Heliyon 8 (2022) e10366

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

# *Bridelia ferruginea* Benth.; An ethnomedicinal, phytochemical, pharmacological and toxicological review

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ARTICLE INFO

*Keywords:*
Pharmacological activities
Traditional medicine
Phytochemicals
Lead compound discovery
*Bridelia ferruginea*

ABSTRACT

*Ethnopharmacological relevance:* *Bridelia ferruginea* belonging to the family Euphorbiaceae, identified as an important commonly growing shrub, is used in traditional medicine for managing arthritis, dysentery, constipation, chronic diabetes, skin diseases, bladder and intestinal disorders, oral infections, thrush, bites and as an arrow poison antidote. This review aims at providing information on the traditional medicinal uses, pharmacological activities, phytochemistry and toxicity studies of *Bridelia ferruginea* to bridge the gap between traditional medicinal uses and preclinical studies on *B. ferruginea* and subsequently lead to the development of valued added medicines from *B. ferruginea*.

*Materials and methods:* Data in this review were compiled using databases such as Google Scholar, Science Direct, Scopus, PubMed, Springer link, Elsevier and Taylor and Francis, articles from peer reviewed journals and other grey literature (short notes, book chapters, short communications) to access all the relevant information available on *B. ferruginea*.

*Results:* *B. ferruginea* contains different phytochemicals including flavonoids, phenolics, phytosterols, triterpenes, saponins, alkaloids and cardiac glycosides. Gallocatechin-(4′-O-7)-epigallocatechin, 3,5-dicaffeoylquinic acid, 1,3,4,5-tetracaffeoylquinic acid and some derivatives of 3-methoxyflavone, such as quercetin-3-methyl ether, quercetin 3-,7,3′,4′-tetramethyl ether, myricetin 3′,4′,5′-trimethyl ether, myricetin 3,3′,4′,5′-tetramethyl ether, myricetin and quercetin 3-O-glucoside specific flavonoids and biflavonoids like apigenin, kaempferol and glycosides of both have been isolated and further characterized from *B. ferruginea*. *B. ferruginea* has several pharmacologically beneficial properties including anti-inflammatory, anti-diabetic, antioxidant, antimicrobial, anti-infective, antipyretic, analgesic, diuretic and natriuretic activities.

*Conclusion:* The wide distribution, traditional medicinal uses and wealth of phytochemicals present in *B. ferruginea* suggests that the plant can be useful in lead compound discovery. Although *B. ferruginea* has been widely studied, further studies on the mechanism of action, bioavailability, pharmacokinetics, toxicity and side effects in humans need to be investigated.

## 1. Introduction

The use of medicinal plants predates human history (Aziato and Antwi, 2016). This knowledge and practice of traditional medicine has influenced innovation and continuous drug development (Baliga, 2012; Prasathkumar et al., 2021). Nearly a third of presently approved conventional medicines originated from plants or are synthesized from compounds initially obtained from plants. With the continuous development of herbs into conventional medicine, drug companies engage in large scale pharmacological screening of it (Baliga, 2012; Maqbool et al., 2019; Vickers and Zollman, 1999).

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https://doi.org/10.1016/j.heliyon.2022.e10366
Received 21 March 2022; Received in revised form 5 June 2022; Accepted 15 August 2022

In Africa, many patients resort to medicinal plants and herbs as first-line treatment in disease management. Inaccessibility to conventional health care for most parts of the African population, cost, the belief that herbs have minimal side effects and cultural acceptability contribute significantly to the persistent and significant use of herbal medicine (Aziato and Antwi, 2016; Baldé et al., 2006; Maqbool et al., 2019; Prasathkumar et al., 2021; Tulunay et al., 2015).

One of such important medicinal plants is *Bridelia ferruginea*, a commonly growing shrub that belongs to the family, Euphorbiaceae. Known widely in many African countries, this knotted shrub appears to be one of the well-studied species with regards to its folklore application and pharmacological properties (Adebayo and Ishola, 2009; Ngueyem et al., 2009). It commonly grows up to a height of 45 feet and girth up to 1.5 m (Adebayo and Joshua, 2018; Ngueyem et al., 2009). The fruits, leaves, bark and roots are commonly prepared as decoctions. Traditionally, *Bridelia ferruginea* is used for managing arthritis, dysentery, constipation, diarrhoea, chronic diabetes, skin diseases, bladder and intestinal disorders, oral infections, contusion, thrush, bites and as an arrow poison antidote. The leaves have been evaluated for antidiabetic (Aja, 2013; Njamen et al., 2012; Onyenibe and Udogadi, 2019), antioxidant (Fabiyi et al., 2012), antimicrobial (Adebayo and Ishola, 2009), repellent (Loko et al., 2017) and fibroblast growth stimulation (Adetutu et al., 2011) properties. The stem and stem bark have demonstrated anti-inflammatory (Olajide et al., 2000), antioxidant (Oloyede et al., 2014), antimicrobial (Adebayo and Ishola, 2009) antityphoid (Dada and Akinyele, 2020), anthelmintic (Adebayo and Joshua, 2018), antiplasmodial (Mbah et al., 2012), analgesic (Akuodor et al., 2011), antipyretic (Olajide et al., 2000) and diuretic (Nene-Bi et al., 2012) properties. The root (Adebayo and Ishola, 2009) and the fruits (Akinpelu and Olorunmola, 2000) are reported as antimicrobial agents.

This review, therefore aims at providing information on the traditional medicinal uses, pharmacological activities, phytochemical constituents and toxicity studies of *Bridelia ferruginea*. This will help to bridge the gap between traditional uses and preclinical studies on *B. ferruginea* and subsequently lead to the development of valued added pharmaceutical products from *B. ferruginea*.

## 2. Materials and methods

Data in this review was compiled using various databases such as Google Scholar, Science Direct, Scopus, Springer link, Elsevier, PubMed and Taylor and Francis, articles from peer reviewed journals and other grey literature (short notes, book chapters, short communications) to access information available on *B. ferruginea*. Literature search was carried out using the following search terms: "*Bridelia ferruginea*", "traditional or ethnomedicinal uses of *Bridelia ferruginea*", "medicinal uses of *Bridelia ferruginea*", "morphology or botany of *Bridelia ferruginea*", "taxonomy *Bridelia ferruginea*", "phytochemical constituents of *Bridelia ferruginea*", "pharmacological activities of *Bridelia ferruginea*" and "toxicity of *Bridelia ferruginea*" to collect thorough and detailed information about the taxonomy, ecology, traditional medicinal uses, pharmacology, biological activities, phytochemistry and toxicity on *Bridelia ferruginea*.

## 3. Botany

### 3.1. Taxonomy, ecology and vernacular names

*Bridelia ferruginea* Benth. commonly known as *Bridelia* belongs to the family Euphorbiaceae (Pettit et al., 2016). It is synonymous to *Bridelia micrantha* var. *ferruginea* (Benth) Müll (WAHP, 2013). Several species of *Bridelia*, about 60–70 are distributed from Africa to Asia (Ngueyem et al., 2009). About 50 of these species are distributed in Madagascar, Tropical Africa, Yemen and in Asia ranging from South China, India and Malaysia throughout Indochina to North Australia, Vanuatu Islands and the Solomons (Ngueyem et al., 2009). In Africa, this shrub commonly occurs in the Guinea savannah and coastal plains predominantly Burkina Faso, Cote d'Ivoire, Togo, Nigeria and Ghana (Boye et al., 1992; Mshana, 2000). Examples of some species in this genus include *Bridelia atroviridis Muell. Arg., Bridelia crenulata Roxb., Bridelia cathartica Bertol. f., Bridelia glauca Bl. f. balansae Tucht., Bridelia balansae Tucht., Bridelia grandis (Pierre ex Hutch), Bridelia moonii Thw., Bridelia monoica (L.) Merr., Bridelia ndellensis Beille., Bridelia micrantha (Hochst) Baill., Bridelia ovata Decne., Bridelia scleroneuroides Pax., Bridelia scleroneura Mull-Arg.* and *Bridelia stipularis Blume* (Ngueyem et al., 2009).

*Bridelia ferruginea* has several names across the world in dialects of different localities. Table 1 highlights some of them.

### 3.2. Plant description

*B. ferruginea* is a shrub or small non-laticiferous scaly tree that develops up to 15 m tall (Boye et al., 1992; Mshana, 2000). The plant develops up to 1.5m in its girth with crooked bole branching down. The stem bark of *B. ferruginea* is dark grey, cracked, rough and slash thin. It is characterized by branches that are long and thin and sometimes (usually when young) equipped with short spines. Leaves have slightly wavy edges, in a size range of small to medium, simple, petiolate with stipules, alternate, spiral or distichous in leaf arrangement. It has a broadly elliptic lamina, with entire margin and an apex that is acute or acuminate. Each flower cluster typically consists of male and female. The male flowers yellowish-green, pedicellate and the female flowers subsessile. It bears fruits that are drupe-shaped, oblong, unilocular or sometimes subglobulose. The fruits have a green pericarp, red then black-blue colour at maturity. The fruits, sometimes are obovoid, 0.8 cm in length, more usually ellipsoid, 0.6 cm in length and especially persistent on its branches (WAHP, 2013; Boye et al., 1992; Mshana, 2000). Figures 1 and 2 show pictures of *B. ferruginea* plant and parts of the plant.

