

Traditional Uses and Pharmacological Potential of *Ficus exasperata* Vahl

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ABSTRACT

In traditional medicine, different parts of *Ficus exasperata* Vahl. (Moraceae) are used as analgesic, antiarthritic, diuretic, wound healing, antiparasitic, vermifuge, abortifacient, ecobolics and for treating hemorrhoids and venereal diseases. The plant parts are also used as animal fodder. The present review is aimed to comprehend the fragmented information available on the botany, traditional uses, pharmacology and toxicology of *F. exasperata* to explore its therapeutic potential and find potential research opportunities in the near future. Among different parts of *F. exasperata*, leaves are of particular importance from the traditional medicinal point of view. Major ethno-medicinal usage has been reported throughout Africa; Nigeria, Cameroon, Ivory Coast and Sierra Leone being the folkloric hubs. The extracts used are mostly remains uncharacterized and no detailed informations are available on the active components except for the class of compounds such as phenolics and tannins being major components. Crude extracts have been reported to exhibit a wide spectrum of *in vitro* and *in vivo* pharmacological activities like, antidiabetic, anticonvulsant, antiinflammatory, antimicrobial, hypolipidemic, antioxidant, antiulcer, anxiolytic and hypotensive. Conflicting results on the toxicity *F. exasperata* has also been reported. Experimental studies have validated a number of traditional claims, however reports suggests some degree toxicity involved. Additionally, not much scientific information is available on the bioactive compounds. Thus, an in-depth research on the standardization and characterization of the extracts and their toxicological evaluation is the need of the hour for its safe and better therapeutic utilization.


Introduction

Plants belonging to *Ficus* species are well known all over the world as “fig plants”.^[1] The genus *Ficus* belongs to the Mulberry family (Moraceae). It is an extremely aggressive genus both by its penetration throughout the globe, establishing new species where numerous and varied niches present themselves, and in the behavior of its trees in claiming their individual territories, most dramatically in the various “strangler” species that begin as an aerial epiphyte atop some other well-established host tree.^[2-4] The genus

Ficus comprises up of nearly 1000 species throughout tropical and warm temperate regions with greatest diversity in South East Asia, tropical South America and Australia. The genus *Ficus* is readily distinguished by the highly characteristic fruits and has often been recognized by the milky juice, the prominent stipule that leaves a scar on falling and the minute unisexual flowers often arranged on variously shaped receptacles.^[5-7] *Ficus* plants have vast traditional role in indigenous system of medicine like *Ayurveda*, *Siddha*, *Unani* and *Homoeopathy*. The bark, leaves, fruits and latex are considered to be very effective in diabetes, skin diseases, ulcers, dysentery, diarrhea, stomachache, hemorrhoids and as carminative, astringent, anti-inflammatory, anti-oxidant and anti-cancer agents.^[8]

Ficus exasperata Vahl. (Moraceae), popularly referred to as “Sandpaper leaf tree” owing to the rough surface of the leaves, is increasingly being used for a number of ailments and hence, studies validating the traditional claims are on the increase.^[9] Available reports indicate that leaves of *F. exasperata* exhibit anti-ulcer, hypotensive, hypoglycemic, hypolipidemic, anti inflammatory, anxiolytic, oxytocin inhibiting, anticonvulsant, antinociceptive, antipyretic, anti microbial, anti candidal, insecticidal and pesticidal activities.^[10-19] However, recent toxicity studies in rats involving crude aqueous and ethanol extract of the leaves have indicated potential hepatic and renal toxicity as reflected by significantly increased

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serum transaminases and bilirubin. The biochemical findings were substantiated by the histopathological studies which indicated that high doses of the ethanol leaf extract could lead to toxic injury in the kidneys which might interfere with renal tubular function and induce renal failure.^[20,21] The present review is aimed to provide a comprehensive account of its traditional uses, pharmacological activity and toxicity in view of the many recent findings on this plant. This review serves as a collective reference for the researchers to take-up intensive toxicological evaluation and characterization of the toxicants present in *F. exasperata* extracts for its optimum therapeutic utilization.

Botanical description, habitat and distribution

F. exasperata is a terrestrial afro-tropical shrub or small tree with scabrous, with ovate leaves that grows up to about 20m tall and prefers evergreen and secondary forest habitats [Figure 1].^[6,7] In India, it is commonly known as Brahma's banyan, rough banyan and sandpaper fig. Leaves (3-20 × 2-12cm) are distichous, alternate, ovate to elliptic, subcoriaceous to coriaceous, apex shortly acuminate, base acute to obtuse, upper surface scabrous having a very rough surface, making them look like sand paper and thus the name, sandpaper tree. Lateral veins; 3-5 pairs, basal pair branched reaching margin at or above middle of the lamina. Petiole; 0.5-4cm long and stipules are 0.2-0.5m long, strigose, caducous. Figs are found either solitary or in pairs in the leaf axils and rarely on older wood. Fresh figs are subglobose, 1-2.5cm, hispidulous, peduncle; 0.5-1m long, basal bracts; 1mm long, scattered on the peduncle.^[7] It bears figs, which usually appear in pairs in the leaf axils. The bark is smooth, grayish cream with brown streaks and it exudes gummy sap. The plant usually grows well in evergreen forests and forest margins, also in secondary forest and riverine vegetation, often as a strangler, sometimes persisting in cleared places at the altitude of 0-2000 meters from sea level. It is widespread in tropical Africa, from Mozambique, Zambia, and northern Angola to Senegal and Ethiopia and also in the southern part of the Arabian Peninsula and India.^[22-26]

