



A review of *Bridelia ferruginea*, *Combretum glutinosum* and *Mitragyna inermis* plants used in zootherapeutic remedies in West Africa: historical origins, current uses and implications for conservation

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ABSTRACT

Context and objectives: West Africa has a very rich ethnozoological heritage due to its rich biodiversity, history and culture. Due to its location in a biodiversity hotspot, its agro-pastoralist traditions and its role during the maritime discoveries of the Renaissance, West Africa has a long list of animals and animal parts that have been used in its folk medicine. These uses can still be found in many historical documents and pharmacopeias. *Bridelia ferruginea*, *Combretum glutinosum* and *Mitragyna inermis* are tropical and subtropical medicinal plants widely used in general traditional African medicine and in West Africa in particular, including Benin, Nigeria, Burkina Faso and Ivory Coast to treat many diseases such as bladder troubles, diabetes, dysentery, arterial hypertension, rheumatism pain. This study aims to do a literature review of these three tropical plants on their biological and pharmacological properties on veterinary medicine

Methodology and Results: A thorough literature search was done and plants little studied *Bridelia ferruginea*, *Mitragyna inermis* and *Combretum glutinosum* were chosen in the search for their anthelmintic activity against gastrointestinal parasitic nematodes of small ruminants in Djallonké. Also to confirm their use in traditional veterinary medicine in West Africa.

Conclusion and application of results: This literature review of their extracts properties showed that the plants possessed wide-reaching pharmacological actions, including anti-diabetic, cardiovascular disease antibacterial, anti-inflammatory, antispasmodic and antiplasmodial and justifies their use in traditional medicine for treating various diseases. This manuscript intends to be a starting point to these future investigations.

Key words: *Bridelia ferruginea*, *Combretum glutinosum*, *Mitragyna inermis*, anthelmintic, Traditional folk medicine, Pharmacological action.

INTRODUCTION

Medicinal plants are used in the whole world and have a growing economic importance (Agra *et al.*, 2007). The use of plant parts to treat human or animal disease is as old as the disease itself and herbal medicine was the major form of medicine in West Africa especially in Benin. Besides, 80% of developing countries population depends on traditional medicines for their primary health care and 25% of the drugs are based on plants and their derivatives (Azu & Onyeagba, 2007). In Benin, medicinal plant knowledge and exploitation remain a permanent priority. Benin medicinal flora is rich and medicinal plant knowledge nowadays has a great development. *Bridelia ferruginea*, *Combretum glutinosum* and *Mitragyna inermis* belong to this flora (Akoègninou *et al.*, 2006) and are well known in many African countries. They appear to be the most studied species regarding their traditional uses and for their pharmacological properties (Ngueyem *et al.*, 2009; Gong *et al.*, 2012). According to ethno-veterinary surveys in Benin as in other African countries, these three plants are used as anthelmintics in traditional human and veterinary medicine (Kabore *et al.*, 2007, Kone *et al.*, 2008; Djoueche *et al.*, 2011). Validation of plants' uses in traditional medicine is not only involved in ethnobotanical studies (Adjanohoun *et al.*, 1999), but also by evaluation of biological and chemical properties (Hounzangbé - Adoté, 2000; Lagnika,

2005). The fact that few plants from the Beninese pharmacopoeia were subject of clinical investigation; it was decided to study anthelmintic properties of these three plants against gastro-intestinal parasites on small ruminants. Because in the whole world, the strongyles are recognized as one of the first causes of production losses (Gbangboché *et al.*, 2005). The treatment of these parasites and other diseases is done using synthetic molecules. While the exclusive use of synthetic drugs in health many obstacles currently limit prophylaxis. First, some parasites have developed resistance to anthelmintics such as benzimidazoles, Levamisole, and even now to ivermectin because of too frequent use (Brunet, 2008). Moreover, routine deworming regress youngs' immunity development (Brunet, 2008). In additional, manufactured drugs are unavailable and more expensive to rural population and when they are effective, these drugs are harmful to environment because of their remanence. This manuscript comprises the first study entirely devoted to a review of all uses of zootherapeutic remedies in West Africa, using historical documents, already published sources and original data from field surveys. We will also highlight some possible conservation problems that those uses might cause for some species of *Bridelia ferruginea*, *Combretum glutinosum* and *Mitragyna inermis* plants.

