

Exploring Knowledge about Different Pharmacological Activities of *Ficus Thoningii* Blume (Moraceae)

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Abstract: A phytochemical study of *Ficus thoningii* has led to the isolation of two previously unreported compounds, thoningiiflavanonol A and thoningiiflavanonol B together with 16 known compounds: shuterin, naringenin, syringic acid, p-hydroxybenzoic acid, genistein, 5,7,3',4',5'-pentahydroxyflavanone, luteolin, methylparaben, aromadendrin, garbanzol, dihydroquercetin, 5,7,3'-trihydroxyflavanone, β -sitosterol, sitosterolglucoside, lupeol acetate, and taraxerol. Their structures were elucidated on the basis of spectroscopic data. The new compounds and extracts displayed potent antioxidant activity. *Ficus thoningii* is an African ethnomedicine plant used to treat a number of diseases. The nutritional, phytochemical, and pharmacological aspects of *F. thoningii* in relation to its therapeutic purposes are numerous. *Ficus thoningii* contains alkaloids, terpenoids, flavonoids, tannins, active proteins, and active proteins. Continue to identify, isolate, and quantify the active ingredients, as well as their medicinal purposes. Chronic toxicity, toxicology, antineoplastic effects, acute toxicity, hypoglycemic effects, antidiarrheal effects, analgesic effects, anti-inflammatory effects, antioxidants, antifungal activity, antimicrobial effects, antiprotozoal properties etc..

Keywords: antioxidant activity; *Ficus thoningii*; Moraceae; thoningiiflavanonols A and B

I. INTRODUCTION

Plant-based remedies have proved to be useful in the treatment and management of diseases and are used Extensively in ethnomedical and ethnoveterinary practice. The prohibitive cost of conventional medicines and their limited Availability especially to rural communities in Africa and other developing regions have driven the continued dependence on Traditional therapeutics. About 75-90 % of the world population still relies on plants and plant extracts as a source of primary Health care (Benzie and Watchel-Galor, 2011). This widespread use of plant derived extracts in disease management has led To an interest in the identification and characterisation of the active compounds which give the extracts their therapeutic Potential. The common wild fig, *Ficus thoningii*, is one of the many fruit-bearing trees that have traditionally been used for Treating diseases in Africa and beyond. Despite its widespread use in



ethnomedicinal systems, *F. thonningii* is a well known Ornamental tree that is also used in improving agroforensic systems. Its leaves are used as fodder and its bark is used for Making bark cloth. Like many woody trees, *F. thonningii* is commonly used in homesteads for fencing, firewood and Construction (Orwa et al., 2009).

Phytochemical composition

F. thonningii contains various biologically active compounds that exhibit physiological effects which could be responsible for its curative potential in a broad range of disease conditions. These non-nutritive chemicals, commonly known as phytochemicals, are naturally produced by the tree as protection against biotic and abiotic stresses. Most researchers used standard qualitative methods for screening for phytochemicals in *F. thonningii*. Qualitative methods can only confirm the presence or absence of a class of compounds without quantifying the specific bioactive compound. Little has been done to isolate and quantify specific compounds found in *F. thonningii*. The main groups of phytochemicals isolated from *F. thonningii* are: alkaloids, terpenoids, flavonoids, tannins and essential oils.

Flavonoids: Flavonoids have been found in various plant parts of *F. thonningii* (Ndukwe et al., 2007; Usman et al., 2010; Greenham et al., 2007). Greenham et al (2007) used flavonoids as a biomarker for determining variation in *Ficus* species. Flavone-C-glycosides have been shown to be present in *F. thonningii* leaves and these were further identified as orientin, vitexin and isovitexin. Amongst the *Ficus* species used in this phylogenetic assessment, *F. thonningii* was the only species that contained stilbenes which were identified as resveratrol, resveratrol glucosides and stilbene glucosides. Stilbenes are a special type of flavonoid produced by plants in response to pathogens and other abiotic stresses such as UV radiation (Chong et al., 2009). Resveratrol and its glycosylated derivatives are derived from the phenylpropanoid pathway and have numerous implications in plant disease resistance and human health as they elicit biological and pharmacological activity (Vitrac et al., 2004).