Synonyms

Ficus asperima Roxb., *Ficus punctifera* Warb., *Ficus scabra* Willd., *Ficus silicea* Sim.^[22,23,27]

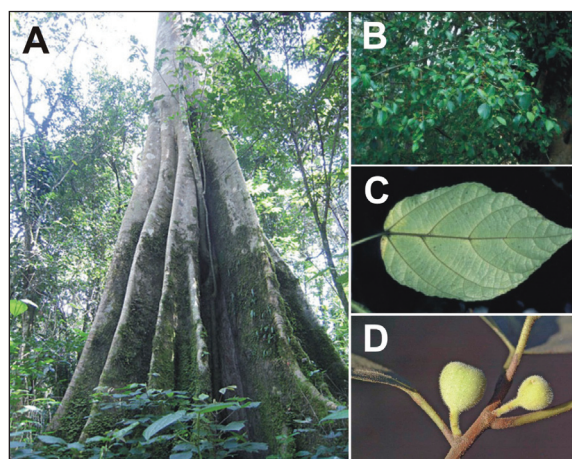


Figure 1: (A) *Ficus exasperata* tree trunk, (B) Foliage, (C) Leaf, (D) Fruits

Common names

English: Sandpaper fig tree, white fig tree, French: Papier de verre, Swahili: Msasa, Banyun (Senegal): Ki ink, sies, sives, Bedik (Senegal): Ga-ny` e, Crioulo (Senegal): Karda, Diola (Senegal): Bu pundun, busas, busasa, buves, buyaya, husas, nina. Sanskrit: Kharapatra.^[25,27]

Taxonomy of *Ficus exasperata* Vahl

Kingdom	Plantae
subkingdom	<i>Viridaeplantae</i>
Phylum	<i>Tracheophyta</i>
Subphylum	<i>Euphyllophytina</i>
Infraphylum	<i>Radiatopses</i>
Class	<i>Magnoliopsida</i>
Subclass	<i>Dilleniidae</i>
Superorder	<i>Urticanae</i>
Order	<i>Urticales</i>
Family	<i>Moraceae</i>
Tribe	<i>Ficeae</i>
Genus	<i>Ficus</i>
Specific epithet	<i>exasperata</i> – Vahl.
Botanical name	<i>Ficus exasperata</i> Vahl.

Traditional uses and phytochemistry

Traditionally, different parts of the *F. exasperata* are used for the following household, industrial and medicinal purposes. The leaves covered with small thorns are used to polish wooden slates and furniture.^[28] The scabrous surface of the leaves also makes it use for scrubbing utensils among the rural population in certain parts of Africa.^[29] Animal keepers use the leaves as a good source of feed. It is fed to goats, sheep,^[30] and chimpanzees.^[31] The leaves are also used in the stabilization of palm oil to potentially enhance keeping qualities through the elimination of saponins and the foaming tendency and enhancement of carotenoid levels in the oils, thereby resulting in reduced free fatty acids, acid value and peroxide value.^[32]

Chimpanzees have been reported to feed on *Ficus exasperata* leaves slowly, singly and without mastication which is suspected because of this peculiar feeding behavior.^[33] This behavior is similar to that of chimpanzee feeding on *A. mossambicensis*.^[34] Koshimizu *et al.*, opinioned that, medicinal plants that are used by nonhuman primates are valuable targets in the search for naturally occurring compounds of biological or physiological significance.^[35]

In African traditional medicine, different parts of this plant (fruit, leaf, sap, bark, and root) are considered medicinally important. In Africa, Yemen and India, various parts of the plant are used as analgesic, antiarthritic, diuretic, vermifuges, febrifuge, abortifacient, ecboic, wound healing, animal fodder and also in general debility, malnutrition, parasitic infection (cutaneous, subcutaneous), leprosy, ophthalmic and oral infections, nasopharyngeal afflictions, arthritis, rheumatism, gout, edema, kidney disorders, diarrhea, dysentery, hemorrhoids and venereal diseases.^[9,22,25]

The leaves of *F. exasperata* are much valued in the treatment of a variety of diseases/disorders. In French Guinea, a decoction of the leaves is used for stomach disorders.^[36] The leaves are used for treatment of hemostatic ophthalmia, coughs, hemorrhoids anxiety disorders, epilepsy, high blood pressure, rheumatism, arthritis, cancer, intestinal pains, colics, bleeding and wounds.^[37-39] In Nigeria, Republic of Congo and Central African Republic the leaves are used as an antipyretic.^[40-43] The leaves are macerated in water and the

decoction is administered orally. The leaves are particularly valued in the treatment of malaria in Cameroonian folk medicine.^[44] In some parts of Cameroon, leaves are used in the treatment of hemorrhoids^[45] and the water extract of the leaves is administered orally in diarrhea.^[46] One glass of extract made by macerating one handful of contused leaves in 1/lof water is given for 4 days in diarrhea.^[46] In Nigeria, the young leaves are prescribed as a common anti-ulcer remedy. Few leaves that are chewed and swallowed three times for 4-8 weeks are believed to produce a complete cure of ulcer.^[10] Dried leaves as such and the infusion are used to treat ulcers and stomachache.^[47,48] A paste made of 50 leaves of *F. exasperata*, 50 leaves of *E. coccinea* and 10 fruits of *Capsicum frutescens* is added to 1/lof water, homogenized and filtered. 150 ml filtrate is given twice daily as a remedy for peptic ulcers.^[49]

