a single host. African mistletoe grows on its own and can produce its own food by photosynthesis like other plants. African mistletoe reduces the overall photosynthetic area of the host plants thereby causing abnormal growth and decrease in productivity [5]. The host plants are deprived of foods that are available for their other activities as a result of prevention from giving off branches at the positions of attachment; this weakens and kills host plants as shown in figure 1. The trees that are infected by African mistletoe lack enough nutrients for basic maintenance of growth and therefore undergo ageing and death [6].

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Fig-1: African mistletoe (*A. dodoneifolius*) parasitizing on the host tree (7)

Ethnomedicinal uses

Many Traditional Medicine Practitioners had used African mistletoe (*A. dodoneifolius*) for a very long time ethnomedicinally to treat various ailments including hypertension, asthma, infection, cancer, malaria, wound and diabetes [8] because use of medicinal plants is the most reliable source of care for many millions of people as medicinal plant is more accessible, affordable and culturally acceptable and trusted [9]. The traditional uses of African mistletoe involve mainly decoction, infusion, maceration and local application [9, 10], it may be use alone or in association with other traditional remedies.

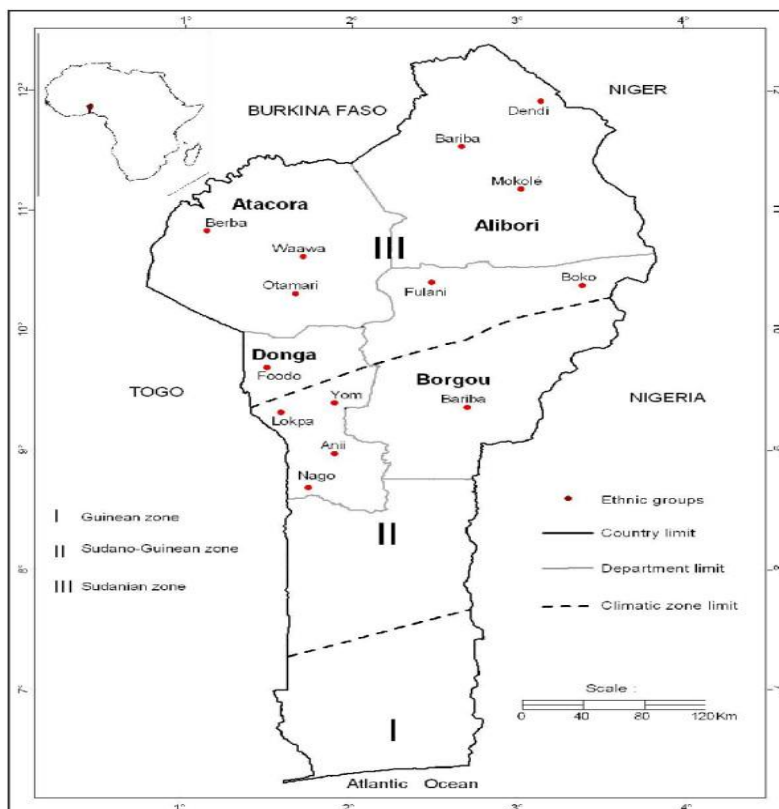


Fig-2: Pattern of ethnomedicinal uses of African mistletoe (*Agelathus dodoneifolius*) in West African (11)

Table-1: Medicinal uses of African mistletoes -9, 10, 11, 12, 13, 14,

Parts	Local names/Common names	Preparations	Medicinal uses	Countries
Leaves, stem barks, young twigs, fruit, whole plant	<i>Kauchi, Afomo onisan, Etulonchi, Elozie, madifo, balanta, Dogon, Grusi, Lightning, matches, mistletoe</i>	Decoction, maceration, herbal tea	Hypertension, diabetes, anxiety, malaria, pain, sterility, asthma, wounds, skin diseases,	Nigeria, Cote dlvoire, Burkin na faso, Senegal, Guinea, Mali, Ghana

Phytochemicals

Phytochemicals are secondary metabolites with diverse physiological and biological activities in plants. The presence of these bioactive substances enhances the pharmacological actions responsible for the therapeutic effects and these substances can be in any part of the plant [15]. Studies have shown that variation in the content of components of the same class may be related to factors such as host plants, genetic origin, geographical location, source, handling, solvent of extraction, extraction time and cultivation conditions are responsible for variation in the content of components of the same class and also analytical techniques employed may also be responsible for the slight variations in the final results obtained [10, 16, 17]. The composition of the chemical constituents of different parts of African mistletoe is the same but only vary in contents as indicated in Table 2.