OBJECTIVES

This study examined native anthelmintic activity against gastro-intestinal parasitic nematode of small ruminants Djallonké (West African Dwarf Sheep)

plants of *Bridelia ferruginea*, *Combretum glutinosum* and *Mitragyna inermis* and confirms their uses in traditional veterinary medicine.

METHODOLOGY AND RESULTS

Botany description

Botany of *Bridelia ferruginea* (figure 1): The genus *Bridelia* Willd consists of about approximately 60–70 species including *B. atroviridis*, *B. cathartica*, *B. ferruginea*, *B. micrantha*, *B. ovate*, *B. siamensis*, *B. tomentosa*, *B. tulasneana*. All are native to Africa, Asia and Australia (Rashid, 2000). *B. ferruginea* and *B. micrantha* appear to have been the most studied. *B. ferruginea* is a small non-laticiferous scaly tree or shrub that grows to about 4 meters high. The plant often bears

spines and may be slash crimson coloured. The leaves may be small to medium sized, simple, alternate, spiral or distichous, broadly elliptic and pubescent. They are also pinnately veined with entire margin and an acuminate or acute apex (GHP, 1992).



Figure 1: Leaves and fruits of *Bridelia ferruginea* (Alissou, 2013)

Botany of *Combretaceae glutinosum* (figure 2): The family *Combretaceae* is distributed in approximately 20 genus with 600 species. The largest genus is *Combretum* and *Terminalia* (Petrovski *et al.*, 2006). *Combretum* is a very large genus, comprising about 250 species and distributed worldwide in the tropics and subtropics. About 140 species occur in tropical Africa including *Combretum glutinosum*. it is a bushy shrub or small tree growing up to 12 m and a deciduous species sprouting in the middle of the dry season. The trunk is usually twisted and low branched, with a rounded, open crown. The lower branches characteristically point downwards. The bark is grey-black and may be smooth or rough with fissures on the upper surface and red to orange slash. The leaves are opposite, verticillate in threes or sometimes subopposite; they are very variable in shape and size, even on the same tree.



Figure 2: Leaves of *Combretum glutinosum* (Alissou, 2013)

Botany of *Mitragyna inermis* (figure 3): The genus *Mitragyna* belongs to Rubiaceae family and is found in swampy territory in the tropical and subtropical regions of Asia and Africa. There is six species: *M. speciosa* (Korth.), *M. tubulosa* (Arn.), *M. parvifolia* (Roxb, Korth), *M. hirsuta* (Havi1), *M. diversifolia* (Wall. ex G. Don) and *M. rotundifolia* (Roxb, O.Kuntze.), widely grow in India and Asia (Puff *et al.*, 2005). Other four species, *M. ciliate*, *M. inermis*, *M. stipulosa* and *M. africanus*, widely grow in west African. *Mitragyna inermis* falls under the Rubiaceae family, and is a medium-to-tall deciduous shrub, growing to around 10 m in height with a trunk of wide diameter and light-colored bark. The leaves are light green and opposite and oval-shaped with a short blunt point, around 6 to 9 cm in length. The young leaves and twigs are red in colour. The tree blooms from May to September into small, fragrant white flowers, in round heads of up to 2 cm in diameter on short stalks. The tree bears fruits year-round that are hard, woody and spherical clusters of capsules. *Mitragyna inermis* is most traditional (ethnomedicinal) uses (Gong *et al.*, 2012).



Figure 3: Leaves and fruits of *Mitragyna inermis* (Alissou, 2013)