In Ivory Coast, the leaves mixed with palm oil used for the management of cardiac arrhythmias. Leaves combined with lemon juice are used for treatment of respiratory tract infections such as asthma, bronchitis, tuberculosis and emphysema.^[9] The viscid non-milky sap is used for the treatment of hemostatic ophthalmia and stomachache. Fresh leaves are used as hemostatic externally^[50] and a polyherbal remedy containing the leaves are used for insomnia.^[51]

In Sierra Leone, dried leaf powder is used to treat vaginal rash and the infusion is taken orally as an abortifacient.^[52] Water extract of the dried leaves is taken orally and also rubbed on the abdomen to stimulate contractions during child birth.^[4] Dried leaf is used for external application in a drug mixture for eruptive skin disease.^[52] In Gambia, the leaves are boiled in water and the steam is inhaled in cases of chest pain.^[53] In Ghana, the sap is used to arrest bleeding. Irene and Iheanachoreported the traditional use of the plant in hastening the expulsion of placenta in cows after calf delivery and its use by traditional birth attendants in hastening childbirth.^[54] The roots are also used to manage asthma, dyspnea and venereal diseases.^[55] In Tanzania, a decoction made from dried root bark is given orally to treat asthma; fresh leaf is rubbed for the inflammation of throat and tonsillitis, and also used to treat common eye problems. Fresh leaves are also used as anthelmintic. Dried flowers are eaten to relieve throat pain and also valued as ascaricide.^[56] *F. exasperata* root paste alone and the bark crushed with the root of *Croton roxburghii* in coconut milk are applied externally to treat eczema.^[57]

Although a number of pharmacological activities are attributed to various extracts of different parts of *F. exasperata*, no information is available on the active components. However, the leaves, stem bark and roots are reported to contain steroids, flavonoids, phlobatannins, tannins and saponins.^[11,58] Ogunleye *et al.*,^[59] reported the presence of saponins, alkaloids, tannins flavonoids and cardiac glycosides in the aqueous of leaf extract. Dongfack *et al.*,^[60] isolated a new unnamed acylglucosylsterol; unusual fatty acid from the leaves. Among various species of genus *Ficus* having wide traditional usage, *F. exasperata* is perhaps the least explored plant with reference to the phytochemical composition. In view of this, it is very essential to characterize various extracts of *F. exasperata* for its optimum therapeutic utilization. Thus, potential exists to carryout in-depth research on the phytochemical composition of *F. exasperata*.

Pharmacological properties

Among different parts of *F. exasperata*, leaves have received much attention from the researchers across the world and have been widely studied for various pharmacological activities such as anti-diabetic, hypotensive, antioxidant, anti-inflammatory, antiarthritic,

antinociceptive, anticonvulsant, anxiolytic, antiulcer, antipyretic, uterotonic and antimicrobial activities. Furthermore, good amount of research has also gone into the toxicological evaluation of its extracts. The following section provides a comprehensive detail on the pharmacological effects of various extracts of *F. exasperata*. The findings of different pharmacological studies are summarized in Table 1.

Antidiabetic/hypoglycemic and hypolipidemic

Despite the efficacy of synthetic drugs in the management of diabetes mellitus, the search for improved and safe anti-diabetic agents from natural sources has increased. The plant kingdom offers a wide field to look for oral hypoglycemic compounds. World Health Organization (WHO) lists more than 400 species to possess hypoglycemic effects.^[61] However, only few of them have been investigated and scientifically validated.^[62-66]

Taiwo *et al.*,^[6] evaluated the effect of aqueous extract of *F. exasperata* leaves on glucose metabolism in fructose induced glucose intolerant rats. Oral glucose tolerance profile of the fructose-fed animals treated with the plant extract was similar to that of the normal control, but the postprandial blood glucose was lower in normal control indicating improved glucose tolerance as assessed by glucose tolerance index. Authors inferred that *F. exasperata* leaf extract ameliorates glucose intolerance induced by fructose feeding in rats and suggested that the extracts might stimulate insulin secretion by the pancreas or/and enhance insulin sensitivity in various organs especially the muscle and the liver in a manner similar to sulfonylureas. Since, glucose and the plant extract were administered simultaneously, the extract might have adsorbed some glucose, inhibited the carbohydrate hydrolyzing enzymes viz., α -amylase, α -glucosidase, sucrase and delayed its diffusion across the intestinal lumen into the blood stream resulting in decreased circulating blood glucose.^[67] However, there is a need for further research to fully elucidate the mechanism of action and it would be very useful if the extract exhibits complementary mechanisms of action with least adverse effects.