## 4. Traditional and ethnomedicinal uses

The stem bark prepared decoction of *Bridelia ferruginea* is employed in oedema, epilepsy and infant irritability treatments. It is also useful in the treatment of gastralgias, dysentery, anaemia and rheumatisms (Lagnika et al., 2012). An extract from the bark is used as a mouth wash (combined

**Table 1.** Vernacular names of *Bridelia ferruginea*.

| Country | Language/Tribe | Vernacular name (s) | References |
|---|---|---|---|
| Ghana | Twi | Opam fufuo | (WAHP, 2013) |
| | Ga Adamgbe | Flatsho | (WAHP, 2013) |
| | Hausa | Kisni | (WAHP, 2013) |
| Togo | Ewe | Akamati, | |
| | Bassar | N'tchintchi | (WAHP, 2013) |
| | Lamba | Kolu | |
| Nigeria | Yoruba | Iroladan, Eepo ira | (Kareem et al., 2010) |
| | Ibo | Ola | (Kareem et al., 2010) |
| | Hausa | Kis(z)ni | (Kolawole et al., 2006) |
| Sierra Leone | Susu | Tholinyi | (WAHP, 2013) |
| | Kissi | Sindio | |
| | Hono | Bembeh | (WAHP, 2013) |
| Mali | Bambara | Saguan | |
| | Noms | Daafi | (WAHP, 2013) |
| | Senoufo | Gnirin-o-tigue | |
| Guinea | Fula Pulaar | Dafi | (WAHP, 2013) |
| | Manding Maninka | Baboni | (WAHP, 2013) |
| | Maninka | Sagba | (WAHP, 2013) |
| Cote d'Ivoire | Manding Maninka | Saba/Sagba, | (WAHP, 2013) |
| | Senufo | Dyimini | (WAHP, 2013) |
| Benin | Baatonun | Bemebenku | (WAHP, 2013) |
| | Gbe Fo | Honsukokué | (WAHP, 2013) |
| | Yoruba | Nago Hira | (WAHP, 2013) |

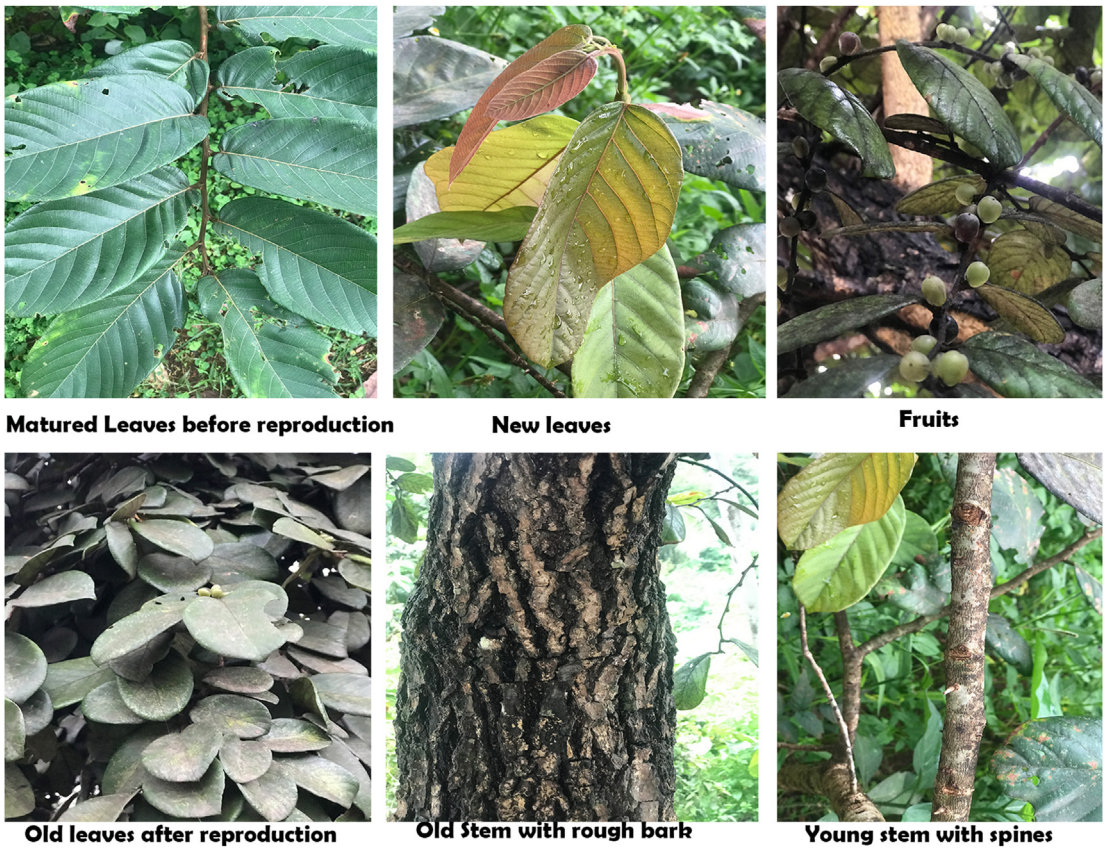



**Figure 1.** Pictures of leaves, stem and fruits of *B. ferruginea* (Source: Centre for Plant Medicine Research (CPMR), Mampong-Akuapem, Ghana Arboretum).


**Figure 2.** Picture of *B. ferruginea;* full plant and branch with leaves (Source; CPMR, Mampong-Akuapem, Ghana Arboretum).

with lime juice to form traditional gargle "*Ogun efu*"), milk coagulant, vermifuge and purgative (Cimanga et al., 1999; Orafidiya et al., 1990). Traditionally, diabetes, arthritis and boils have been managed using *B. ferrugenia* (Njamen et al., 2012). In western Nigeria, the stem and stem bark are useful in managing various oral infections such as oral candidiasis while the bark is used in northern Nigeria as a cure for infections caused by poisoned arrow wounds (Ayensu, 1978; Irobi et al., 1994). The roots, bark and leaves are constituents of an infusion by the Yorubas (Nigeria) mostly given to children (Burkill, 1994). Ethanolic stem bark extracts' activity against *Salmonella typhi* (Dada and Akinyele, 2020) may justify its traditional application in the management of enteric fever. The leaves and bark decoctions are used as malaria therapy in some parts of

Nigeria (Odugbemi et al., 2007). In Southeastern Nigeria, some local healers prepare this remedy by soaking and squeezing the material in water and a cupful given as a daily dose for 3–7 days. Hausa and Fulani tribes (Northern Nigeria) also use the stem bark as a skin cancer medication (Abubakar et al., 2007). It is also reported to have water purification properties (Kolawole and Olayemi, 2003).

In Togo, the root bark is a remedy for intestinal and skin disorders (Bruyne et al., 1997). Additional activities of the bark extract reported are trypanocidal (Ekanem et al., 2008), antimicrobial (Owoseni et al., 2010) and anti-inflammatory (Olajide et al., 2003).

In Congo, the stem bark decoction is a remedy for toothache, cystitis, intestinal disorders, roundworm infestation, diarrhoea and female sterility (Oliver-Bever, 1986).

In Cote D'Ivoire, the stem back decoction is for managing gonorrhoea, diarrhoea and dysentery or as a purgative (Gill, 1992). The bark extract is combined with *Costus* for managing minor epilepsy (Akubue and Mittal, 1982). Skin conditions are managed using the stem and root barks. Tea made from the pulped bark is used for treating fevers, stiffness, headaches and rheumatic pains and also as a local application treatment for oedemas (Addae-Mensah, 1992).

The leaves of *B. ferruginea* are for managing dysentery in Cameroon (Talla et al., 2002), whereas the fruits, for mycotic stomatitis (Ampofo, 1979).

In Guinean traditional medicine, *B. ferruginea* is used to treat infectious diseases such as sexually transmitted diseases (Magassouba et al., 2007). Pharmacological studies on various extracts of *B. ferruginea* supports its use as an antidiabetic in different parts of West Africa (Afolabi et al., 2018; Bakoma et al., 2018; Onyenibe and Udogadi, 2019). Extracts of the stem bark have shown antimicrobial activity against some of the causative microorganisms of secondary upper respiratory tract and enteric infections (Jose and Kayode, 2009).

Other traditional uses of various parts of *B. ferruginea* include epilepsy, rashes, cough, diuretic, asthma, analgesic, gout and impotence (Addae-Mensah, 1992; Ayensu, 1978; Mshana, 2000; Olajide et al., 2000). Figure 3 shows a summary of some of the diseases managed with *B. ferruginea*.

## 5. Phytochemistry

Different phytochemicals reported to be found in various parts and extracts of *B. ferruginea* include phenolics, phytosterols, cardiac glycosides, triterpenes, tannins, flavonoids, saponins and alkaloids (Abubakar et al., 2018; Cimanga et al., 2001; Ndukwe et al., 2007). Quinones, catechic tannins, gallic acid, sterols, alkaloids, polyterpenes, reducing sugars, polyphenols, flavonoids and saponosides are some phytochemicals identified in the aqueous stem bark extract (Nene-Bi et al., 2009). In a bioassay guided fractionation, Cimanga et al. (1999) and Bruyne et al. (1997) isolated from the 80% acetone stem bark extract gallocatechin-(4′-O-7)-epigallocatechin (1), 3,5-dicaffeoylquinic acid (2), 1,3,4,5-tetracaffeoylquinic acid (3) in addition to some derivatives of 3-methoxyflavone, which include quercetin 3-methyl ether (4), quercetin 3,7,3′,4′-tetramethyl ether (5), myricetin 3′,4′,5′-trimethyl ether (ferrugin) (6), myricetin 3,3′,4′,5′-tetramethyl ether (7), myricetin (8) and finally quercetin 3-O-glucoside (9). The structures of these compound (1–9) are shown in Figures 4 and 5, with compound (4)–(9) composed from a parent structure (A) in Figure 5 and their corresponding moieties in Table 2. These constituents have been screened against both the classical and alternative pathways of the compliment system, with the biflavanol (1) and the two caffeoyl ester quinic acids (2) and (3) showing the strongest inhibitory activity on the classical pathway with reference to rosmarinic acid. In addition, biflavanol (1), the two derivatives of quinic acids (2) and (3) and three derivatives of 3-methoxyflavones (5, 7 and 8) had a better inhibitory effect on the alternative pathway than the standard rosmarinic acid (Cimanga et al., 1999).