Tannins: Using the vanillin assay, tannin concentrations in *F. thonningii* leaves have been estimated to be about 90 mg/100 g dry matter (Bamikole et al., 2004). The ferric chloride test and the tannic acid test have confirmed the presence of tannins in methanolic, n-butanolic and aqueous extracts of *F. thonningii* leaves (Ndukwe et al., 2007; Usman et al., 2009).

Alkaloids: Alkaloids are low molecular weight, nitrogen containing compounds that have remarkable physiological effects (Ramawat et al., 2009). This has led to their use as pharmaceuticals, stimulants and narcotics). *F. thonningii* contains alkaloids (Ndukwe et al., 2007, Ahur et al., 2010) but reports of specific alkaloids isolated from *F. thonningii* are scanty in literature.

Terpenoids: Triterpenes are derived biosynthetically from squalene (Hambone, 2008) and produce several pharmacologically active groups such as steroids, saponins and cardiac glycosides (Ramawat et al., 2009). Triterpenes isolated in *F. thonningii* stem bark extracts include saponins and anthraquinone glycosides (Ndukwe et al., 2007;

Usman et al., 2009). Saponin concentrations in *F. thonningii* leaves were shown to be as high as 300 mg/100 g dry matter (Bamikole et al., 2004).

The Moraceae family is a rich plant source of cardiac glycosides which are ubiquitous in the *Ficus* genus e.g. in *F. racemosa*, *F. religiosa* (Joseph and Raj, 2011); Poongothai et al., 2011. Cardiac glycosides are inhibitors of Na⁺/K⁺-ATPase and have been used in the treatment of heart failure and atrial arrhythmias (Prassas and Diamandis, 2008).

Essential oils: *F. thonningii* leaves contain essential oils composed mainly of 6, 10, 14 trimethyl-2-pentadecanone (18.8%), phytol (14.7%), acorenone (7.6%) and β -gurjunene (6.3%) (Ogunwande et al., 2008).

Other phytochemicals: Other phytochemicals with antinutritional properties present in *F. thonningii* include phytate (130 mg/100 g DM) and oxalate (230 mg/100 g DM) (Bamikole et al., 2004). Despite the presence of these antinutritional factors, the leaves of *F. thonningii* still possess high feed value evidenced by their high palatability and digestibility when used as fodder. *F. thonningii* leaves were shown to contain other secondary metabolites such as lignins, lignans, active carbohydrates and proteins which might also add to its remarkable pharmacological and biological activity (Ahur et al., 2010).

II. PHARMACOLOGICAL ACTIVITY

Antimicrobial effects

Antibiotics have proven very effective in the fight against infectious diseases. However, inappropriate use and abuse of antibiotics has led to the development of antibiotic-resistant, pathogenic microbial strains. As a result, there is a great interest in the search for alternative, plant-based medicines with antimicrobial activity. The antimicrobial activity of the *Ficus* genus is well documented (Kuetee et al., 2009; Kuetee et al., 2008; Mandal et al., 2000). The antimicrobial activity of plant medicines seems to depend on the efficacy of the extraction and the solvent used plays an important role (Cowan, 1999). In traditional medicine, palm wine is sometimes used in place of water in the preparation of remedies (Aibinu et al., 2007). Most of the antimicrobial bioactive compounds are aromatic or saturated organic compounds and hence can easily be extracted using ethanol or methanol. However, some compounds partition exclusively in particular solvents e.g. xanthoxylines, totarol, quassinoids, lactones and phenones will partition in methanol only, while polyacetylenes, sterols and propolis will partition in ethanol (Cowan, 1999). From their results on the antimicrobial properties of *F. thonningii*, Usman and colleagues (2009) reported that n-butanol and residual aqueous extracts had better antimicrobial activity than crude methanolic extracts.