Adewole *et al.*,^[12] evaluated the hypoglycemic potential of *F. exasperata* leaf extract in streptozotocin-induced diabetic rats (spontaneously-hypertensive and obese Zucker rats). 4 weeks of treatment with the extract (100mg kg⁻¹) significantly decreased hyperglycemia, polyurea, and hyperlipidemia and enhanced serum insulin levels. Authors concluded that *F. exasperata* leaf extract possesses hypoglycemic and hypolipidemic properties supporting its folkloric, ethnomedical use in the management of diabetes among people of Western Nigeria. However, data on histopathology of the pancreas would be crucial to know whether the extract helps in regeneration of the pancreatic islets or stimulate insulin secretion by the residual β -cells. In another study, oral administration of *F. exasperata* leaf extract (aqueous) caused significant reductions in plasma total triacylglycerol, cholesterol and β -hydroxybutyrate concentrations in alloxan-induced diabetic rats. Authors concluded that the extract is useful in lowering blood lipids in experimental diabetes.^[21] In an acute study, oral administered of aqueous extract of *F. exasperata* leaves at a dose of 2gkg⁻¹ reduced blood glucose by 68% in alloxaninduced diabetic rats at the end of 150 min duration.^[59]

Hypotensive

Hypertension is a major risk factor for the development of coronary heart disease, peripheral vascular disease, congestive heart

Table 1: Pharmacological activity of *Ficus exasperata* Vahl

Activity studied	Parts used	Extract	Dose	Observation	Reference
Antiarthritic	Leaves	Hydroethanol (30:70v/v)	30-300mg kg ⁻¹ , p.o.	Dose dependent reduction of the arthritic edema in the ipsilateral paw, suppressed the pathological changes in bone and inhibited the radiological index	[69]
Antibacterial/antimicrobial	Leaves	Methanol	–	Inhibited <i>P. aeruginosa</i> , <i>S. typhi</i> , <i>S. aureus</i> , and <i>E. coli</i> with MIC values of 75.0, 1.0, 5 and 1.25mg mL ⁻¹	[58]
	Stem bark	Methanol	–	Inhibited the growth of <i>P. aeruginosa</i> and <i>S. Typhi</i> with MIC values of 75 and 1.25mg mL ⁻¹	[58]
	Root	Methanol	–	Inhibited the growth of <i>P. aeruginosa</i> , <i>S. typhi</i> , <i>S. aureus</i> , <i>E. coli</i> and <i>Vibrio cholerae</i> with MIC values of 50, 5.0, 1.5, 1.25 and 1.25mg mL ⁻¹ , respectively.	[58]
	Leaves	Ethanol	–	Moderate antimicrobial activity against <i>E. coli</i> and <i>S. albus</i> with MIC values of 300 and 700mg mL ⁻¹ , respectively	[18]
	Root bark	Essential oil	–	Significant inhibition of <i>C. albicans</i> with minimum inhibition concentration (MIC) of 1.1µg mL ⁻¹ compared to amphotericin B having MIC value of 0.39µg mL ⁻¹	[1]
Anticonvulsant	Leaves	Hydroethanol (30:70v/v)	30-300mg kg ⁻¹ , p.o.	Delayed onset and decreased duration of pentylenetetrazole- and picrotoxin-induced convulsions. Decreased duration of maximal electroshock-induced tonic hind limb extension of mice.	[15]
Anti-inflammatory	Leaves	Hydroethanol (30:70v/v)	30-300g kg ⁻¹ , p.o.	Dose dependent anti-inflammatory activity against carrageenan-induced foot edema in chicks (IC ₅₀ 46.05 mg kg ⁻¹)	[13]
Antinociceptive	Leaves	Hydroethanol (30:70v/v)	30-300mg kg ⁻¹ , p.o.	Significant anti-nociceptive activity against formalin-induced nociception in mice	[13]
Antioxidant	Leaves	Hydroethanol (30:70v/v)	–	Dose dependent DPPH radical scavenging activity, lipidperoxidation inhibition in brain homogenates and significant reducing capacity	[69]
Antipyretic	Leaves	Hydroethanol (30:70v/v)	30-300g kg ⁻¹ , p.o.	Weak antipyretic activity against yeast-induced pyrexia in rats	[13]
Antiulcer	Leaves	Aqueous	200-800mg kg ⁻¹ , p.o.	Dose dependent antiulcerogenic activity against aspirin-induced ulcerogenesis in rats. Delayed intestinal transit, increased pH, and decreased the volume and acidity of gastric juice.	[10,48]
Anxiolytic	Leaves	Hydroethanol (30:70v/v)	30-300mg kg ⁻¹ , p.o.	Dose dependent anxiolytic activity similar to diazepam in open field, the elevated plus-maze, and the hole-board test models.	[14]
Hypoglycemic	Leaves	Aqueous	100mg kg ⁻¹ , p.o.	Significant reduction in blood glucose and serum lipids in streptozotocin-induced diabetic rats	[12]
	Leaves	Aqueous	250mg kg ⁻¹ , p.o.	Improved glucose tolerance in fructose-induced glucose intolerance in rats	[16]
	Leaves	Aqueous	2g kg ⁻¹ , p.o.	Decreased blood glucose by 68% in alloxan-induced diabetic rats	[59]
Hypolipidemic	Leaves	Aqueous	–	Decreased plasma total triacylglycerol, cholesterol and b-hydroxybutyrate levels in alloxan-induced diabetic rats	[21]
Hypotensive	Leaves	Aqueous	10-30mg kg ⁻¹ , p.o.	Significant reduction in mean arterial blood pressure	[11]
	Leaves	Aqueous	100mg kg ⁻¹ , p.o.	Normalization of microanatomy of the blood vessels and significant reduction in blood pressure	[12]
Insecticidal	Leaves	Powder	–	Resulted in significant dose dependent mortality of <i>Callosobruchus maculatus</i> and <i>Sitophilus zeamais</i> over 72h	[19]
Oxytocin inhibiting	Leaves	Aqueous	0.5-1 × 10 ⁻² mg mL ⁻¹	Significant inhibition of oxytocin-induced uterine contractions <i>in vitro</i>	[17]
Toxicity	Leaves	Ethanol	50-500mg kg ⁻¹ , p.o.	Dose dependent increase in body weight, relative kidney weight, serum urea and sodium suggesting kidney damage	[54]
	Leaves	Aqueous	2.5-20g kg ⁻¹ , p.o.	No changes in behavior, body weight and temperature was found in single dose study, while daily dosing for 14 days induced pyrexia, decreased red blood cell count, hemoglobin and hematocrit values. An LD ₅₀ value of 540mg kg ⁻¹ i.p. was deduced.	[9]
	Leaves	Ethanol	50-150mg kg ⁻¹ , p.o.	Significantly increased Aspartate aminotransferase (AST), alkaline phosphatase (ALP), alanine transaminase (ALT) and total bilirubin in rats. Histology of liver and kidney cortex revealed several damages, especially in the kidney cortex.	[95]
	Leaves	Hydroethanol (20:80v/v)	–	No toxic effect was observed in brine shrimp lethality, inhibition of telomerase activity, and induction of chromosomal aberrations <i>in vivo</i> in rat lymphocytes	[95]