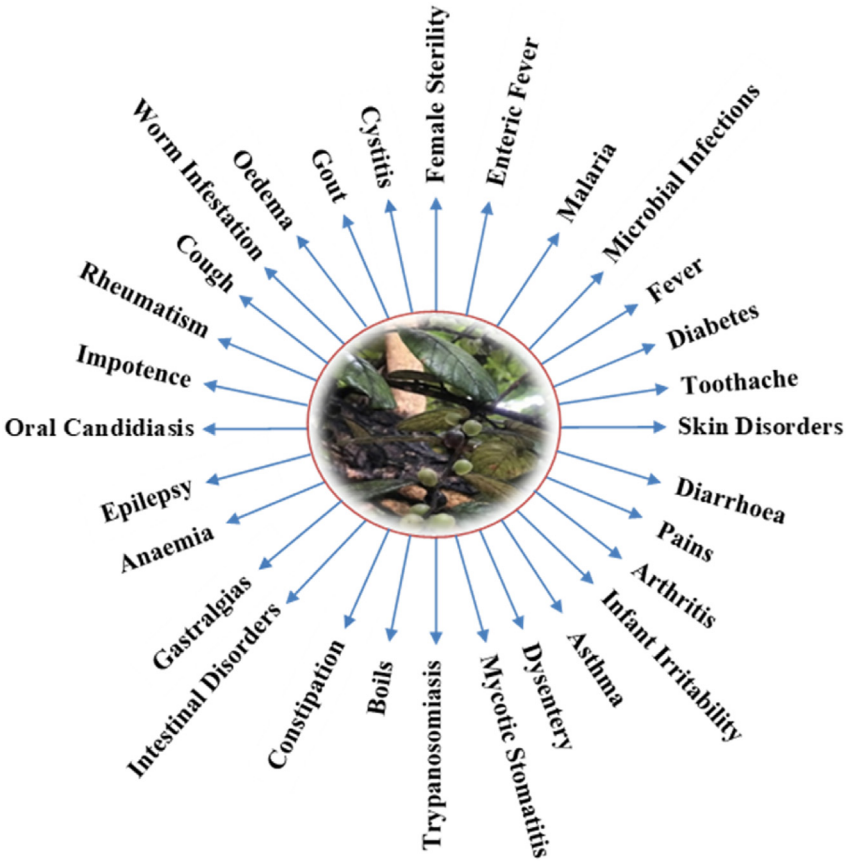
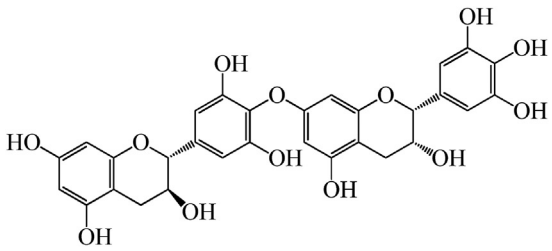
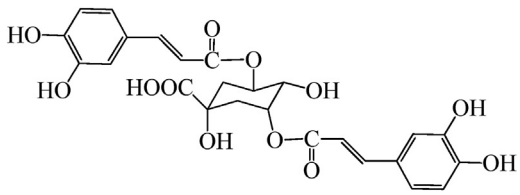


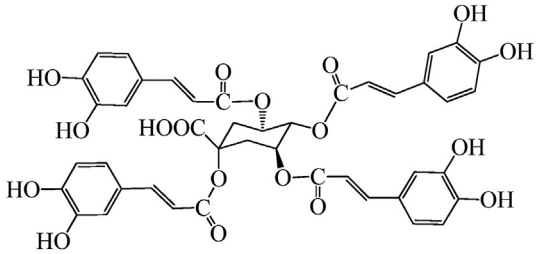

**Figure 3.** Some diseases treated traditionally using *B. ferruginea*.



Gallocatechin-(4'-O-7)-epigallocatechin (1)



3,5-dicaffeoylquinic acid (2)



1,3,4,5-tetracaffeoylquinic acid (3)

**Figure 4.** Quinic acid derivatives isolated from *B. ferruginea.*

Specific flavonoids and biflavonoids isolated and characterized from the methanolic plant extract include apigenin (10), kaempferol (11) and glycosides of both (Oliver-Bever, 1986), and their structures shown in Figure 5. Most medicinal plants containing apigenin are used in the management of gastrointestinal inflammation, bacterial infections and muscle spasticity. Apigenin is also known to inhibit the secretion of histamine and hence reduces allergic reactions. Kaempferol is known to regulate blood sugar levels especially through the inhibition of the aldolase reductase activity and help prevent neuropathy and retinopathy which are diabetic complications (DuPont et al., 2004). It controls lipid metabolism and can significantly decrease the risk of atherosclerosis and related disorders (DuPont et al., 2004). Due to its antioxidant activity, kaempferol is well noted for protecting cells from oxidative stress, stabilizing connective tissues and strengthening blood vessels. It also regulates the secretion of interleukin-6 (IL-6) and interleukin-8 (IL-8) and inhibits monocyte chemotactic protein-1 (MCP-1) (DuPont et al., 2004).

Other compounds isolated from *B. ferrugenia* include epigallocatechin (12), rutin (13), gallocatechin (14), quercetin (15), quercetin-3-neohesperidoside (16) and myricetin-3-glucoside (17), myricetin-3-rhamnoside (myricitrin) (18) (Addae-Mensah and Achenbach, 1985; Bruyne et al., 1997; Ngueyem et al., 2009) with their structures shown in Figure 5. These compounds are mostly present in the leaf extract. Gallocatechin-(4′-O-7)-epigallocatechin (1), epigallocatechin (12) and gallocatechin (14) are prodelphinidin, a subclass of the pro-anthocyanidins or condensed tannins which are part of the flavonoid family. The name prodelphinidin is due to their ability to liberate delphinidin on hydrolysis by an acid. Pro-anthocyanidins have numerous biological activities both in epidemiological and in vitro studies. The tendency of these flavonoids to complex metallic ions and proteins hence acting as an antioxidant may explain their anti-inflammatory, anti-diabetic, anti-bacterial and anti-cancer effects (Hertog et al., 1993; Semwal et al., 2016). The presence of gallocatechin-(4′-O-7)-epigallocatechin (1) and its isomeric pro-anthocyanidins in an extract or diet can be beneficial for the prevention of some chronic diseases particularly those related to cardiovascular health (Hertog et al., 1993). Cytotoxic lignan derivatives 5′-demethoxy-β-peltatin-5-O-β-D-glucopyranoside (19) and β-peltatin-5-O-β-D-glucopyranoside (20), which are related structurally to podophyllotoxin have been isolated from 50% (v/v) dicloromethane methanolic root extract of *B. ferrugenia* and are reported to show similar cytotoxic and cytostatic effects against NCI's 60 human tumor cell panel (Rashid et al., 2000). Further analysis by Rashid et al. (2000) indicates that both compounds bind to tubulin, which is quite consistent with many podophyllotoxin-like lignans (MacRae and Towers, 1984). Teniposide and etoposide are tubulin-interactive anti-mitotic drugs clinically used to manage tumors but are semi-synthetic derivatives of podophyllotoxin (Rashid et al., 2000). This is an indication that, depending on the concentrations of 5′-demethoxy-β-peltatin-5-O-β-D-glucopyranoside (19) and β-peltatin-5-O-β-D-glucopyranoside (20) in the roots, standardized and partially purified or modified extracts of the roots of *B. ferrugenia* could be used as a potential anti-tumour agent clinically. However, factors bordering on the selectivity index, acute and chronic toxicities and further efficacy evaluations of the extracts should be carefully considered.

The lignan derivatives (19) and (20) were isolated together with their parent lignans β-peltantin (21) and Desoxypodophyllotoxin (22). Figure 6 shows the structures of the compounds.

The methanolic dried leaf extract also yielded 14 compounds in a study by Afolayan et al. (2019). The structure of these compounds are depicted in Figures 5 and 7. The authors reported for the first time the isolation of a type of stearic acid composed of a fatty acid monoester of 2-O-β-D-glucosylglycerol (23), 6β-hydroxy-(20R)-24-ethylcholest-4-en-3-one (24a), 6β-hydroxy-(20R)-24-ethylcholest-4,22-dien-3-one (24b), lutein (25), vomifoliol (26), corilagin (27), kaempferide-3-O-β-D-glucoside (28), isomyricetin (29) and quercitrin (30) from the methanolic leaf extract in addition to myricetin (8), isoquercetin (31), myricitrin (18), rutin (13) and β-sitosterol glucoside (32). It was noted that, Lutein (25) acted strongly on CB2 receptor and against leishmania, while myricitrin (8) inhibited *E. coli.*

## 6. Pharmacological activities

Pharmacological studies carried out on different extracts of *Bridelia ferruginea* have revealed various pharmacological properties of the plant. These include anti-inflammatory, anti-diabetic, antioxidant, antimicrobial, anti-infective, analgesic, antipyretic, repellent, insecticidal, fibroblast growth stimulation, diurectic and natriuretic activities summarized in Table 3. The studies support the traditional medicinal use of *B. ferruginea* in disease management and treatment.

