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Research Article

Aphloia theiformis (Vahl.) Benn.: A Plant with Various Therapeutic Properties

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Abstract

Aphloia theiformis (Vahl.) Benn. is an evergreen medicinal plant possessing multiple therapeutic virtues. Traditional use of the plant among folk populations of Madagascar, Comoros Island, Mascarenes Islands, Seychelles Archipelago, and tropical Africa was geared towards the management of dysentery, fever, rheumatism, ulcers, jaundice, gastrointestinal infections, skin infections, cataract, and diabetes mellitus. Multiple lines of evidence from the literature appraise the biological activities of *Aphloia theiformis*. Recent *in vitro* studies support the inhibitory action of *Aphloia theiformis* methanol leaves extract on key enzymes related to diabetes, obesity, hypertension, Alzheimer's disease, and kidney stone formation. Such findings have led to the identification of mangiferin. *Aphloia theiformis* was also reported to possess anti-malaria, anti-Chikungunya, and "anti-aging" properties. The present monograph tries to comprehensively establish the ethnopharmacological uses, biological activities, as well as the botanical description of *Aphloia theiformis*. It is expected that this comprehensive monograph will support further scientific studies in order to validate other traditional use of *Aphloia theiformis*, hence opening avenues for the development of novel therapeutic entities.

Keywords

Indian Ocean Islands; Mangiferin; Medicinal Plant; Therapeutic Properties

Introduction

A strong body of evidence generated by ethnobotanical studies praise the use of medicinal plants by cultures across the globe [1]. Indeed, herbal medicinal systems, practices, and knowledge have been transmitted from one generation to the next over the years [2]. It has been postulated that up to 80% of the population of developing countries still rely on traditional medicine for their primary health case, either because of cultural tradition or scarcity of modern treatment facilities [3]. A substantial number of scientific studies attest that there is currently a renewed interest in medicinal plants for the development of novel therapeutic agents geared towards the prevention and treatment of various pathologies.

Aphloia theiformis (Vahl.) Benn. is presently the only known flowering species of the Aphloiaceae family [4]. Ethnobotanical evidences substantiate the use of *A. theiformis* by folk cultures of Madagascar, Comoros Island, Mascarenes Islands, Seychelles Archipelago, and tropical Africa for the management of several human ailments [5]. The binomial nomenclature includes the epithet '*Aphloia*' which stems from the Latin word 'a' meaning 'without' and 'phloios' meaning 'bark/skin/flower', while '*theiformis*' comes from 'thea'

which means 'tea' and 'formis' stands for 'form' [5,6]. *A. theiformis* is commonly known as 'Fandamane' or 'Bois goyave/gouyave' in Mauritius, 'Change écorce/Bois change écorce' or 'Gouyavier marron/Gouyave marron' in Réunion Island, 'Bois d'anémone' in Rodrigues, 'Bwa merl/Bois merle' in Seychelles, 'Voafotsy', 'Fandramanana', or 'Maramanana' in Madagascar [7].

In an endeavor to valorise *A. theiformis*, this paper attempts to present recent findings on the biological properties of *A. theiformis* and aims at extending knowledge on its botanical description, ethnopharmacological uses, and phytochemical profile to the scientific community.

Botanical Description

A. theiformis is an evergreen treelet reaching 10 to 15 m height (Figure 1A). The trunk, measuring 30 cm in diameter, is black to blackish brown, deciduous in patches; the underlying bark is smooth and pale brown. The young branches are reddish and striated. Mature leaves are variable in shape with narrow to broadly elliptic or narrowly oboval to oboval-elliptic blade. The leaf margin is denticulate to glandular-dentate and measure between 3-8 cm long and 1.5-4.5 cm wide (Figure 1B) [8]. Flowers are auxiliary, solitary or in bunch with white to pale yellow sepals measuring between 5-6 mm in diameter (Figure 1C). The fruits are sub-globular to ovoid-pyriform, turn white at maturity and measure 6-8 mm long and 4-6 mm in diameter (Figure 1D) [5].

Figure 1: A: *Aphloia theiformis* whole plant, **B:** *Aphloia theiformis leaves*, **C:** *Aphloia theiformis* flowers, **D:** Different plant parts of *Aphloia theiformis* [8] 1: flowering branch, 2: flower head, 3: developing fruit, 4&6: different types of young leaves, 5: mature leaf, 7: branch with male flower, 8: male flower, 9: fruit.

Ethnopharmacological Uses

Literature search revealed the extensive use of *A. theiformis* in traditional medicine. *A. theiformis* has been used alone or in combination with other medicinal plants for the management of various diseases including dysentery, fever, rheumatism, ulcers, jaundice, gastrointestinal infections, skin infections, cataract, decrease cholesterol level, diabetes, wound healing, as a diuretic, and anti-pyretic [5,9,10]. Table 1 summarises the preparation methods involving the use of *A. theiformis* for the management of different human ailments.