Table-2: Phytochemistry of *Agelathus dodoneifolius* (African mistletoe) 7, 10, 12, 13, 14

Chemical constituents	Parts	Extracts / Fractions	Remarks
Alkaloids	Twigs, leaves, stem bark	Water, methanol, ethanol	+
Tannins	Twigs, leaves, whole plant	Water, methanol	++
Saponins	Twigs, leaves, whole plant	Water, methanol	+
Sterols	Twigs, leaves, whole plant	Water, methanol	+
Terpenes	Twigs, leaves, whole plant	Water, methanol	++
Glycosides	Twigs, leaves, stem bark, whole plant	Water, methanol	+
Phenols	Twigs, leaves	Water, methanol	++
Anthraquinones	Twigs, leaves, whole plant	Water, methanol	+
Reducing sugars	Twigs, whole plant	Water	+
Resins	Twigs	Water	+
Volatile oils	Twigs	Water	-

Pharmacology

Antiplasmodial activities

The African mistletoe (*A. dodoneifolius*) methanolic extract was evaluated for *in vivo* and *in vitro* antiplasmodial activities against *Plasmodium berghei* and clinical isolates of *Plasmodium falciparum* respectively. *A. dodoneifolius* showed maximum inhibition (78.7 ± 1.6 , 80.1 ± 1.0 and $69.8 \pm 1.2\%$) of parasitaemia and moderate anti-plasmodial activity *in vitro* ($21.54 \mu\text{g/ml} > \text{IC}_{50} > 50 \mu\text{g/ml}$) among *Parkia biglobosa* (host plant) and *Vernonia ambigua* [7]. The water extract of *A. dodoneifolius* indicated a dose-dependent inhibition of parasitaemia in the *in vivo* antiplasmodial tests likewise, the *in vitro* screening demonstrated a strong and concentration-dependent activity ($21.54 \mu\text{g/ml} < \text{IC}_{50} < 50 \mu\text{g/ml}$) of the extract against the clinical isolates of *Plasmodium falciparum* [13]. Abdullahi *et al.*, 2015 demonstrated that the methanol whole plant extract of African mistletoe and its methanolic fraction produced significant ($p < 0.01$) and dose -dependent chemo -suppressive effect and this correlated with in the survival times of the infected mice [15].

Analgesic, antipyretic and anti-inflammatory activities

The analgesic, antipyretic and anti-inflammatory activities of methanolic extract of African mistletoe had been investigated by Abdullahi *et al.*, 2016. The extract exhibited a significant ($p < 0.01$) and dose-dependent inhibition of the acetic acid-induced abdominal constriction in mice, increased threshold for pain perception dose-dependently in the hot plate test in mice and decreased acute and delayed phases of formalin-induced pain dose dependently ($p < 0.01$). The extract also produced a significant ($p < 0.01$) dose-dependent anti-inflammatory effect in Carrageenan-induced oedema in rats. Significantly decreased dose -dependent rectal temperature in rats was also exhibited by the extract [16].

Boly *et al.* had also reported the anti-inflammatory effect of *A. dodoneifolius* and its potential use for the treatment of neutrophil-dependent inflammatory diseases, dose-dependent inhibitory effects on the oxidant activities of neutrophils was observed by all the tested extracts [17].

Antimicrobial activities

Research has shown that the mistletoe plant exhibited a wide spectrum of antimicrobial activities against certain multiple drug resistant bacterial and fungal isolates of farm animals including the inhibition of the growth of *Bacillus* sp. *Agrobacterium tumefaciens*, *Escherichia coli*, *Salmonella* sp, *Proteus* sp, and *Pseudomona* ssp [2].