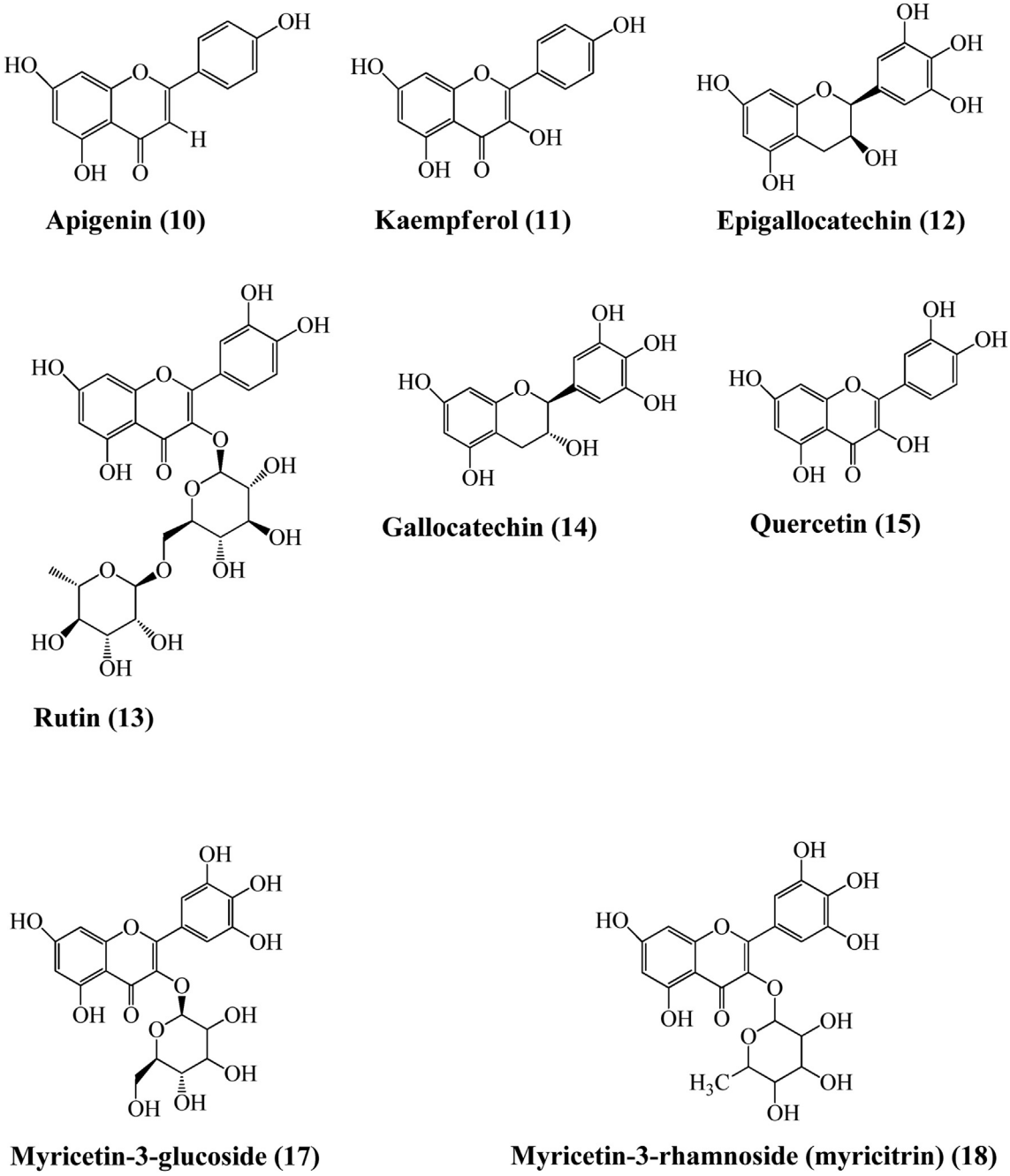



**Figure 5.** Other polyphenolic compounds isolated from *B. ferruginea.*

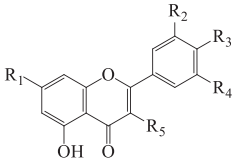
### *6.1. Anti-inflammatory properties*

There was significant inhibition of carrageenan-induced oedema in the rat paw of aqueous *B. ferruginea* stem bark extract treated rats (Olajide et al., 1999). 3 hours post carrageenan inhibitory values of oedema were 22, 22, 57 and 58% for doses of 10, 20, 40 and 80 mg/kg of aqueous stem bark extract, respectively whiles indomethacin (5 mg/kg) gave a 72% inhibition. In this test, extract ID50 was 36 mg/kg. For the mouse paw oedema test, a significant inhibition of oedema was not observed in comparison to the control group. Again, it showed a low activity as compared to that of the rat model although over a period of 5 h, a reduction of paw size was observed (Olajide et al., 1999). *B. ferruginea* extract showed a significant as well as concentration related inhibition of the dry weight of cotton pellet granuloma with values of inhibition of 20, 27, 34 and 43% for 10, 20, 40 and 80 mg/kg doses respectively. 80 mg/kg *B. ferruginea* extract exhibited similar degree of granuloma tissue formation inhibition as Hydrocortisone (Olajide et al., 1999).

Evaluation of the anti-inflammatory property of aqueous stem bark extract of *B. ferruginea* was carried out using tumor necrosis factor-alpha (TNFα) mediated models. The group of mice pre-treated with 10–80 mg/kg *B. ferruginea* extract demonstrated an inhibition of septic shock syndrome in a dose-dependent manner, with extract dose 80 mg/kg producing activity comparable to pentoxifylline (100 mg/kg). Animals pretreated with *B. ferruginea* or pentoxifylline caused statistically significant ($P < 0.05$) reduction in serum enzyme activity of alanine and aspartate aminotransferases. In the skin of mice, there was suppression of LPS-induced dye leakage at doses 10–80 mg/kg of *B. ferruginea* extract (Olajide et al., 2003).

The aqueous *B. ferruginea* extract at concentrations 10, 20, 40 and 80 mg/ear revealed significant (P‹ 0.05) ear oedema inhibition by 17.5,

**Table 2.** The moieties of compounds with parent structure (A) isolated from *B. ferruginea*.



A

| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|---|---|
| Quercetin-3-methyl ether (4) | OH | OH | OH | H | OMe |
| Quercetin-3,7,3′,4′-tetramethyl ether (5) | OMe | OMe | OMe | H | OMe |
| Myricetin-3′,4′,5′-trimethyl ether (6) | OH | OMe | OMe | OMe | OH |
| Myricetin-3,3′,4′,5′-tetramethyl ether (7) | OH | OMe | OMe | OMe | OMe |
| Myricetin (8) | OH | OH | OH | OH | OH |
| Quercetin-3-*O*-glucoside (9) | OH | OH | OH | H | O-β-D-glu |
| Kaempferide-3-O-β-D-glucoside (28) | OH | H | OMe | H | O-β-D-glu |
| Isomyricetin (29) | OH | OH | OH | OH | O-β-D-glu |
| Quercitrin (30) | OH | OH | OH | H | O-αl-rha |
| Isoquercetin (31) | OH | OH | OH | H | O-β-D-glu |

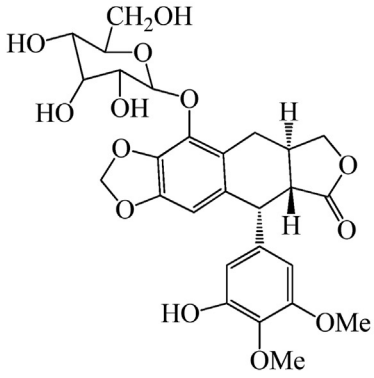
37.3, 63.5 and 87.3%, respectively. Indomethacin (100 mg/ear), the reference drug gave an inhibition of 85.7% (Olajide et al., 2000).

Foot thickness determination in animals is a method for assessing treatment efficacy and anti-inflammatory activity. A dose-related foot thickness reduction was detected in rats which had been treated with the extract each day for a 14-day period. At 80 mg/kg of extract, inhibition of arthritic swelling was at a percentage of 64.8, in comparison with the reference drug indomethacin, which produced a 71.2% inhibition at 1 mg/kg per day (Olajide et al., 2000).

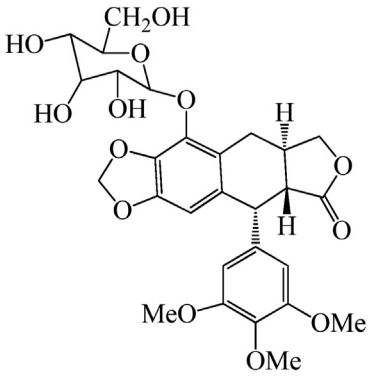
The mechanism(s) underlying *B. ferruginea's* anti-inflammatory activity was further determined using the extract's effect on vascular permeability. Aqueous extract of *B. ferruginea* reduced vesical oedema and vascular permeability increase by cyclophosphamide. The intensity of peritoneal inflammation by acetic acid in mice was also reduced demonstrating the ability of the extract to inhibit small blood vessels' permeability. The amount of dye leakage at highest concentration of extract, 80 mg/kg was 29.5μg and that of indomethacin 5 mg/kg, 21.0 μg (Olajide et al., 2000).

### 6.2. Anti-diabetic activity

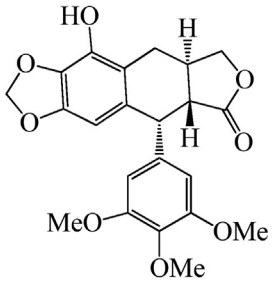
Semi ethanolic extract of *B. ferruginea* exhibited a dose dependent α-glucosidase inhibitory activity with a value of 1.4 ± 0,04 μg/mL as IC50. A higher α-glucosidase inhibitory activity was showed by the extract in comparison to acarbose the reference drug (IC50 726 ± 15 μg/mL) (Bothon et al., 2012). The methanolic leaf extract of *B. ferruginea* was tested by Onyenibe & Udogadi (2019) for its antidiabetic property using



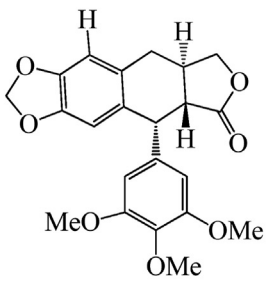
**5'-demethoxy-β-peltatin-5-O-β-D-glucopyranoside (19)**



**β-peltatin-5-O-β-D-glucopyranoside (20)**

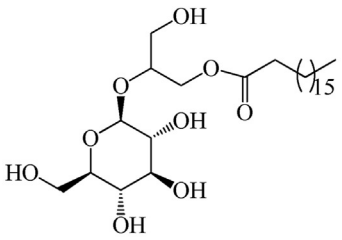


**β-peltatin (21)**

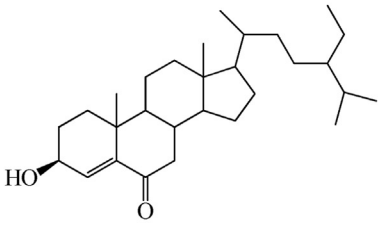


**Desoxypodophyllotoxin (22)**

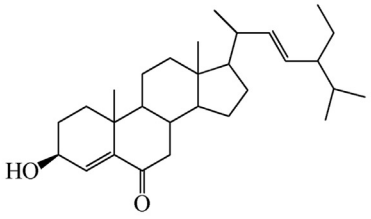
**Figure 6.** Lignans (**21**) and (**22**) and their derivatives (**19**) and (**20**) isolated from the roots of *B. ferruginea*.