Scientific name of plants	Plant part	Indication	Method of preparation and/or administration	Source
Aphloia theiformis, Terminalia bentzoe	Leaves, bark	Dysentery	10-15 leaves of *Aphloia theiformis*, 5-6 pieces of bark of *Terminalia bentzoe* can be consumed 2-3 times daily	[5]
Aphloia theiformis, Erythroxylum laurifolium, Cocos nucifera	Leaves, bark, roots	Fever	Few leaves of *Aphloia theiformis*, bark of *Erythroxylum laurifolium*, roots of *Cocos nucifera*. Half cup can be consumed 3 times daily	[5]
Aphloia theiformis, Antidesma madagascariense, Toddalia asiatica	Leaves	Jaundice	Prepare decoction using leaves of *Aphloia theiformis*, *Antidesma madagascariense*, *Toddalia asiatica*	[6]
Aphloia theiformis	Leaves	Diuretic	An tea prepared using dried leaves of *Aphloia theiformis* (20 g for 1 L of water) can be consumed 3-4 times daily	[11]
Aphloia theiformis, Combretum micranthum	Leaves	Fever, jaundice, ulcer, rheumatism, gastrointestinal infections	–	[11]
Aphloia theiformis	Leaves	Stomach pains	Decoction prepared from leaves of *Aphloia theiformis*	[5]
Aphloia theiformis	Leaves, roots	Impetigo	Decoction prepared from leaves and roots of *Aphloia theiformis*	[5]
Aphloia theiformis, Piper nigrum, Cinnamomum verum	–	Refreshing	*Aphloia theiformis* mixed with *Piper nigrum* or *Cinnamomum verum* is consumed as refreshing drink	[5]
Aphloia theiformis, Dracaena reflexa, Centella asiatica	Leaves	Teething children	A decoction prepared from the leaves of *Aphloia theiformis*, *Dracaena reflexa*, and *Centella asiatica*	[5]
Aphloia theiformis	Roots	Skin infections	A root decoction of A*phloia theiformis* is used to wash skin infections	[6]
Aphloia theiformis	Leaves	Nail infection	A leaf poultice is applied to infected nail	[5]
Aphloia theiformis	Roots	Laxative	Decoction is prepared from the roots of *Aphloia theiformis*	[5]
Aphloia theiformis	Bark	Chikungunya	Decoction is prepared from the bark of *Aphloia theiformis*	[12]
Erythroxylum laurifolium, Aphloia theiformis, Cassia fistula, Antidesma madagascariense, Heimia myrtifolia	Leaves, bark,	Lower back ache caused by kidney stones or urinary infections	Decoction prepared from *Erythroxylum laurifolium* stem bark, *Aphloia theiformis* leaves, *Cassia fistula* leaves, *Antidesma madagascariense* leaves, *Heimia myrtifolia* leaves. Three cups can be taken orally per day in the morning, at noon and at night.	[13]
Aphloia theirformis	Leaves		In traditional Malagasy medicine, an infusion of the leaves is used to treat fever and stomach aches	[14]

Table 1: Ethnopharmacological data on *Aphloia theiformis*.

Major Chemical Constituents

Preliminary phytochemical screening of the crude methanol and aqueous extracts prepared from the leaves of *A. theiformis* indicated the presence of alkaloids, phenols, flavonoids, saponins, and anthraquinones. Tormentic acid ester glucoside, 23-hydroxytormentic acid ester glucoside, and 6β-hydroxytormentic acid ester glucoside were isolated and identified from *A. theiformis* methanol leaves extract [15]. More recently, a group of authors reported the presence mangiferin (Figure 2), a xanthone glucoside, in *A. theiformis* methanol leaves extract [16].

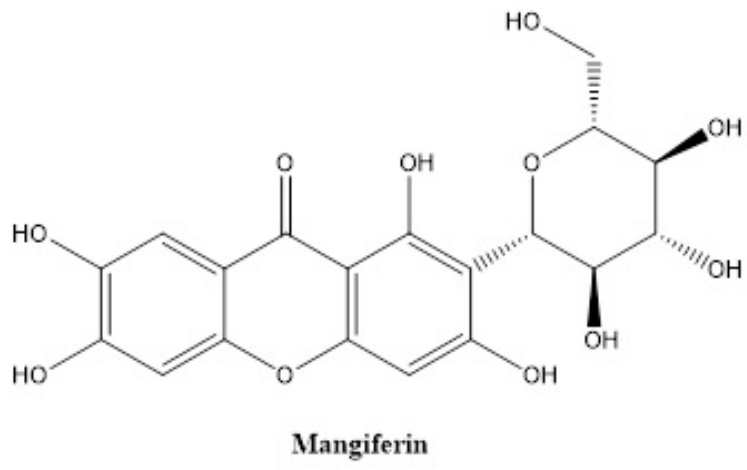

Figure 2: Structure of mangiferin [17].