failure, stroke and renal failure^[68] and it is one of the major causes of sudden death. Despite considerable progress in the management of hypertension by conventional drugs, use of herbal remedies to reduce high blood pressure is common among rural populations.

Ayinde *et al.*,^[11] studied the hypotensive effect of *F. exasperata* leaf aqueous extract in rabbits at doses of 10, 20 and 30mg kg⁻¹. The findings indicated that the extract possesses dose dependent hypotensive effect in normal rabbits. However, administration of

either atropine or chlorpheniramine (2.5mg) significantly reduced the hypotensive activity of the extract suggesting probable stimulation of muscarinic receptors in the heart or release of histamine into the circulatory system thereby causing the initial fall in blood pressure as the possible mechanism of hypotensive action of the extract. The maximum reduction in mean arterial blood pressure recorded was 38.3mm Hg at the dose of 30mg kg⁻¹.

Adewole *et al.*,^[12] evaluated the hypotensive potential of *F. exasperata* leaf extract in streptozotocin-induced diabetic rats (spontaneously-hypertensive and obese Zucker rats). Oral administration of the extract (100mg kg⁻¹) for 4 weeks significantly reduced blood pressure and restored the microanatomy of the blood vessels to almost normal levels. Histopathological examination of the aortic blood vessels showed extensive collagen fiber formation as well as perivascular fibrosis; these changes were significantly reversed towards normalization by the extract suggesting the usefulness of *F. exasperata* in hypertension. Considering the above results, it is felt that scope exists to evaluate the angiotensin converting enzyme inhibitory activity of the extract to elucidate the possible mechanism of action.

Antioxidant

Hydro-ethanol extract (30:70v/v) of *F. exasperata* leaves showed significant dose dependent DPPH radical scavenging activity comparable to that of n-propyl gallate with an IC₅₀ value of 0.499g mL⁻¹. Further, the extract also exhibited significant dose dependent inhibition of lipid peroxidation in rat brain homogenates *in vitro* as reflected by significantly lower thiobarbituric acid-reactive substances with an IC₅₀ value of 1.283g mL⁻¹. The extract also showed significant reducing capacity in potassium ferricyanide system.^[69]

Fresh leaves of *F. exasperata* are regularly included during the milling or pounding stage by the natives of Nigeria to improve the quality and stability of palm oil which could be attributed to its antioxidant potential. Umerie *et al.*,^[32] evaluated the beneficial effects of the leaves on oils obtained from the ripe fruits of *Elaeis Guineensis* and *Elaeis Guineensis* Var *Virescens*, in the traditional processing procedures; cooking and soaking the fruits in water. Saponification, acid and peroxide values and free fatty acid contents were determined to assess the quality of oils. Results indicated that, both the oils contained appreciable amounts of carotenoids, flavonoids and sterols, but only the *Elaeis Guineensis* Var *Virescens* contained saponins. The use of the *Ficus* leaves increased the carotenoid levels in both the oils, while in *varvirescens* oil it eliminated saponins and foaming tendencies but reduced the sterol levels. Oils processed by soaking of fruits and use of the *Ficus* leaves had slightly greater saponification values, while oils processed by cooking of fruit and use of leaves had reduced free fatty acids (FFA), acid and peroxide values. Authors concluded that the use of *F. exasperata* leaves results in better stabilized oil with potentially good keeping qualities.^[32]