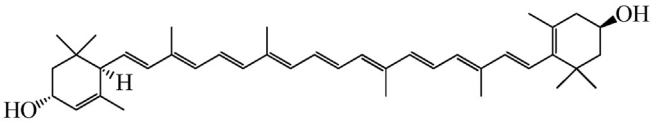

2-O-β-D-glucosylglycerol (23)



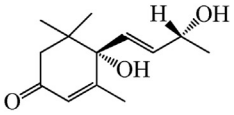

6β-hydroxy-(20R)-24-ethylcholest-4-en-3-one (24a)



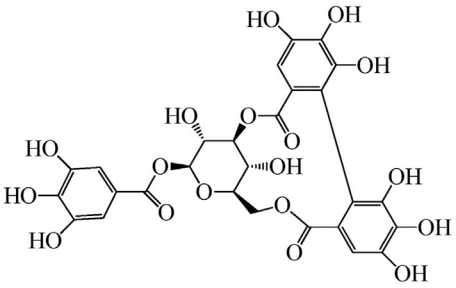

6β-hydroxy-(20R)-24-ethylcholest-4,22-dien-3-one (24b)



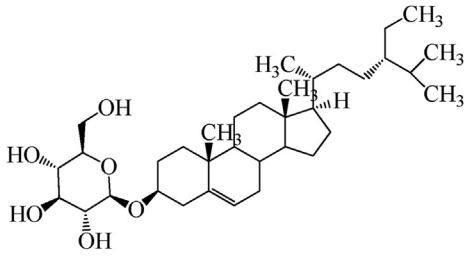

Lutein (25)




Vomifoliol (26)




Corilagin (27)




β-sitosterol glucoside (32)

**Figure 7.** Other compounds isolated from the methanolic leaf extract of *B. ferruginea*.

male wistar rats (140–160g). The rats were grouped into four sets (n = 5). Three of the groups received I.P. Streptozocin (50 mg/kg) for induction of hyperglycemia and the last served as the normal control. The level of blood sugar was measured employing ACCU- CHEK Glucometer and glycated hemoglobin (HBA1c) was analyzed using HPLC. The plant extract (50 mg/kg) significantly ($P < 0.05$) lowered the levels of blood sugar similar to glibenclamide (6 mg/kg). It was also observed that, the HBA1c (%) ranged from 4.6 ± 0.2 (Normal Control) to 11.8 ± 0.1 (Negative Control- Untreated diabetics). Treatment with *B. ferruginea* leaf extract (7.25 ± 1.6) and control drug, glibenclamide (7 ± 0.3) lowered significantly ($p < 0.05$) the levels of HBA1c (%) in relation to the negative control (11.8 ± 0.1). An observation made between treated and normal control groups was not significantly ($p > 0.05$) different (Onyenibe and Udogadi, 2019). In the oral glucose tolerance test (2 g/kg), sugar levels determined between 15-120 min later, showed a rapid clearance of blood sugar levels in the *B. ferruginea* extract (50 mg/kg) administered group in relation to the negative control (Onyenibe and Udogadi, 2019).

A single administered dose of *B. ferruginea* methanolic leaf extract significantly ($p < 0.05$) reduced Fasting blood sugar levels in sucrose-induced, glucose-intolerant rats. Again, blood glucose was significantly reduced by the extract (from 167 ± 23 mg/dL to 126 ± 5 mg/dL) in

**Table 3.** Pharmacological activities of *Bridelia ferruginea*.

| Pharmacological activity | Plant part | Extract tested | Model(s) | Dose range | Positive control | Result/Effect | Reference |
|---|---|---|---|---|---|---|---|
| Anti-inflammatory activity | Stem bark | Aqueous | Carrageenan-induced paw oedema | 10–80 mg/kg p.o. ID50 | Indometacin 5 mg/kg | Significant inhibition of carrageenan-induced paw oedema | (Olajide et al., 1999) |
| | Stem bark | Aqueous | Cotton pellet granuloma method | 10–80 mg/kg od | Hydrocortisone 15 mg/kg | Suppressed granulomatous tissue formation | (Olajide et al., 1999) |
| | Stem bark | Aqueous | Lipopolysaccharide (LPS)-induced septic shock method | 10–80 mg/kg | Pentoxifylline 100 mg/kg, i.p. | Reduction in death for groups of animals treated with *B. ferruginea*<br>Significant ($P < 0.05$) reduction in alanine and aspartate aminotransferases levels | (Olajide et al., 2003) |
| | Stem bark | Aqueous | LPS-induced vascular permeability method | 10–80 mg/kg | Pentoxifylline (100 mg/kg) | A concentration-related dye leakage inhibition was observed. 80 mg/kg of extract showed a similar degree of dye leakage inhibition as pentoxifylline (100 mg/kg) | (Olajide et al., 2003) |
| | Stem bark | Aqueous | Croton oil-induced ear oedema | 10-80 mg/ear | Indomethacin (100 μg/ear) | Dose-dependent inhibition of ear oedema | (Olajide et al., 2000) |
| | Stem bark | Aqueous | Adjuvant-induced arthritis | 10–80 mg/kg | Indomethacin (1 mg/kg) | Dose-related reduction in foot thickness was observed | (Olajide et al., 2000) |
| | Stem bark | Aqueous | Haemorrhagic cystitis induced by cyclophosphamide | 10–80 mg/kg | Indomethacin (5 mg/kg, p.o.) | Reduction in vesical oedema. Reduction in vascular permeability increase due to cyclophos- phamide | (Olajide et al., 2000) |
| | Stem bark | Aqueous | Acetic acid-induced vascular permeability | 10–80 mg/kg | Indomethacin (5 mg/kg, p.o.) | Reduced intensity of the peritoneal inflammation caused by acetic acid | (Olajide et al., 2000) |
| anti-diabetic activity | Bark | Semi ethanolic | a-glucosidase inhibition | | Acarbose | Higher α-glucoxidase inhibitory activity than acarbose | (Bothon et al., 2012) |
| | Leaves | Methanolic | Streptozotocin induced diabetes (50 mg/kg) and subsequent oral glucose tolerance test (2 g/kg) | 50 mg/kg | Glibenclamide 6 mg/kg | Significant ($P < 0.05$) decrease in blood sugar levels comparable to Glibenclamide. Relative to the negative control, the extract treated group had a rapid clearance in blood sugar level | (Onyenibe and Udogadi, 2019) |
| | Leaves | Methanolic | Induction of glucose intolerance and Glucose tolerance test | 50 mg/kg | Tolbutamide (50 mg/kg) and metformin (38 mg/kg) | Significant hypoglycaemic activity was observed (sucrose-fed, glucose-intolerant rats) | (Njamen et al., 2012) |

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**Table 3** (*continued*)

| Pharmacological activity | Plant part | Extract tested | Model(s) | Dose range | Positive control | Result/Effect | Reference |
|---|---|---|---|---|---|---|---|
| | Leaves | Aqueous | Alloxan induced diabetes test 100 mg/kg | 200, 400 and 800 mg/kg | | At dose 800 mg/kg, blood glucose level was significantly ($P < 0.05$) decreased (7th day of treatment) | (Aja, 2013) |
| | Leaves | Aqueous | Oral hyperglycemia test | 500–1500 mg/kg | Glibenclamide 10 mg/kg | Induction of hyperglyceamic effect | (Houndjo et al., 2017) |
| Antioxidant activity | Bark | Semi ethanolic | DPPH radical scavenging assay | | Ascorbic acid | Possesses antioxidant Property | (Bothon et al., 2012) |
| | Bark | Semi ethanolic | Ferric reducing/ antioxidant power (FRAP) assay | | | Possesses antioxidant Property | (Bothon et al., 2012) |
| | Bark | Semi ethanolic | Oxygen radical absorbance capacity (ORAC) assay | | | Possesses antioxidant property | (Bothon et al., 2012) |
| | Stem bark | Ethanolic | Lipid peroxidation assay | 3.3 μg/mL-39.6 μg/mL | | Inhibits thiobarbituric acid reactive species (TBARS) formation | (Oloyede and Babalola, 2012) |
| | Stem bark | Ethanolic | Iron chelation assay | (1–10 μg/mL) | | Chelates iron | (Oloyede and Babalola, 2012) |
| | Leaves | n-hexane and ethyl acetate (successive extraction)<br>β-*Amyrin acetate* fraction | DPPH antioxidant assay | | α-tocopherol and gallic acid separately | Quite significant IC50 value of 158.2 μg/mL compared to gallic acid, 201.1 μg/mL | (Fabiyi et al., 2012) |
| | Stem bark peelings | Ethanolic | DPPH antioxidant assay | 10–100 mg/mL | Ascorbic acid | Exhibits antioxidant activity | (Oloyede et al., 2014) |
| | Stem bark peelings | Ethyl acetate | DPPH antioxidant assay | 10–100 mg/mL | Ascorbic acid | Exhibits antioxidant activity | (Oloyede et al., 2014) |
| | Stem bark peelings | Aqueous | DPPH antioxidant assay | 10–100 mg/mL | Ascorbic acid | Exhibits antioxidant activity | (Oloyede et al., 2014) |
| | Leaves | Ethanolic | DPPH antioxidant assay | | L- ascorbic acid | Antioxidant activity with IC50 12.5 ± 0.3 μg/mL | (Adetutu et al., 2011) |
| | Leaves | Ethanolic | Hydrogen peroxide assay | 250–15.6 μg/mL | Catalase (250 IU/mL) | Protected cells from damage | (Adetutu et al., 2011) |
| Anti-microbial activity | Stem bark | Methanolic | Agar diffusion method and minimum inhibitory concentration (MIC) method | 10–250 mg/mL (Agar diffusion method)<br>0.5–100 mg/mL (MIC) | | Concentrations of 100–250 mg/mL showed antimicrobial activity against *S. aureus*, while 10-250mg showed activity against *C. albicans*. No inhibition was recorded for *E. coli, K. pneumoniae, B. anthracis, S. typhi, P. aeruginosa* and *P. mirabilis*. MIC values for *S. typhi* and *C. albicans* were 60 and 10 respectively | (Adebayo and Ishola, 2009) |