Antiprotozoal properties

Traditional healers report the use of *F. thonningii* in the treatment for malaria (Chinsembu and Hedimbi 2010; Titanji, 2008). A study carried out to evaluate the antiplasmodial activity of *F. thonningii* against *Plasmodium falciparum* the protozoan parasite that causes malaria reported no significant antiplasmodial activity (Jansen et al., 2010). *F. thonningii* possibly just possesses good insect repellent properties and hence reduces the contact of the vector with humans, minimising incidence of malaria transmission (Jansen et al., 2010; Innocent, 2008). Amongst the compounds isolated in *F. thonningii* essential oils is the C-15 compound; 6, 10, 14 trimethyl-2-pentadecanone an aliphatic methyl ketone which has been reported to possess insect repellent properties. The repellent properties of 6, 10, 14 trimethyl-2-pentadecanone at a concentration of 10 % (w/v), were comparable to those of the commercial repellent, N, N diethyl-m-toluamide (DEET) (Innocent, 2008).

Using mice inoculated with *Trypanosoma brucei gambiense*, Youan et al. (1997) reported that *F. thonningii* possessed neither trypanocidal nor trypanostatic activities against the parasite. They reported a survival rate of 0 % in mice after three days of inoculation as compared to that of 100% for the controls melarsoprol and pentamidine both of which are commercial drugs used in the treatment of human African trypanosomiasis. However, *F. thonningii* was shown to exhibit high amoebicidal activity against *Entamoeba histolytica* at a concentration of 100 μ g/ml as compared to the control metronidazole, a commercial drug (Moundipa et al., 2005).

Antifungal activity

The traditional use of *F. thonningii* in the treatment of athlete's foot rot suggests that the presence of antifungal compounds. Oyelana et al., (2011) showed that leaf extracts of *F. thonningii* (25 and 50 mg/ml) had antifungal activity

against *Aspergillus niger*, *Aspergillus flavus*, *Botryodiplodia theobromae*, *Fusarium oxysporum*, *Fusarium solani*, *Penicillium chrysogenum*, *Penicillium oxalicum* and *Rhizopus stolonifer*. The extracts were also reported to show a significant arrest of mycelia growth. Another study carried out on *Ficus microcarpa* (synonym for *F. thonningii*, in South Asia), reported the presence of two antifungal chitinases from the latex of its aerial roots (Taira et al., 2005). These proteins, GLx Chi-C and Chi-B, exhibit strong antifungal activity by binding to fungal cell walls and hydrolysing the fungal cell wall component, chitin (Taira et al., 2005; Hou et al., 1998).

Anthelmintic properties

The proteolytic compound ficin in *Ficus thonningii* latex justifies its use as an anthelmintic agent. Ficin is a cysteine endopeptidase that is found in the latex of many *Ficus* spp and is known to digest living intestinal parasites (Etkin and Ross, 1982; Krief et al., 2005). This is in harmony with the reports that the tree is used as a vermifuge (Mali and Mehta, 2007)

Antioxidant

Flavonoids are good antioxidants which scavenge and reduce free radical formation (Grassi et al., 2010). The Cglucosylflavonoids (orientin, vitexin and isovitexin) isolated from *F. thonningii* possess antioxidant properties and have been identified in many medicinal plants such as the pigeon pea (*Trollius ledebouri* Reichb), linseed oil (*Linum usitatissimum*) and in rooibos tea (*Aspalathus linearis*) (Joubert and Ferreira, 1996; Von Gadow et al., 1997). Orientin possesses free radical scavenging activity based on its ene-diol functionality i.e. its dihydroxy substituents in the B ring and the double bond characteristic of the C-ring (Joubert and Ferreira, 1996). Vitexin and isovitexin have also been reported to possess antioxidant activities though to a lesser extent than orientin due to a missing OH on the C ring. In addition to flavonoid antioxidant activity, the stilbenes present in *F. thonningii* also exhibit antioxidant activity. Resveratrol and its methylated derivative, trans-3,3', 5,5'- tetrahydroxy-4-methoxystilbene, possess antioxidative effects against oxidative stress induced by reactive nitrogen species and reactive oxygen species (Olas et al., 2008; Olas et al., 2003). Resveratrol and its derivatives have also been shown to reduce peroxynitrite which is one of the most potent reactive nitrogen species (Olas et al., 2008). High levels of peroxynitrite are generated in inflammation based disease conditions (Ischropoulos and Al Mehdi, 1995). The anti-inflammatory properties of *F. thonningii* are probably a result of the action of these stilbenes and flavonoids. There is also a likelihood of synergistic interactions between the flavonoids and stilbenes that are present in *F. thonningii* (Wu et al., 2009). Owing to its antioxidant activities, *F. thonningii* has been shown to possess protective effects on the erythrocyte membrane from acetaminophen induced membrane peroxidation (Ahur et al., 2010). The antihaemolytic and haematinic potential is possibly due to its antagonistic activity against the depletion of glutathione and hence prevention of the generation of free radicals which result in oxidative stress (Ahur et al., 2010)