METABOLITES OCCURRING IN THE PLANTS

Phytochemical studies carried out in *Bridelia ferruginea*, *Combretum glutinosum* and *Mitragyna inermis* have showed the presence of many classes of secondary metabolites, including quinones, catechic and gallic tannins, alkaloids, sterols, polyterpenes, polyphenols, reducing compounds, flavonoids, saponins, phenols and tannins (Akuodor *et al.*, 2011; Sore *et al.*, 2012;). Several unusual compounds have also been isolated from the three plants like lignans (deoxypodophyllotoxin, 5'-demethoxy-[beta]-peltatin-5O-[beta]-D-glucopyranoside, [beta]-peltatin, [beta]-peltatin-5-O[beta]-D-glucopyranoside) isolated from *Bridelia ferruginea* roots (Rashid, 2000;); flavonoids (quercetin, quercetrin, rutin, myricitrin, myricetin-3-O-[beta]-glucoside, ferrugin) and a biflavanol (gallocatechin-[4-O-7]-epigallocatechin) (Cimanga, 2001), gallocatechin- (4'-O-7)-epigallocatechin has been found in *Bridelia ferruginea* bark (De Bruyne *et al.*, 1997), while rutin and quercetin, are present in *Bridelia ferruginea* leaves (Addah-Mensah & Munenge, 1989). Gallic acid, ellagic acid, flavonoid, glycosides and four tannins have been isolated from the leaves of *Combretum glutinosum*. The tannins are 2,3-(S)-hexahydroxydiphenoyl- D-glucose, punicalin,

punicalagin and combreglutinin (Traore, 1999). The presence of indole and oxindole alkaloids from the leaves of *Mitragyna inermis* have been described by Shellard & Sarpong. (1967). From the bark of *M. inermis*, two 27-nortriterpenoid glycosides, named inermiside I and II were isolated and their structures determined based on extensive 2D-NMR and MS spectral analysis as 6-deoxy-β-D-glucopyranosyl-[3-O-β-D-glucopyranosyl-(16)-β-D-glucopyranosyl]-pyrocincholate and 6-deoxy-β-D-glucopyranosyl-pyrocincholate, respectively (Cheng *et al.*, 2002).

PHARMACOLOGICAL ACTIVITY

Bridelia ferruginea, *Combretum glutinosum* and *Mitragyna inermis* are tropical and subtropical medicinal plants widely used in traditional African to treat a range of diseases. Studies carried out by various workers have shown that the plants have several properties, which justify the plants' medicinal use. Many classes of constituents, including quinones, tannins, alkaloids, sterols, polyphenols, reducing compounds, flavonoids and saponins are usually responsible for the plants' activity such as antibacterial and antifungal effects, antispasmodic effect, anti-inflammatory effect and antidiabetic activity (Table 1).

Table 1: Bioactivities of drugs obtained of *Bridelia ferruginea*, *Combretum glutinosum* and *Mitragyna inermis*

Botanical Name	Biological Activity	Part Tested	Bioassay Models	Results	References
<i>Bridelia ferruginea</i> benth	Antimicrobial screening	Crude extracts from the root, stem bark and leaves	Agar diffusion method	Crude root extract inhibited the growth of <i>Escherichia coli</i> , <i>Staphylococcus aureus</i> , <i>Salmonella typhi</i> , <i>Proteus mirabilis</i> and <i>Candida albicans</i> at concentrations of 40, 100, 60, 60, and 80 mg/ml respectively. Stem bark had minimum inhibitory concentration (MIC) of 60 mg/ml on <i>Salmonella typhi</i> and 10 mg/ml on <i>Candida albicans</i> .	Adebayo <i>et al.</i> , 2009
		Ethanol, methanol and acetone extracts of bark		Methanol extract was the most effective on <i>Bacillus subtilis</i> and <i>Escherichia coli</i> while ethanol extract was most effective on <i>Staphylococcus aureus</i> .	Kayode <i>et al.</i> , 2009
		Crude ethanolic, methanolic and water extracts of leaves and bark		Half strength (10 g/ml) concentration of the bark ethanol and methanol extracts was the minimum inhibitory concentration against <i>Citrobacter</i> sp. and <i>Bacillus subtilis</i> . While quarter strength (5 g/ml) concentrations of the bark methanol and ethanol extracts were the minimum inhibitory concentration against <i>Staphylococcus aureus</i> and <i>Micrococcus luteus</i> .	Owoseni <i>et al.</i> , 2010
	Laxative effect	Aqueous extracts from the stem bark		Extract for concentrations ranging from 10 ⁻⁵ mg/ml to 10 ⁻¹ mg/ml, caused an increase of the rhythmical contraction of guinea pig <i>Taenia coli</i> smooth muscle. It suggested the presence of cholinomimetic substances in the crude extract of <i>Bridelia ferruginea</i>	Nene - Bi <i>et al.</i> , 2009
	Anti diabetic effects	Aqueous extracts from the leaves	Oral glucose tolerance test	Oral glucose tolerance test showed that pregnancy induced glucose intolerance in the rats. However, <i>B. ferruginea</i> caused a reduction in glycaemic response to glucose challenge and an increased glucose tolerance in rats that had pregnancy-induced glucose intolerance. Thus, diabetogenic effect of pregnancy was ameliorated by oral administration of aqueous extracts of <i>B. ferruginea</i> to pregnant albino rats.	Taiwo <i>et al.</i> , 2012
	Antioxidant activity	Ethanolic extract of stem bark	2,2- diphenyl-1-picrylhydrazyl (DPPH) radical scavenging, Ferric reducing	Ethanolic extract of <i>Bridelia ferruginea</i> bark in this study showed inhibition against the formation of thiobarbituric acid reactive species (TBARS) induced by iron (II) sulphate (60µM FeSO ₄) in the brain and liver homogenates of the albino rat used. The extract was found to have different	Omotade <i>et al.</i> , 2012