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**Table 3** (*continued*)

| Pharmacological activity | Plant part | Extract tested | Model(s) | Dose range | Positive control | Result/Effect | Reference |
|---|---|---|---|---|---|---|---|
| | Root | Methanolic | Agar diffusion method and minimum inhibitory concentration (MIC) method | 10–250 mg/mL (Agar diffusion method)<br>0.5–100 mg/mL (MIC) | | 50–250 mg/kg of extract showed inhibition against *E. coli* and *S. typhi*. 100–250 mg/mL showed activity for *P. mirabilis*, and *C. albicans*. 150–250 mg/mL for *S. aureus*. No activity was recorded for *K. pneumoniae, B. anthracis* and *P. aeruginosa*. MIC values for *E. coli, P. mirabilis, C. albicans* and *S.typhi.* was 40, 60, 80 and 60 respectively | (Adebayo and Ishola, 2009) |
| | Leaves | Methanolic | Minimum inhibitory concentration (MIC) method | 0.5–100 mg/mL | | No MIC values were recorded for the leaves against *E. coli, K. pneumoniae, S. aureus, S. typhi, P. aeruginosa, B. anthracis, C. albicans* and *P. mirabilis* | (Adebayo and Ishola, 2009) |
| | Stem bark | Methanolic | Agar well diffusion and minimum inhibitory concentration (MIC) using dental microbes | 50–400 mg/mL (Agar well diffusion method)<br>0.1–51.2 mg $mL^{-1}$ (MIC) | *Chlorhexidine gluconate* (0.625–5% w/v) (Agar well diffusion method) | Dose dependent antimicrobial activity against *P. aeruginosa, Streptococcus spp, S. aureus, L. acidophilus* but no activity against tested fungal strains. *Chlorhexidine gluconate* showed activity against all the tested bacteria and fungi. *B. ferruginea* methanolic extract showed highest MIC at a concentration of 25.6 mg/mL for *P. aeruginosa, S. aureus, L. acidophilus* and for *Streptococcus spp,* 0.1 mg/mL | (Orabueze et al., 2016) |
| | Fruit | Methanolic | Agar well diffusion<br>Minimum inhibitory concentration | 20 mg/mL | Streptomycin (1 mg/mL) | *B. subtilis* (NCIB 3610), *C. pyogenes* (LIO), *E. coli* (NCIB 86), *P. vulgaris* (NCIB67), *P. aeruginosa* NCIB (950), *S. dysenteriae* (LIO) and *S. aureus* (NCIB 8588) were found to be sensitive to the extract, however *K. pneumoniae* NCIB (418) and *C. albicans* (LIO) were not sensitive to both the extract and standard. Again, *E. coli* (NCIB 86) was not sensitive to the standard. The MIC ranged from 0.63–10.0 mg/mL | (Akinpelu and Olorunmola, 2000) |

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**Table 3** (*continued*)

| Pharmacological activity | Plant part | Extract tested | Model(s) | Dose range | Positive control | Result/Effect | Reference |
|---|---|---|---|---|---|---|---|
| | Leaves | Methanolic | Agar disc diffusion method<br>MIC | 1 mg of extract for 10 mL of Tween 80 | Streptomycin (10 μg), erhytromycin (5 μg), tetracycline (10 μg), penicillin (1 i.u.), chloramphenicol (10 μg) | Growth inhibition of *P. frutescens* and *S. faecalis*<br>MIC (9 ± 0.7–10 ± 2 mg/mL) | (Talla et al., 2002) |
| | Leaves | Ethyl acetate | Agar disc diffusion method<br>MIC | 1 mg of extract for 10 mL of Tween 80 | Streptomycin (10 μg), erhytromycin (5 μg), tetracycline (10 μg), penicillin (1 i.u.), chloramphenicol (10 μg) | Growth of *B. subtilis, S. aureus* and *S. faecalis* was inhibited. No activity against *P. frutescens and E. coli*<br>MIC (5 ± 0.9–9.5 ± 2 mg/mL) | (Talla et al., 2002) |
| | Leaves | Hexane | Agar disc diffusion method<br>MIC | 1 mg of extract for 10 mL of Tween 80 | Streptomycin (10 μg), erhytromycin (5 μg), tetracycline (10 μg), penicillin (1 i.u.), chloramphenicol (10 μg) | Growth of *B. subtilis, S. aureus, S. faecalis, P. frutescens* and *E. coli* were inhibited<br>MIC (4 ± 1–13 ± 1 mg/mL) | (Talla et al., 2002) |
| | Bark | Ethanolic | Agar well diffusion method<br>MIC | 100 μL (agar well)<br>20–100% (MIC) | Ciprofloxacin disc | *Pseudomonas aeruginosa, Bacillus sp., Actinobacillus sp., Streptococcus pyogenes* ATCC 19615, *Staphylococcus aureus* and *Klebsiella pneumonia* ATCC 10031 were sensitive to the extract | (Akinsete & Adebayo-tayo, 2017) |
| Trypanocidal activity | Stem bark | Methanolic | Parasitaemia determination | 20 mg/kg | | Parasite (*Trypanosoma brucei*) reduction in infected rats treated with the extract | (Ekanem et al., 2008) |
| Anti-infective activity | Ripe Stem bark | Aqueous | Bacterial sensitivity testing | 0.1 ml | Ceftazidime 30 μg, ceftriaxone 30 μg, gentamicin 10 μg | Extract possesses antifungal anti-bacterial properties | (Dada-Adegbola et al., 2010) |
| Anti-typhoid activity | Stem bark | Ethanolic | Anti-typhoid sensitivity test | 50–5000 mg/mL | Ciprofloxacin | Varied zones of growth inhibition observed in the clinical and typed isolates | (Dada and Akinyele, 2020) |
| | Stem bark | Ethanolic | MIC, MBC | 50–5000 mg/mL | Ciprofloxacin | The MIC, MBC values were 300, 300 and 2600, 1000 mg/mL for clinical and typed *S. typhi* respectively | (Dada and Akinyele, 2020) |
| | Stem bark | Ethanolic | *In vivo* assay | 50–5000 mg/kg | Ciprofloxacin | Decrease in *S. typhi* shed | (Dada and Akinyele, 2020) |
| Anthelminthic activity | Leaves | Acetone<br>Methanolic | Egg hatch assay | 75–2400 μg/mL | Thiabendazole at 500 μg/mL | The methanol extract had a dose dependent effect on egg hatching of *Haemonchus contortus* however the reduction in egg hatching for its acetone extract was not dose dependent | (Alowanou et al., 2019) |
| | Leaves | Acetone | | 75–1200 μg/mL | Levamisole at 250 μg/mL | | (Alowanou et al., 2019) |

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**Table 3** (*continued*)

| Pharmacological activity | Plant part | Extract tested | Model(s) | Dose range | Positive control | Result/Effect | Reference |
|---|---|---|---|---|---|---|---|
| | | Methanolic | Larval migration inhibition assay | | | Non-concentration dependent reduction ($p < 0.05$) in the larval migration of *H. contortus* with inhibition values from 17.36 to 67.52% however, levamisole exhibited a higher larval migration inhibition of 92.6% | |
| | Leaves | Acetone<br>Methanolic | Adult worm motility inhibition assay | 75–2400 μg/mL | Levamisole | *B. ferruginea* and levamisole caused significant ($p < 0.001$) adult *H. contortus* motility reduction in a non-concentration dependent manner | (Alowanou et al., 2019) |
| | Stem bark | Aqueous | Curative test | 100–400 mg/kg | Chloroquine 10 mg/kg | Possesses considerable antiplasmodial activity | (Mbah et al., 2012) |
| Analgesic activity | Stem bark | Aqueous | Acetic acid induced writhing response method | 25, 50 and 100 mg/kg | Aspirin 150 mg/kg | Significant ($P < 0.05$) and dose dependent decrease in the number of writhing movements | (Akuodor et al., 2011) |
| | Stem bark | Aqueous | Tail immersion test | 25, 50 and 100 mg/kg | Morphine 10 mg/kg | 100 mg/kg extract produced a nociceptic effect comparable to morphine 10 mg/kg | (Akuodor et al., 2011) |
| | Stem bark | Aqueous | Writhing test induced by acetic acid | 10–80 mg/kg | Indomethacin (5 mg/kg, p.o.) | Possesses analgesic activity | (Olajide et al., 2000) |
| Antipyretic activity | Stem bark | Aqueous | Yeast-induced hyperpyrexia method | 25, 50 and 100 mg/kg | Drugamol 20 mg/kg, i.p | Significant rectal temperature reduction | (Akuodor et al., 2011) |
| | Stem bark | Aqueous | Yeast-induced hyperpyrexia | 10–80 mg/kg orally | Indomethacin (5 mg/kg, p.o.) | 40 and 80 mg/kg of extract exhibited some antipyretic effect | (Olajide et al., 2000) |
| Repellent and insecticidal activities | Leaves | Aqueous | Contact toxicity by topical application and Fumigation toxicity bioassay | 2.5, 5.0, and 7.5% | | 7.5% exhibits repellent activity<br>Possesses insecticidal activity | (Loko et al., 2017) |
| | Leaves | Acetone | Contact toxicity by topical application and Fumigation toxicity bioassay | 2.5, 5.0, and 7.5% | | 5% exhibits repellent activity<br>Possesses insecticidal activity | (Loko et al., 2017) |
| | Leaves | Ethanolic | Contact toxicity by topical application and Fumigation toxicity bioassay | 2.5, 5.0, and 7.5% | | Possesses repellent and insecticidal activity | (Loko et al., 2017) |
| | Leaves | Methanolic | Contact toxicity by topical application and Fumigation toxicity bioassay | 2.5, 5.0, and 7.5% | | 5% exhibits repellent activity<br>Possesses insecticidal activity | (Loko et al., 2017) |