Analgesic effects

F. thonningii has been reported to possess analgesic properties that are comparable to aspirin in both peripheral and central induced pain. Using the acetic acid induced writhing reflex model in mice, Otimenyin (2004) demonstrated that methanolic extracts of *F. thonningii* (500 mg/kg) administered intraperitoneally had a percentage inhibition (79.7%) comparable to aspirin (80%) showing that *F. thonningii* has analgesic effects that can be useful in the management of peripherally induced pain. Otimenyin (2004) also reported the analgesic effects of the plant in central pain using the hot plate test method in mice.

Anti-inflammatory effects

The anti-inflammatory properties of *F. thonningii* have been validated using egg albumin and carageenan induced oedema in rats (Otimenyin, 2004; Coker et al., 2009). Phytol, the aliphatic diterpene found in *F. thonningii* has anti-inflammatory effects and has been reported as a potential therapeutic agent for the treatment of rheumatoid arthritis and possibly other chronic inflammatory diseases such as asthma (Ogunlesi et al., 2009). Unsaturated phytol exhibits antioxidant activity and is believed to be the side group that gives tocotrienols their higher antioxidant effects as compared to tocopherols (Yu et al., 2005).

Cardioprotective effects

Ficus thonningii possesses cardio-suppressant and hypotensive properties. Ethanolic stem bark extracts of *F. thonningii* were shown to exhibit positive chronotropic and inotropic effects on both electronically driven and spontaneously beating atrial muscle strips (Musabayane et al., 2007). This study also reported an attenuating effect of *F. thonningii* extracts (120 mg/kg b.w given for 5 weeks) on mean arterial pressures. The cardioprotective effects of *F. thonningii* could be credited to the presence of resveratrol. Resveratrol has been reported to prevent and slow the progression of various diseases which include cancer and cardiovascular diseases (Baur and Sinclair, 2006). It has also been shown to possess vasoprotective and reno-protective effects (Ramawat et al., 2009).

Hypoglycemic effects

Ethanolic extracts of *F. thonningii* have been shown to exhibit hypoglycaemic effects in rats (Bwititi and Musabayane, 1997). Oral glucose tolerance tests performed on diabetic and non diabetic rats treated with stem bark ethanolic extracts of *F. thonningii* showed a dose dependant hypoglycaemic effect comparable to that of metformin which was used as a positive control (Musabayane et al., 2007). These hypoglycemic effects validate the ethnomedicinal use of the plant extracts in the treatment of diabetes mellitus. The presence of phytol in *F. thonningii* could contribute to its hypoglycaemic effect. Phytanic acid, a compound produced from the metabolism of phytol is also reported to possess hypoglycaemic and hypolipidaemic effects as shown by Heim et al. (2002). In rats, phytanic acid increases the expression of glucose transporters and glucokinase and hence increases glucose uptake in the hepatocytes (Heim et al., 2002). *F. thonningii* extracts also contain the stilbene resveratrol which has been reported to exhibit hypoglycemic effects by enhancing glucose uptake by muscle cells and by activating hepatic AMPK (Minikawa et al., 2011)

Antineoplastic effects

We were not able to find any published report on the tumoricidal and antimutagenic properties of *F. thonningii*. However, other related species such as *Ficus hispida* (Linn) have been shown to exhibit antineoplastic activity against human breast cancer cell lines (Pratumvinit et al., 2009). Aqueous extracts of *Ficus carica* were shown to inhibit Ehrlich's ascite carcinoma, S180 sarcoma, Hep A hepatocarcinoma and Lewis lung carcinoma (Ma et al., 2002). There is thus need to investigate the potential antineoplastic effects of *F. thonningii* extracts.