Antibacterial activities

The antibacterial activity of the stem bark and leaves extracts of mistletoe plant (*A. dodoneifolius*) had been validated by Inusa *et al.*, 2018. The two extracts displayed the largest diameter of inhibition zone of (17 mm) and (15 mm) at the concentration of 10 mg/ml respectively [12].

Antiulcer activities

The antiulcer activity of ethanolic leaf extract African mistletoe was tested on wistar rats' stomach. The incidence of ulceration was reduced in a dose dependent manner by oral administration of aqueous ethanolic leaf extract at the dose of (500-1500mg/cm³) to Aspirin induced ulcerated wistar rats for one week [14].

Ouedraogo *et al.* [11] isolated dodoneine from the plant, a dihydropyranone that exhibited a relaxing effect on precontracted rat aortic rings [21].

Hypotensive effects

Ouedraogo *et al.* investigated the effects of different *A. dodoneifolius* ethanolic fractions on rat blood pressure and aortic relaxation. A dose-dependent decrease in both systolic and diastolic blood pressure without any significant change in heart rate was observed. Also, the extract caused relaxation of rat pre-contracted aorta in a concentration-dependent manner [18].

Veterinary use

In veterinary, *A. dodoneifolius* is used in the treatment of asthma, an allergic disease (neutrophils-mediated inflammatory disease) which is also found in horses [19, 20]. The leaves of *A. dodoneifolius* is used for treating skin diseases in form decoction mixed with salt administered orally (1L) twice daily to cattle [10]. Traditional Medicine practitioners also use the African mistletoe as animal remedies for treating infertility.

Modulatory activities

The effects of the aqueous decoction and the diethyl ether, ethyl acetate and butanolic fractions of *A. dodoneifolius* DC Danser (Loranthaceae) on reactive oxygen species (ROS) production and myeloperoxidase (MPO) have been investigated. The findings reveal the interesting potential of *A. dodoneifolius* fractions to modulate the inflammatory response by decreasing the oxidant response of neutrophils without causing any toxicity [21].

DPPH free radical scavenging activities

Study has shown that *A. dodoneifolius* has excellent natural antiradical scavenging activities. *A. dodoneifolius* dried and powdered leaves exhibited a significant dose dependent radical scavenging activity with EC₅₀ values of 8.20 ± 0.25 and 13.20 ± 0.37 µg/mL, respectively. It has also been reported that *A. dodoneifolius* subfractions represent potential sources of natural antioxidants and they are antimyeloperoxidase compounds [22].

Mechanisms of action

A. dodoneifolius harvested from host plants such as like orange (*Citrus* sp.), guava (*Psidium guajava*), *Vitellaria paradoxa* (Sheer butter), *Anacardium occidentale* (cashew), *Mangifera indica* (mango), *Annona squamosa* (sugar apple), *Azadirachta indica* (Neem), *Acacia nilotica*, *Mangifera indica*, *Phyllanthus niruri*, *Parkia biglobosa* and *Ziziphus spina-christi*. *A. dodoneifolius* is a parasite of the xylem tissue of these host plants and depends on its host for water, nutrients and some carbon compounds by a series of chemical exchange [23]. This dependence may be responsible for its antiplasmodial activity since the host plants have known antiplasmodial activities [24, 25]. Studies have also shown possible similarities in the phytochemical constituent as well as the pharmacological activities between a parasitic plant and its host due to the intimate and complex chemical exchange between the parasite and the host plant [24, 25].

The antiplasmodial activities of African mistletoe may be attributed to the antioxidant effect of African mistletoe. The presence of polyphenolic compounds may be responsible for the antioxidant activities, the antioxidant activity of polyphenolic compounds like flavonoids, tannins and phenolic compounds is mainly due to their redox properties, which can play an important role in adsorbing and neutralising free radicals, quenching singlet and triplet oxygen, or decomposing peroxides [26]. The antiplasmodial activity of these antioxidant phenolic compounds may also be by elevating the red blood cell oxidation and inhibiting the parasite's protein synthesis and also counteract the oxidative damage induced by the malaria parasite [27]. Therefore, another mechanism of explaining the antiplasmodial activity of *A. dodoneifolius* is the antioxidant activities of the secondary metabolites present in the plant.