			antioxidant power (FRAP)	antioxidant potentials in a manner that was concentration dependent, the result showed 36.9µg/ml of the extract to have the most potent inhibition at 54.16% and 8.46% for the brain and liver respectively.	
		Semi-ethanolic extracts of barks	the Oxygen Radical Absorbance Capacity (ORAC)	Extracts have antioxidant property and α-Glucosidase inhibitory activity (IC50 = 1.4 ± 0.04 µg / ml) for <i>B. ferruginea</i> higher than the reference compound acarbose (IC50 = 726 ± 15 mg / ml).	Bothon <i>et al.</i> , 2012
		Hexane and ethyl acetate extract from leaves	Antioxidant assay and Artemia salina test	The test showed an IC50 value of 158.2µg/ml, which is quite significant, compared with that of the gallic acid, 201 µg/ml. Artemia salina test showed an acute toxicity with LC50 value of 319 µg/ml and lethal dose with LC50 value of 5.86 µg/ml indicating that that <i>B. ferruginea</i> could be a source of cytotoxic and antioxidant agents.	Atolani <i>et al.</i> , 2012
	Anti-inflammatory activity	Aqueous extract of the stem bark	Tail immersion mice test and Yeast-induced hyperpyrexia test	Extract significantly attenuated the spinalpain sensation against conduction heat in mice. The maximum nociceptic effect was observed at higher dose (100 mg/kg) which was comparable to that of morphine (10 mg/kg).The extract at the dose of 25, 50 and 100 mg/kg caused a more significant reduction in rectal temperature.	Akuodor <i>et al.</i> , 2011;
<i>Combretum glutinosum</i> Perrot. Ex DC	Antischistosomal	Aqueous extract of dried leaf	<i>In vitro</i> assay	Aqueous extract of dried leaf has miracidicidal and cercaricidal activity on <i>Schistosoma mansoni</i> at concentration for drug: 1,000 ppm	Elsheikh <i>et al.</i> ,1990
	Antimicrobial activity	Methanolic and water extract from leaves and stem bark	Agar diffusion method	Methanolic extract of the stem bark showed the highest level of inhibition on <i>Salmonella typhi</i> and <i>Escherichia coli</i> while the aqueous extract showed less response.	Yahaya <i>et al.</i> , 2012.
		Aqueous extracts from stem bark and root		Antibacterial activity showed a minimum inhibitory concentration (MIC) value of 0.86 mg/ml for 1.41 mg/ml for <i>Combretum glutinosum</i> against <i>Staphylococcus aureus</i> .	Sore <i>et al.</i> , 2012
	Molluscicidal	Methanol extract of dried fruit, dried root or dried stem	<i>In vitro</i> toxicity bioassay	No molluscicidal effect of aqueous extract against <i>Bulinus globosus</i> (snail) at concentration for all drugs: 100.0 ppm.	Sofowora <i>et al.</i> ,1980
	Antimalarial activity	Methanol and hydromethanol extracts from the leaves	<i>In vitro</i> antimalarial assay	Extracts was screened against Vietnamese <i>Plasmodium falciparum</i> chloroquine-resistant strain W2 <i>in vitro</i> . Hydromethanol extracts of <i>Combretum glutinosum</i> was the	Ouattara <i>et al.</i> , 2006