Biological Activities

In vitro testing of the crude methanol extract revealed inhibitory action against enzymes related to diabetes (IC_{50} 67.71, 55.20, 19.73 μg ml^{-1} for α-amylase, α-glucosidase, and glycogen phosphorylase, respectively), obesity (IC_{50} 939.97, 696.22 μg ml^{-1} for pancreatic lipase and cholesterol esterase, respectively), Alzheimer's disease (IC_{50} 186.04 μg ml^{-1} for acetyl cholinesterase), hypertension (IC_{50} 162.17 μg ml^{-1} for angiotensin converting enzyme), and kidney stone formation (IC_{50} 148.80 μg ml^{-1} for urease). *In silico* molecular docking showed that mangiferin, identified in the crude methanol extract of *A. theiformis* leaves, docked to the afore-mentioned enzymes, showing π-π interactions and hydrogen bonds mostly. The anti-diabetic properties of *A. theiformis*, documented from traditional use, can thus be attributed to the presence of mangiferin. Additionally, *A. theiformis* expressed antiglycation properties and retarded glucose diffusion *in vitro*. Besides, *A. theiformis* methanol leaves extract significantly ($p<0.05$) scavenged nitric oxide (IC_{50} 37.05 μg ml^{-1}), 2, 2-diphenyl-2-picrylhydrazyl (IC_{50} 64.42 μg ml^{-1}), and hypochlorous acid (IC_{50} 41.24 μg ml^{-1}) radicals compared to ascorbic acid (IC_{50} 77.65, 189.91 and 59.18 μg ml^{-1} for respective assays) [18].

The immunomodulatory and anti-inflammatory activities of *A. theiformis* collected in Comoros Island has been investigated. The authors reported that the phenolic rich fraction of *A. theiformis* exhibited immunosuppressive effect on lymphocyte, immunostimulant effect on monocytes and granulocytes at high doses, and anti-inflammatory-like effect *in vivo* [19]. The methanol bark extract reduced nitrite release from macrophages with an IC_{50} value of 19 μg ml^{-1} showing promising anti-inflammatory effects [20].

The solvent-free extract of *A. theiformis* aerial parts obtained from microwave extraction showed potent antiviral effect against ZIKV strains of Africa and Asia and clinical isolates of dengue virus. The extract acted directly on viral particles, preventing attachment to cell surface and entry in host cells [4]. Recently, a group of researchers indicated that *A. theiformis* displayed high anti-Chikungunya activity, justifying its use during the Chikungunya outbreaks in Reunion Island in 2006 [11]. *A. theiformis* methanol bark extract (IC_{50} 13.3 μg ml^{-1}) showed antiplasmodial activity against 3D7 chloroquine sensitive strain of *Plasmodium falciparum*, the most noxious *Plasmodium* species responsible for malaria in man [21]. The anti-microbial activity of *A. theiformis* methanol leaves extract against *Staphylococcus aureus, Salmonella enteritis, Pseudomonas aeruginosa, Enterobacter cloacae, Bacillus subtilis, Sclerotinia sclerotium*, and *Candida albicans* using the disc diffusion technique has also been reported [22]. The "anti-aging" and photo-protective properties of *A. theiformis* leaves of Madagascar have been attributed to the presence of xanthones, such as, mangiferin [10]. Mangiferin was reported to inhibit the activity of elastase (IC_{50} 139.64 μM) and collagenase (IC_{50} 253.57 μM), two enzymes targeted for the development of anti-aging agents [23]. As a consequence, pure extract of mangiferin (85-93% w/w) obtained from *A. theiformis* leaves of Madagascar has been developed for the cosmetic industry [14].

Cytotoxicity studies on human embryonic kidney cell line

HEK-293 using the iCELLigence system have showed that the crude methanol extract and active fractions (IC_{50} values > 20 µg ml^{-1}) of the leaves of *A. theiformis* exhibited negligible cytotoxic activity [17]. Besides, *A. theiformis* methanolic bark extract exhibited moderate cytotoxic activity against WI38 (IC_{50} 58.3 µg ml^{-1}), WS1 (IC_{50} 61 µg ml^{-1}) fibroblasts, and A-549 epithelial cells (IC_{50} 40 µg ml^{-1}) [20,21].

Conclusion

In an attempt to validate ethnopharmacological data, scientific evaluation is essential. Thus, this paper appraised the therapeutic potential of *A. theiformis* by providing an account of different studies undertaken to evaluate its biological activity. *A. theiformis* has proved to be a promising plant possessing potent biological activities such as anti-microbial, antioxidant, anti-diabetic, and immunomodulatory properties. Additionally, findings summarised here, highlight the therapeutic function of mangiferin, a phytochemical ubiquitously present in *A. theiformis* leaves, and substantiate the need for further focus on this lead molecule for the development of novel drugs. However, to further appraise the traditional use of *A. theiformis* further scientific *in vivo* evaluations are crucial.

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