Antidiarrheal effects

F. thonningii is extensively used for treating diarrhoea in both livestock and humans (Njoronge and Kubunga, 2009). The antimicrobial properties are usually the result of the anti-secretory, anti-inflammatory and antibacterial effects of tannins and astringent phenolics such as triterpenoids and saponins. Tannins and tannic acid reduce secretion by denaturing proteins of the intestinal mucosa forming protein tannates which make the mucosa more resistant to chemical alteration (Tripathi, 1994). Plants with anti-diarrhoeal properties also act by decreasing intestinal motility, stimulating water absorption and reducing electrolyte secretion (Njoronge and Bussman, 2006).

Toxicology

The scientific validation of potential acute and chronic toxic effects of plant medicines is crucial in light of their widespread use and the common misconception that green medicine is always safe.

Acute toxicity

An acute toxicity study was carried out by Anigu et al. (2008) to investigate the short term toxic effects of aqueous *F. thonningii* leaf extracts in adult Wistar rats. The LD50 of extracts administered orally was shown to be above 3000 mg/kg body weight. Animals showed 100% mortality after intraperitoneal administration of 600 mg/kg body weight of the same extracts and the LD50 intraperitoneally was reported to be 584 mg/kg. In another acute toxicity test, the median lethal dose of ethyl acetate leaf extracts of *Ficus thonningii* administered orally was shown to be above 5000 mg/kg body weight in adult Wistar rats (Ahur et al., 2010).

Sub-chronic / Chronic toxicity

Studies carried out to evaluate the sub-chronic and chronic effects demonstrate that *F. thonningii* is safe if used in low doses. Coker et al. (2009) reported no histopathological changes in the liver, kidney, spleen, ovary, uteri and lungs of adult female Wistar rats treated with methanolic extracts (200, 400 and 1000 mg/kg body weight) of *F. thonningii* leaves for 21 days. Oral administration of aqueous extracts (250 and 500 mg/kg body weight) for 15 days in adult Wistar rats resulted in no mortality, no haematological derangements and no clinical signs of toxicity observed within 72 hours after administration (Aniagu et al., 2008). Their histopathological findings however suggested possible testicular, hepatic and lung toxicities (Aniagu et al., 2008).

Cytotoxicity

The cytotoxicity of stem-bark ethanolic extract of *Ficus thonningii* on kidney cell lines was investigated by Musabayane et al. (2007). No toxicity was observed in both distal and proximal tubule cell lines after treatment with plant extracts (600-100 µg/ml). Distal tubule cells lines showed a dose dependent increase in metabolism and viability.

Conclusions and Perspectives

Ficus thonningii is extensively used by ethnomedical practitioners for treating various ailments. The pharmacodynamic basis supporting the use of *F. thonningii* extracts in ethnomedicinal systems has been established and pharmacological studies have demonstrated the anti-inflammatory, analgesic, antimicrobial, anthelmintic, antioxidant, cardioprotective, hypotensive and hypoglycaemic effects of the plant extracts. The remarkable therapeutic effects exhibited by *F. thonningii* are a result of the presence of an array of phytochemicals which include flavonoids, alkaloids, tannins, stilbenes, terpenoids and other active proteins. However, instead of merely screening for the presence or absence of broad phytochemical classes, researchers should seek to identify and quantify the specific compounds that are responsible for the physiological effects that *F. thonningii* exhibits. Further elucidation of the molecular mechanisms underlying the activity of these chemicals is also critical to evaluate the possibility of using the plant extracts for future drug development. Research could also shed light on the effect of *F. thonningii* on the nervous system, the endocrine system as well as its interaction with the immune system in fighting disease. More work can be done to characterise the nutritional and phytochemical composition of *F. thonningii* fruits and to evaluate their use as both a dietary and medicinal supplement.

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