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**Table 3** (*continued*)

| Pharmacological activity | Plant part | Extract tested | Model(s) | Dose range | Positive control | Result/Effect | Reference |
|---|---|---|---|---|---|---|---|
| | Leaves | Propanolic | Contact toxicity by topical application and Fumigation toxicity bioassay | 2.5, 5.0, and 7.5% | | 5 and 7.5% have repellent activity. Possesses insecticidal activity | (Loko et al., 2017) |
| Cytotoxicity | Leaves | n-hexane and ethyl acetate (successive extraction) | Brine shrimp assay | | Cyclophosphamide | $LC_{50}$ values of 319 μg/mL and 5.86 μg/mL for acute and lethal doses respectively | (Fabiyi et al., 2012) |
| | | β-*Amyrin acetate* fraction | | | | | |
| Fibroblast growth stimulation activity | Leaves | Ethanolic | *In vitro* fibroblast growth stimulation test | 1–60 μg/mL | DMEM/10% FCS | 5 μg/mL showed significant ($p < 0.001$) FS5 fibroblasts growth | (Adetutu et al., 2011) |
| Diuretic and Natriuretic activity | Stem bark | Aqueous | Volumetric urinary excretion | 10 mg/kg | Furosemide 10 mg/kg, hydrochlorothiazide 15 mg/kg and spironolactone 20 mg/kg | Significant water overload elimination | (Nene-Bi et al., 2012). |

glucose intolerant rats after a 6-day treatment. The proposed mechanism of action of *B. ferruginea* was suggested as relating to insulin sensitivity improvement (Njamen et al., 2012).

Aqueous *Bridelia ferruginea* leaves extract effect on alloxan induced diabetic rats was a significantly ($P < 0.05$) reduced blood glucose level on day 7, of treatment at highest dose (800 mg/kg). Bioactive compounds like flavonoid, terpenoids, glycosides and alkaloids present may be contributing to its hyperglycaemic effects (Aja, 2013).

*Bridelia ferruginea* aqueous leaf extract induced antihyperglycaemic effect at the 60$^{th}$ minute with a reduction rate of 1.27% at concentrations of 500 and 1000 mg/kg; and this continues until the 300$^{th}$ minute with the maximum value occurring at 120 minutes (23.66%). At dose 1500 mg/kg however, the antihyperglycaemic property was observed only at the 120$^{th}$ minute with 6.11% reduction rate (Houndjo et al., 2017).

### 6.3. Antioxidant activity

DPPH radical scavenging assay of the semi ethanolic *B. ferruginea* bark extract showed an IC50 value of 5 ± 0.3 μg/mL whiles the IC50 of L-ascorbic acid, the positive control was 1.25 ± 0.07 μg/mL. *B. ferruginea* had 4.4 ± 0.06 μmol Fe II/g DW for the FRAP value. *B. ferruginea* had 5133 ± 161 μmol Trolox/g DW for the ORAC value (Bothon et al., 2012).

Antioxidant properties of the ethanol leaves extract of *B. ferruginea* were assessed using the lipid peroxidation and iron chelation assays. The extracts (3.3 μg/mL-39.6 μg/mL) had different antioxidant potential, with 36.9 μg/mL of the extract being most potent with inhibition at 54.16% for the brain and 82.46% for the liver. The ability for the extract to chelate iron was assessed using extract concentration ranging from 1-10 μg/mL. At dose 2 μg/mL, the extract was most potent and very effective against iron (Oloyede and Babalola, 2012).

*A beta*-amyrin acetate fraction obtained from the successive extraction of the dried powdered leaves was used for an antioxidant assay. A higher antioxidant potential with an IC50 value of 158.2 μg/mL compared to gallic acid with an IC50 of 201.1 μg/mL and α- Tocopherol which had IC50 of 4.577 μg/mL was obtained for *B. ferruginea* (Fabiyi et al., 2012).

The ethanolic, aqueous and ethyl acetate stem bark extracts of *B. ferruginea* exhibited a strong antioxidant activity in the order of decreasing degree; Aqueous > Ethanolic > Ethyl Acetate. A higher IC50 was exhibited by the aqueous extract (0.85 mg/mL) compared to 1.34 and 1.41 mg/mL for the ethanolic and ethyl acetate extract respectively hence conferring highest antioxidant activity to the aqueous extract (Oloyede et al., 2014).

The ethanolic leaf extract revealed the maximum protection against $FS_5$ cells damage by $H_2O_2$ which was similar to catalase (82% at 250 μg/mL). The ethanolic extract of the leaves possessed antioxidant activity with an IC50 of 12.5 ± 0.3 μg/mL comparable to L-ascorbic acid with 7.3 ± 0.1 μg/mL using DPPH assay (Adetutu et al., 2011).

### 6.4. Antimicrobial and anti-infective activity

The methanolic extracts of *B. ferruginea* were screened for its antimicrobial properties. The extracts had a varied range of activity on *Escherichia coli, Proteus mirabilis, Staphylococcus aureus, Salmonella typhi* and *Candida albicans*. At different concentrations of 40, 100, 60, 60, and 80 mg/mL, the root extracts caused inhibition of growth of *E. coli, S. aureus, S. typhi, P. mirabilis* and *C. albicans* respectively. An MIC of 60 mg/mL on *S. typhi* as well as 10 mg/mL on *C. albicans* was recorded for the stem bark. The methanolic extract of the leaves exhibited no antimicrobial activity against the organisms (Adebayo and Ishola, 2009).

The methanolic stem bark extract was investigated for efficacy against dental microorganisms to validate folklore use of *B. ferruginea* in oral infections (Orabueze et al., 2016). At concentrations ranging from 50 mg/mL to 400 mg/mL, *B. ferruginea* extract showed a dose dependent antibacterial sensitivity against clinical oral isolates of *Streptococcus spp, Lactobacillus acidophilus, Staphylococcus aureus* and *Pseudomonas*

*aeruginosa* with inhibitory zones ranging from 25.00 – 34.00; 19.50–27.00; 16.00–22.50; and 15.25–22.25 mm respectively. The extracts however showed no activity against the tested strains of fungi (*Aspergillus fumigatus* and *Candida albicans*). *Chlorhexidine gluconate* (standard) at concentrations ranging from 0.625 to 5% showed antibacterial and antifungal effect with zones of inhibition ranging from 16.00 – 26.50; 12.00–18.50; 28.00–35.00; 33.00–38.00; 32.00–38.00 and 31.00–39.00 for *Candida albicans, Aspergillus fumigatus, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus spp* and *Lactobacillus acidophilus* respectively. The MIC of *B. ferruginea* against *Streptococcus spp* was calculated as 0.1 mg $mL^{-1}$ and 25.6 mg $mL^{-1}$ for *S. aureus, L. acidophilus and P. aeruginosa* (Orabueze et al., 2016).

*A major* problem on the production and health of small ruminants are gastrointestinal nematodes (Alowanou et al., 2019). A study to evaluate the effectiveness of *Bridelia ferruginea* as an anthelmintic agent against *Haemonchus contortus* an abomasal nematode in small ruminants was conducted. The ability of methanol and acetone extracts of *B. ferruginea* to cause disruption of the life cycle of *H. contortus* was studied using the egg hatch, larval migration, and adult worm motility assays. Methanolic extract of *B. ferruginea* at doses 75 and 2400 $\mu g/mL^{-1}$ exhibited concentration dependent effects on egg hatching where as its acetone extract effects were not concentration dependent (Alowanou et al., 2019). The ovicidal activity observed may be attributed to the penetration of actives in the extract into the eggshell which interferes with blastomeres segmentation or cause larvae paralysis inside embryonated eggs (Wabo et al., 2011). The results of the leaf extracts on stage three larvae, as determined by the larval migration inhibition test of *H. contortus*, were concentration independent. A significantly reduced ($p < 0.05$) larval migration was observed with inhibition ranging from 17.36 to 67.52%. However, levamisole exhibited a higher larval migration inhibition of 92.6%. A non-concentration dependent effect was observed in the extracts ability to affect the adult worm mobility (Alowanou et al., 2019).

The fruit was investigated by agar well diffusion method for its antimicrobial property and the MICs determined (Akinpelu and Olorunmola, 2000). At an extract concentration of 20 mg/ml *B. subtilis* (NCIB 3610), *C. pyogenes* (LIO), *E. coli* (NCIB 86), *P. vulgaris* (NCIB67), *P. aeruginosa* NCIB (950), *S. dysenteriae* (LIO) and *S. aureus* (NCIB 8588) were found to be sensitive to the extract with zones of inhibitions 12, 14, 20, 13, 12, 18 and 18mm respectively. However, *K. pneumoniae* NCIB (418) and *C. albicans* (LIO) were not sensitive to both the extract and Streptomycin (1 mg/mL). Again, *E. coli* (NCIB 86) was not sensitive to Streptomycin (1 mg/mL). The MIC ranged from 0.63 (*S. dysenteriae* (LIO)) – 10.0 mg/mL (*P. aeruginosa* NCIB (950)). This outcome may validate some traditional uses of *B. ferruginea* (Akinpelu and Olorunmola, 2000).

Hexane, ethyl acetate and methanol extracts of *B. ferruginea* had their antimicrobial activity against *Streptococcus faecalis, Echerichia coli, Bacillus subtilis, Staphylococcus aureus* and *Pseudomonas frutescens* tested for. Hexane extracts inhibited the growth of all five organisms. The ethyl acetate was promising only against *B. subtilis, S. aureus* and *S. faecalis* whereas the methanolic extract did for *Pseudomonas frutescens* and *Streptococcus faecalis*. With reference to the MICs determined, the effect of the ethyl acetate extract against *Streptococcus faecalis* ($5 \pm 0.9$ mg/mL) and *Staphylococcus aureus* ($8 \pm 1.5$ mg/mL), of methanolic extract against *Streptococcus faecalis* ($9 \pm 0.7$ mg/mL) and of hexane extract against *Bacillus subtilis* ($8 \pm 0.5$ mg/mL), *S. faecalis* ($4 \pm 1$ mg/mL), were the most note worthy (Talla et al., 2002).