				most active (5µg/ml < IC50 < 50 µg/ml).	
<i>Mitragyna inermis</i> (Willd.) Kuntze	Cardiovas- cular affects	Bark aqueous extract		Extract produced relaxation in isolated porcine coronary artery at concentration up to 3 mg/ml. This relaxation involved partial depolarization (KCl 20, 40 mM) and NO synthase inhibitor-sensitive mechanisms	Ouedraogo <i>et al.</i> , 2004
	Antiplasmodial activity	Hydroethanolic extract, hydroacetonic extract and aqueous extract	Plasmodium Lactate Dehydrogenase (PLDH) method	Extracts have been tested <i>in vitro</i> against Chloroquine-resistant strain (K1) and chloroquine-sensitive strain (3D7) of <i>Plasmodium falciparum</i> . Aqueous extracts exhibited the best results against K1 with the 50% inhibitory concentration (IC50) values of 0.54±0.18, 1.72±0.99, 1.54±0.04 g/mL for <i>M. inermis</i> leaves. Hydroethanolic extract from the leaves of <i>M. inermis</i> gave also IC50 value of 0.87±0.10 g/mL with 3D7.	Zongo <i>et al.</i> , 2011
		Ethanol and pentane extracts from Stem and root	Radioactive micro- method	Extracts of these plants were tested on three strains of <i>Plasmodium falciparum</i> , FcB1-Colombia and FcM29-Cameroon (chloroquine-resistant strains) and a Nigerian chloroquine-sensitive strain. But extract has effects on the symptoms of malaria (fever, headaches, and so on) rather than on the parasite itself at least in regards with our results on the parasite inhibition	Mustofa <i>et al.</i> , 2000
	Anti-diabetic effect	Stem bark ethanol extract		Hypoglycaemic effects of the ethanol extract of <i>M. inermis</i> on blood glucose levels of alloxan induced diabetic albino rats have been investigated. The results revealed that the plant possessed hypoglycaemic activity. Doses of 250, 350 and 450 mgkg ⁻¹ body weight intraperitoneally (i.p.) were administered to the rats but the 350 mg/kg ⁻¹ dose exhibited the highest hypoglycaemic potentials.	Adoum <i>et al.</i> , 2012

	Antibacterial activity	Methanol leaf extract	Disc diffusion method	Extract showed antibacterial activity on <i>Staphylococcus aureus</i> , <i>Escherichia coli</i> and <i>Klebsiella pneumonia</i> with minimum inhibitory concentration of 50 mg/ml, 50 mg/ml and 25 mg/ml respectively. The activity was concentration dependent having no effect on tested concentration of 35.5 mg/ml and 75 mg/ml on <i>Staphylococcus aureus</i> and <i>Escherichia coli</i> while at 18.75 mg/ml on <i>Klebsiella pneumoniae</i> . The extract was bactericidal at concentration of 100 mg/ml on <i>Staphylococcus aureus</i> and <i>Klebsiella pneumoniae</i> while 200 mg/ml on <i>Escherichia coli</i>	Wakirwa et al., 2013
		Water insoluble residue and fractions and crude ethanol extract of stem bark		.Ethanol crude extract, water insoluble residue and ethyl acetate fraction did not inhibit growth of <i>Escherichia coli</i> , but inhibited growth of <i>Staphylococcus aureus</i> , <i>Proteus mirabilis</i> , <i>Streptococci pyogenes</i> and <i>Salmonella typhi</i> . n-Butanol fraction failed to inhibit growth of <i>Staphylococcus aureus</i> but inhibited growth of other bacteria tested. Except <i>Streptococci pyogenes</i> , all tested bacteria were inhibited by residue of water-soluble crude ethanol extract.	Tor-Anyiin et al., 2012