Antiinflammatory

Inflammation is a disorder involving localized increases in the number of leukocytes and a variety of complex mediator molecules and prostaglandins are ubiquitous substances that indicate and modulate cell and tissue responses involved in inflammation.^[70] The inflammatory response has received great deal of interest in the field of medical research as well as plants based drug discovery, which continues to provide new and important leads against

various pharmacological targets including pain and inflammation.^[71] Since, different parts of *F. exasperata* are used in African traditional medicine for inflammatory conditions, the anti-inflammatory properties of hydroethanol extract (30:70v/v) of *F. exasperata* leaves against carrageenan-induced foot edema in 7 day old chicks were investigated.^[13] The extract (10-300mg kg⁻¹ p.o.) showed significant, dose dependent anti-inflammatory as reflected by reduction of foot volume induced carrageenan. The extract also significantly decreased carrageenan-induced edema with an IC₅₀ of 46mg kg⁻¹, thus validating the folklore usage of *F. exasperata* as an anti-inflammatory agent. Although, the study clearly demonstrates the anti-inflammatory potential of *F. exasperata* extract, studies involving its effect of cyclooxygenases, lipooxygenases and phospholipases are needed for better management of pain and inflammation.

Antiarthritic

Rheumatoid arthritis (RA) is an autoimmune, chronic inflammatory disorder characterized by swollen joints, synovial inflammation and joint destruction resulting in severe pain, swelling, stiffness and loss of function in the joints.^[72-74] Adjuvant-induced arthritis is an experimental rat model characterized by chronic, polyarticular, erosive type of arthritis that shares some features with human rheumatoid arthritis.^[75,76] Abotsi *et al.*,^[69] evaluated the antiarthritic activity of hydroethanol extract (30:70v/v) of *F. exasperata* leaves against Freund's adjuvant-induced arthritis in rats. Oral administration of the extract (30-300g kg-1) for 29 days showed significant dose dependent reduction of the arthritic edema in the ipsilateral paw of rats to an extent of 34% and also significantly prevented the spread of the edema from the ipsilateral to the contralateral paws indicating inhibition of systemic spread. The extract also suppressed the pathological changes in bone and inhibited the radiological index by 95%, compared to untreated rats indicating the antiarthritic potential of the extract.

Antinociceptive

The formalin test is one of the most widely used methods for the rapid and easy screening of pharmacological targets in drug evaluation.^[77,78] Intraplantar injections of formalin evoke a characteristic biphasic licking response. In the early phase (0-10in post formalin injection) formalin directly stimulates nociceptors that corresponds to acute neurogenic pain which is sensitive to central analgesics.^[79] The late phase involves inflammatory components with the release of different pain mediating substances sensitive to nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids as well as analgesics with central effects.^[80-82] Oral administration of hydroethanol leaf extract at doses of 30, 100 and 300mg kg⁻¹, 30min before the injection of formalin showed significant and dose dependent inhibition of formalin-induced paw licking and biting by 15-66% and 52-77%, respectively in the early and late phases.^[13]

Anticonvulsant

Epilepsy is a neurological disorder characterized by unpredictable and periodic occurrence of a transient alteration of behavior due to the disordered, synchronous and rhythmic firing of populations of brain neurons.^[83] The conventional antiepileptic agents like phenytoin, carbamazepine and sodium valproate have several

serious side effects notably neurotoxicity.^[84] Thus, researchers have turned their attention on exploration of natural products for novel and efficacious antiepileptic compounds that not only to abolish the occurrence of seizures but also helps to lead a self-sustained life. Woode *et al.*,^[15] evaluated the anticonvulsant effect of hydroethanol extract (30:70v/v) of *F. exasperata* leaves against seizures induced by pentylenetetrazole, picrotoxin or maximal electroshock in mice. The extract (30-300g kg⁻¹, p.o.) significantly delayed the onset and decreased the duration of pentylenetetrazole and picrotoxin-induced convulsions and also reduced the duration of maximal electroshock-induced tonic hind limb extension. In rotarod experiment, the extract significantly decreased the time spent on the rotating rod. The authors concluded that, *F. exasperata* extract possesses significant anticonvulsant activity in mice and thus validating its use as an antiepileptic agent in African traditional medicine.