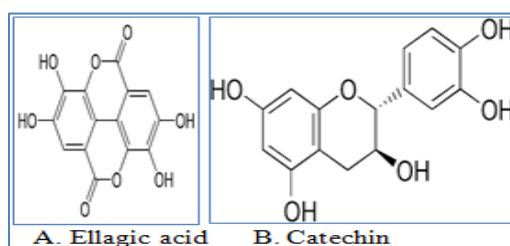


Fig-3: Structure of polyphenolic compounds [17]

Polyphenolic bioactive substances such as steroids, terpenoids and flavonoids are responsible for the anti-inflammatory activity of many plants [28]. These polyphenolic compounds inhibit the growth of various cancer cell lines and also possess antioxidant, anti-inflammatory, anti-hepatotoxic and anti-ulcer properties [29]. The inhibition of some key inflammatory enzymes such as cyclooxygenase, lipoxygenase, protein kinase C (PKC) and phosphoinositide 3-kinase (PI3-kinase) or from the inactivation (or scavenging) of free radicals are attributed to the anti-inflammatory effects of polyphenols [28, 30]. This explains the use of African mistletoe in the treatment of inflammatory diseases such as asthma, an allergic disease [19, 20].

Research has shown that African mistletoe mediated its antinociceptive activity peripherally which is related to its analgesic property. This peripherally mediated action is dependent partly on the inhibition of lipo-oxygenases and/or Cyclo-oxygenase. Diluted acetic acid administered to the peritoneal cavity induces viscera-motor responses acting indirectly by promoting the release of endogenous mediators are released causing the induction of the peritoneal cavity leading to the stimulation of the terminals of the primary afferent fibres, resulting to the nociceptive feeling [31].

Multiple mechanisms involving both peripheral and central pathways of pain perception may also be associated with the nociceptive activity of the *A. dodoneifolius*. This correlates with the suppression of both phases of pain by the mistletoe plant which supports the dual activity involving both the centrally mediated and peripherally localized pain mechanisms. The anti-pyretic activity of the extract may be attributed to inhibition of prostaglandin synthesis within the hypothalamus [32].

Ouedraogo *et al.* Isolated dodoneine from the plant, a dihydropyranone that exhibited a relaxing effect on precontracted rat aortic rings, dodoneine is attributed to the vasoactive effect of the extract [33].

Toxicity

The important parameter used to determine the safety of any drug is known as toxicity, preliminary toxicity carried by Builders *et al.*, 2012; Eyya *et al.* 2017; Builders, 2018;. [34, 35] Builders *et al.*, 2020 indicated that water extract of *Agelanthus dodoneifolius* was likely to be non-toxic. The LD₅₀ of the water extract of the twig or leaf of *A. dodoneifolius* was found to be greater than 5000 mg/ kg p.o [36]. The oral and intraperitoneal LD₅₀ of the methanolic extract was found to be greater than 5000 mg/kg and 3800 mg/kg body weight respectively [15]. Baso and Mudi, 2017 investigated the LD₅₀ of the aqueous ethanolic extract of the leaf of *A. dodoneifolius* to be greater than 5000 mg/ kg p.o. Absence of lethality or toxic symptoms shows that the extract of *A. dodoneifolius* is acutely non-toxic [14].

To further confirm the non-toxicity of African mistletoe, Builders *et al.*, 2020 investigated sub-acute toxicity (21-days) studies with *Agelanthus dodoneifolius* on rats to determine its consequences on food and fluid intake, body weight, haematological, biochemical, and mortality. Significantly (P < 0.05) and highly significant (P < 0.01) progressive decrease in food, fluid intake and body weight different from control on rats treated with the extracts were observed. Both haematological and liver function indices increased significantly compare to the control by the water extract. The renal function parameters were not significantly different in all the groups [36].

CONCLUSION

African mistletoe (*Agelanthus dodoneifolius*) possesses enormous medicinal properties which have been scientifically and experimentally documented. This might serve as a source of new lead compound of novel chemical structure. Therefore, further study is recommended to identify and isolate the active components responsible for these activities.

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