DISCUSSION

In this review, *Bridelia ferruginea*, *Combretum glutinosum* and *Mitragyna inermis* possessed wide-reaching pharmacological actions, including anti-diabetic, cardiovascular disease antibacterial, anti-inflammatory, antispasmodic and antiplasmodial activity. In studies evaluating of three plants antibacterial activity, agar diffusion assays method was used and the extracts used were obtained with different solvents (ethanol, chloroform, methanol, petroleum ether, water). Activities were observed against the following bacterial species: *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Salmonella* species, *Streptococcus* species, *Proteus vulgaris*, *Klebsiella* species, *Sarcina lutea*, *Micrococcus luteus* and *Bacillus subtilis* (Owoseni et al., 2010), except extract of *Bridelia ferruginea*'s leaf which had no antimicrobial activity against any of the clinical isolates (Adebayo et al., 2009). In general, this study showed that leaves and stem bark of *Bridelia ferruginea*, *Combretum glutinosum* and *Mitragyna inermis* was the organ mostly used and different extracts from leaves and stem bark at different concentrations significantly inhibited the growth of *Staphylococcus aureus*, *Candida albicans*, *Staphylococcus epidermidis*, *Escherichia coli*, *Streptococcus lactis*, *Proteus vulgaris*, *Proteus mirabilis*, *Streptococcus pyogenes* and *Klebsiella* sp. Besides activity showed against *Staphylococcus aureus* and *Candida albicans* may justify the use of the *Bridelia ferruginea* bark as mouthwash in Nigerian and Ivorian traditional medicine (Ozerov et al., 1994). *Mitragyna inermis* and *Combretum glutinosum* were selected by ethnobotanical survey as plants commonly used by traditional healers for the treatment of malaria (Mustofa et al., 2000 ;). Extracts of these plants were tested *in vitro* on three strains of *Plasmodium falciparum*, FcB1-Colombia and FcM29-Cameroon (chloroquine-resistant strains) or Vietnamese *Plasmodium falciparum* chloroquine-resistant strain W2 and a Nigerian

CONCLUSION

Results of this review contribute to the validation of the popular use of *Bridelia ferruginea*, *Combretum glutinosum* and *Mitragyna inermis* in the treatment of bacterial, fungal, malaria and viral infections and cardiovascular problems, among others. Anthelmintic properties of these

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chloroquine-sensitive strain for an evaluation of antiplasmodial activity *in vitro* (Zongo et al., 2011). These plants could be effectively more active on *Plasmodium falciparum* on human, as it is the case for plants containing prodrugs non active by themselves but which can be metabolised to active drugs (Mustofa et al., 2000). The antioxidant and anti-inflammatory properties were only evaluated in this review for leaves and barks of *Bridelia ferruginea* by DPPH and carrageenan-induced paw edema tests in mice assays respectively. Extracts of the barks had the highest DPPH and ABTS free radical scavenging activity (Bothon et al., 2012) and for anti-inflammatory activity aqueous extract of the stem bark was the most active (Akuodor et al., 2011). These findings provide some evidence for the traditional use of *Bridelia ferruginea* for the rheumatic pain, diarrhoea, dysentery, intestinal disorders, female sterility, as anthelmintic for roundworm and in the treatment of cystitis in Nigeria and Congo Kinshasa (Cimanga et al., 2001). Adoum et al. (2012) and Taiwo et al. (2012) demonstrated an antidiabetic effect of leaves and bark's extracts of *Bridelia Ferruginea* and *Mitragyna inermis*. In their studies, the dose of 250 mg/kg and 350 mg/kg of the extract was respectively the most effective, among the doses tested. It produced a significant hypoglycemic and antidiabetic activity. This study demonstrated the potential antidiabetic properties of extract of *Bridelia Ferruginea* and *Mitragyna inermis* for both type 1 and type 2 diabetes, justifying its traditional use in the treatment of this disease. All of the above results contribute to justify the use of the plant in traditional medicine for treating various conditions, particularly infections and diabetes. This study has showed that the three plants treat several diseases because of their different properties and. Through this review, we have the certitude that leaves of plants have never been studied for their anthelmintic properties and will enable us to continue our PhD thesis.

plants were not found in this study thus we can screen anthelmintic activities of *Bridelia ferruginea*, *Combretum glutinosum* and *Mitragyna inermis* leaves against gastrointestinal parasites of small ruminants to confirm their use in traditional veterinary medicine plants.

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