Anxiolytic

Anxiety affects nearly one-eighth of the world population and benzodiazepines, a major class of compounds used for its treatment presents a narrow margin of safety between the anxiolytic effect and unwanted side effects has prompted research into natural products having less undesirable effects.^[85,86] The anxiolytic activity of hydroethanol extract (30:70v/v) of *F. exasperata* leaves was assessed at doses of 30, 100 & 300g kg⁻¹ (p.o.) in 3 animal models of anxiety; open field test, elevated plus-maze and hole board test in mice. The extract exhibited significant dose dependent anxiolytic activity similar to diazepam in all the anxiety models. In open filed test, number of center entries, percentage number of center entries, center time and percentage center time were increased. Similarly, the frequency and duration of open arm exploration in the elevated plus-maze was increased tract treatment. In hole-board paradigm, the frequency and duration of head-dips were increased without any significant changes in locomotor activity at all doses tested.^[14]

Antiulcer

Peptic ulcer occurs due to an imbalance between aggressive (acid-pepsin) and defense (mucus) factors.^[48] Since, young leaves of *F. exasperata* are prescribed as a common anti-ulcer remedy in Nigeria, the anti-ulcer activity of aqueous extract of the leaves (200, 400 & 800mg kg⁻¹) was evaluated against aspirin-induced ulcer in Wistar rats.^[48] The extract showed a significant, dose dependent decrease in ulcer index and delayed the small intestinal transit in mice, an effect considered beneficial in ulcer patients. Intestinal transit time was inhibited by The reduction in the charcoal meal transit was dose dependent and a maximum inhibition of 81% was observed at the dose of 400mg kg⁻¹, thus significantly delaying the gastric emptying. The extract also increased the pH and reduced the volume and total acidity of the gastric secretion.

Antipyretic

Pyrexia refers to elevated body temperature which may be a result of infection, inflammation or other disease states and antipyretic are drugs, which reduce the elevated body temperature.^[87] A number of medicinal plants are considered valuable antipyretics in folk medicine.^[88] Yeast-induced pyrexia commonly known as pathogenic fever is widely used laboratory model to study the antipyretic

effects of drugs and the medicinal plants.^[89] Woode *et al.*,^[13] reported that, oral administration of hydroethanol leaf extract at doses of 100 and 300mg kg⁻¹ produced slight antipyretic effect between 5th and 7thh after intraperitoneal injection of yeast, after which temperature raised gradually. The authors concluded that the extract possesses weak antipyretic activity at doses of 100 and 300mg kg⁻¹. However, Bafor *et al.*,^[43,44] evaluated the effects of hexane, ethylacetate, and aqueous extracts of *F. exasperata* leaves on normal body temperature and yeast-induced pyrexia in mice as traditional African healers extensively use the leaves for fevers particularly malarial fever. The results indicated that, all the extracts possess time dependent antipyretic activity with reasonable onset and duration of action against yeast-induced pyrexia in mice, however hexane and aqueous extracts were found to be more potent. It was also noted that, the extracts did not have any significant effect on normal body temperature. The study thus provided experimental evidence justifying its use by traditional healers and the natives for febrile conditions.

Uterotonic

There have been contradictory usages of *F. exasperata* leaves with respect its effect on uterus. Some herbal practitioners use them for relaxing the uterus,^[90] while others use them for enhancing uterine contractions.^[91] Considering this observation, Bafor and co-workers extensively studied the effects of various concentrations of aqueous leaf extract of *Ficus exasperata* on uterine contractions *in vitro*.^[17,92,93] Aqueous leaf extract of *F. exasperata* at the dose of 1.0×10^{-2} mg mL⁻¹ inhibited oxytocin-induced uterine contractions without significantly affecting acetylcholine or ergometrine-induced uterine contractions in isolated rat uterus. The results also indicated that the extract had no significant effect on the amplitude and frequency of spontaneous contractions.^[17] In another study, the extract at doses of 2.5×10^{-2} - 100×10^{-2} mg mL⁻¹ directly stimulated uterine contractions and significantly increased the frequency but not the amplitude of spontaneous contractions similar to that of acetylcholine. The authors opinioned that, as the extract stimulate uterine contractility at higher doses, it might be helpful in easing childbirth.^[92] In order to determine the mechanism of action, the contractile effect of extract (5×10^{-2} - 100×10^{-2} mg mL⁻¹) and oxytocin were examined in the presence of atropine, indomethacin, verapamil, phentolamine and diphenhydramine. The results indicated no significant difference in the EC₅₀ and E_{max} of the extract in the presence of atropine, verapamil and indomethacin. However, diphenhydramine and phentolamine significantly inhibited the extract suggesting stimulation of uterine contractility by the extract might be due to the activation of histamine H1- and/or α -adrenergic receptors, interference with calcium channels and/or stimulation of prostaglandin synthesis in utero.^[93]

Antimicrobial

The ethanol extract of *F. exasperata* leaves showed moderate anti-bacterial activity against *Escherichia coli* and *Staphylococcus albus* with minimum inhibitory concentrations (MIC) of 300 and 700mg mL⁻¹, respectively, while that of *S. albus* 700mg mL⁻¹. However, the crudeplant extract in combination with the protein synthesis inhibitors exhibited significant antibacterial activity.^[18] The methanol leaf extract inhibited the growth of *P. aeruginosa*, *S. typhi*, *S. aureus*, and *E. coli* with MIC values of 75.0, 1.0, 5 and 1.25mg mL⁻¹,

respectively. The stem bark methanol extract inhibited the growth of *P. aeruginosa* and *S. Typhi* with MIC values of 75 and 1.25g mL⁻¹, respectively. Similarly, the methanol extract of the root inhibited the growth of *P. aeruginosa*, *S. typhi*, *S. aureus*, *E. coli* and *Vibrio cholerae* with MIC values of 50, 5.0, 1.5, 1.25 and 1.25mg mL⁻¹, respectively. Authors stated that, *F. exasperata* leaf, stem bark and root contains bioactive substances with the highest inhibitory activities against some human pathogenic organisms.^[58] In another study, the volatile oil from the root of *F. exasperata* exhibited a significant zone of inhibition against *Candida albicans*. The (MIC) was found to be 1.1µg mL⁻¹ in yeast nitrogen broth compared to the current drug of choice amphotericin B (0.39g mL⁻¹). Authors inferred that *F. exasperata* volatile oil could be a promising lead for new antifungal drug especially as a potent vehicle in antifungal drug design.^[11]

Toxicity studies

Several toxicity studies have been conducted on various extracts of *F. exasperata* leaves. Few have shown potential toxic effects, while others have rendered the extracts to be relatively safe. A summary of the toxicity studies is presented here.

Oral administration of the ethanol leaf extract (50, 100 and 150mg kg⁻¹) for 8 weeks significantly increased the levels of aspartate aminotransferase (AST), alkaline phosphatase (ALP), alanine transaminase (ALT), total bilirubin and conjugated bilirubin in Wistar rats. The histological architecture of the liver and kidney cortex revealed several damages, especially in the kidney cortex. Authors indicated that the explicit use of *F. exasperata* leaf extract in herbal medicine might be dangerous to health.^[94] Similarly, oral administration of the ethanol extract (50, 200 and 500mg kg⁻¹) significantly increased body weights, mean relative kidney weights, serum urea and sodium concentrations in a dose dependent manner in albino rats suggesting that higher doses of the extract could affect kidney function.^[95]

In an acute toxicity study, oral administration of single dose of the aqueous leaf extract (2.5, 5, 10, and 20g kg⁻¹) did not produce any mortality and changes in behavior and any other physiological activity in mice over 24h. the extract did not affect the body temperature, body weights, blood cell counts and hemoglobin. The LD₅₀ value could not be determined in oral administration route; however it was determined by intraperitoneal administration of the extract (0.1, 0.2, 0.4, 0.8 and 1.0mg kg⁻¹). An LD₅₀ value of 0.54g kg⁻¹ was deduced for the extract through intraperitoneal administration. The extract was further evaluated for 14 day toxicity study, wherein mice were dosed with the extract (2.5, 5, 10, and 20g kg⁻¹) daily for 14 days. The results indicated significant increase in body temperature and a significant decrease in the red blood cell count, hemoglobin and hematocrit values. It was concluded to be relatively safe for short-term oral administration.^[9] In another study, hydroethanol extract (20:80v/v) of leaves from *F. exasperata* showed no toxic effects in brine shrimp lethality test, inhibition of telomerase activity, and induction of chromosomal aberrations *in vivo* in rat lymphocytes rendering it relatively safe for possible human consumption.^[95]

Recent toxicity studies in rats involving crude aqueous and ethanol extract of the leaves have indicated potential hepatic and renal toxicity as reflected by significantly increased serum transaminases and bilirubin. The biochemical findings were substantiated by the histopathological studies which indicated that high doses of the ethanol leaf extract could lead to toxic injury in the kidneys which might interfere with renal tubular function and induce renal failure.^[20,21]

In another acute toxicity study involving a Nigerian polyherbal tea containing *Anthocleista vogelii*, *Ficus exasperata* leaves and *Viscum album*, a 100% mortality was produced at the dose of 20.0g kg⁻¹ in mice over 72h. However, no mortality occurred in animals that received <5.0g kg⁻¹ of the extract. Based on these findings an LD₅₀ value of 9.0g kg⁻¹ was assigned to the extract. In a sub-chronic toxicity model, dosing of the rats with the extract (100, 250 and 500g kg⁻¹) significantly reduced plasma glucose and low density lipoprotein (LDL) and increased high density lipoprotein (HDL)-cholesterol compared to control rats. The study also evidenced no significant changes in body weights, (AST) and creatinine levels but ALT levels were significantly decreased suggesting the safety of the formulation.^[96]

Considering the conflicting results on the toxicity of *F. exasperata* extracts reported by various researchers,^[94-96] systematic toxicological screening of standardized extracts is the urgent need. The phytochemical composition of the extracts becomes crucial here, in order to identify the bioactive component and the toxic metabolite. Although, the plant is traditionally used for the management of various diseases and disorders, its continued usage for medicinal purposes might do more harm than good if toxicity exists. Therefore, in-depth toxicological evaluation is needed to throw more light on the safety of *F. exasperata*.

Conclusions

Based on the available literature it is evident that different parts of *Ficus exasperata* possess rich therapeutic values. However more scientific studies by application of modern techniques are required to support the use of this plant or their parts in traditional medicines. Studies are also warranted to evaluate the potential of this plant to be explored as animal fodder to minimize the demands and competition for protein rich foods. It is expected that this review will be of high use to isolate novel bioactive compounds as well as develop novel drugs from *F. exasperata*. Also, *in vitro* and *in vivo* studies are required to evaluate the safe use of this plant or their parts.

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