The ethanolic bark extract was effective against *Pseudomonas aeruginosa, Bacillus sp., Staphylococcus aureus, Actinobacillus sp., Streptococcus pyogenes* ATCC 19615 *and Klebsiella pneumonia* ATCC 10031 with inhibitory growth zones from 15 – 23 mm. Some test bacteria that demonstrated susceptibility to the positive control (ciprofloxacin), were highly susceptible to the crude extract. The MIC of the crude extract against all the organisms was 20% (20 µl/mL). On the other hand, some test organisms that exhibited resistance to ciprofloxacin, the positive control, were highly susceptible to the extract of *B. ferruginea* confirming *B. ferruginea*'s broad spectrum activity. After partitioning the ethanolic bark extract into fractions, different antibacterial activities were observed. Ethyl-acetate fraction showed the maximum growth inhibition against all the organisms used with inhibitory values from 11 - 18 mm. This was followed by dichloromethane fraction on four of the pathogenic organisms (6–11 mm) and the hexane fraction on two of the organisms (7–11 mm) (Akinsete & Adebayo-tayo, 2017).

The trypanocidal activity of the methanolic stem back extract of *B. ferrugenia* was evaluated in vivo. A 20 mg/kg daily dose of methanolic stem bark extract was intraperitoneally administered at 72 h post-infection with *Trypanosoma brucei*. The infected-untreated group experienced a continuous rise in parasite count. The infected group treated with the methanolic stem bark extract recorded a reduction in parasite percentage. A reduction of 11%, 40%, 54%, 76% and 64% was recorded on days 5, 6, 7, 8 and 9 respectively for the infected-treated group. Day 8, post infection recorded the peak percentage parasite reduction of 76%. Overall, treatment with the extract extended the lives of the animals by 2 days compared to group that was infected and untreated (Ekanem et al., 2008).

*Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus* and *Proteus mirabilis* showed varying degree of susceptibility to the aqueous matured stem bark of *B. ferruginea* ranging from diameter of inhibition 10–20 mm and 18–24 mm in the gram-negative and gram-positive bacteria respectively. Activity against both Gram positive and Gram-negative bacterial isolates was exhibited by the standard antimicrobial agents (Ceftriaxone 12–30 mm, Gentamicin 0–28 mm). *Candida* species showed varied susceptibility. *Candida albicans* had a diameter ranging from 18–25 mm. *Candida tropicalis, Candida krusei* and *Candida glabrata* 22mm, 20mm and 24mm respectively. Vaginal isolates of the *Candida spp* showed better response of 22–25mm compared to that of the throat and blood stream with zone of inhibition of 18 mm (Dada-Adegbola et al., 2010).

The anti-typhoid activities of *Bridelia ferruginea* ethanolic stem bark extract in *Salmonella typhi* infected albino rats to validate it traditional use in some rural parts and cities in Nigeria was investigated in-vivo. The anti-typhoid sensitivity pattern of *S. typhi* (clinical and typed isolates) to ethanolic extract exhibited a concentration dependent degree of susceptibility. The extract was found to be bacteriostatic (MIC) and bactericidal (MBC) at 300, 300 and 2600, 1000 mg/mL in clinical and typed isolates respectively. There was a decreasing shed in *S. typhi* in groups treated with the extract and Ciprofloxacin (Dada and Akinyele, 2020).

The anthelmintic activities of aqueous stem back (peelings) extract of *Bridelia ferruginea* were investigated against *Pheretima posthuman*, a Nigerian earthworm. The extract (25–100 mg/mL) displayed concentration dependent anthelmintic activity. The time taken for earthworm paralysis and death at the highest concentration (100 mg/mL) for the extract was $11.01 \pm 0.55$ and $82.22 \pm 0.47$ min whiles standard (Piperazine citrate) was $10.95 \pm 0.13$ and $37.20 \pm 0.14$ min (Adebayo and Joshua, 2018).

Mice infected with *Plasmodium berghei* produced reduction in mean parasitemia in a concentration dependent manner when administered with the aqueous extract of the stem bark however, lesser than chloroquine (standard). A daily increase in parasitemia was showed by the negative control group. A mean survival time of 30 days was recorded for Chloroquine (10 mg/kg), $9.0 \pm 2.0$ days for negative control, whereas $25.5 \pm 1.2$, $28.0 \pm 0.9$ and $29.2 \pm 0.5$ days was observed for stem bark extract doses of 100, 200, and 400 mg/kg respectively (Mbah et al., 2012).

### 6.5. Analgesic activity

Aqueous *B. ferruginea* stem bark extract (25, 50 and 100 mg/kg) reduced reasonably the duration of writhing. 100 mg/kg of extract and aspirin gave a percentage writhing inhibition of 88.35 and 82.55% respectively. With the tail immersion test, the highest nociceptic activity

occurred at dose 100 mg/kg comparable to morphine at 10 mg/kg (Akuodor et al., 2011).

Aqueous *B. ferruginea* stem bark extract produced notable effect for writhing test in mice induced by acetic acid which indicates analgesic activity (Olajide et al., 2000).

### 6.6. Antipyretic activity

In yeast-provoked rise of body temperature in rats, *B. ferruginea* had a significant antipyretic effect. However, this was not comparable to drugamol (standard drug) (Akuodor et al., 2011).

40 and 80 mg/kg of *B. ferruginea* extract demonstrated some antipyretic activity. Lowering of rectal temperatures of yeast induced hyperthermic mice was observed (Olajide et al., 2000).

### 6.7. Repellent and insecticidal activities

*B. ferruginea* powder has been demonstrated to possess non dose dependent repellent activity against *D. porcellus*. Powder concentration of 2 and 10%w/w belong to the repellency class II while 5 and 7%w/w belong to repellency class III. The repellent activity of Antouka (synthetic insecticide) on *D. porcellus* was greater compared to the plant powders after the first- and twelfth-hour post treatment. Their recorded $RD_{50}$ values were 5.4% and 5.9% (w/w) respectively. The level of the repellent activity of the *B. ferruginea* leaf extracts increased with time. Aqueous extract (7.5%), acetone extract (5%), ethanol extract (2%, 5% and 7.5%), methanol extract (5%) and propanol extract (5% and 7.5%) showed *D. porcellus* repellent activities (Loko et al., 2017).

### 6.8. Cytotoxicity

β-*Amyrin acetate* fraction of *B. ferruginea* leaf extract revealed cytotoxic potential. The $LC_{50}$ value for acute dose was 319 μg/mL and that for lethal dose was 5.86 μg/mL. Compared to the standard (cyclophosphamide $LC_{50}$ value of 2506 μg/mL), β-*Amyrin acetate* fraction showed extreme toxicity indicating a potential source of cytotoxic agents in cancer chemotherapy (Fabiyi et al., 2012).

### 6.9. Fibroblast growth stimulation

Stimulating fibroblast cell growth can be used to test for wound healing activity. *Bridelia ferruginea* ethanolic leaf extract on fibroblasts proliferation of human dermal skin presented a significant response ($p < 0.001$) that was biphasic with increase in growth at concentrations up to 5 μg/mL (28% increase). The growth of fibroblast reduced to levels comparable to that of cells grown in minimal growth factors between 15 and 60 μg/mL. An increase in toxic constituents may possibly account for this occurrence. The possibility of cytotoxicity shown by the crude ethanolic extract at concentrations higher than 5 μg/mL implies that the use of higher concentrations in disease management should be done with caution (Adetutu et al., 2011).

### 6.10. Diuretic and natriuretic activity

*B. ferruginea* used traditionally for managing hypertension and as a diuretic was evaluated for its diuretic and natriuretic activity. 24 hours after intraperitoneal administration in the rat, the aqueous stem bark extract showed a significant water overload elimination ($p<0.01$). The extract increased natriuresis and kaliuresis respectively by 55.71% ($p<0.01$) and of 49.80 ($p<0.01$). There was a significant ($p<0.01$) increase in plasma sodium level (natremy) (Nene-Bi et al., 2012).

### 6.11. Toxicity

*B. ferruginea* aqueous stem bark extract was administered daily for 90 days to assess its effect on general behaviour, mortality, body weight, as well as food and water consumption in Wistar rats. Blood was collected after the period of administration to assess the extract's effect on hematological and biochemical parameters, and organs were harvested for histopathological studies. Extract concentrations between 100 and 400 mg/kg showed no major toxicity signs with no mortality and no significant body weight changes. Significant changes ($p < 0.05$, $p < 0.01$, $p < 0.001$) occurred in food and water intake. Hematological and biochemical parameters were not significantly ($p > 0.05$) modified, however at the highest tested dose, 400 mg/kg, there was a significant ($p < 0.05$) decrease in the relative kidney weight in female group with no indications of tissue damage in the histopathological analysis (Nene-Bi et al., 2016). Again, the aqueous stem bark extract (250–4000 mg/mL) administered orally and intraperitoneally in an acute toxicity study exhibited no significant signs of toxicity and no mortality with $LD_{50}$ estimated as >4000 mg/kg. Aqueous extract at higher doses of 1000, 2000 and 4000 mg/kg orally administered for 60days to examine its effects on biochemical, hematological and histopathological parameters was studied. Differences observed in organ and animal weights, biological and hematological parameters were not significant ($p \geq 0.05$) however, lipid peroxidation level increased significantly ($p < 0.05$) and sperm count decreased for the treated group as compared to the control group (Awodele et al., 2015).

*B. ferruginea* stem bark extract was tested for its safety in an acute toxicity assay in mice at dose 10–5000 mg/kg p. o. No mortality was recorded when mice were observed for 24 h post hot water extract oral administration even at the highest tested dose, giving the estimated $LD_{50}$ to >5000 mg/kg (Mbah et al., 2012). Ezike et al. (2011) also estimated the oral $LD_{50}$ of the methanolic stem bark extract to be 2,154 mg/kg in an acute toxicity study in mice. The effect of *B. ferruginea* stem bark hydro-alcoholic extract, orally administered repeatedly for a 28-day period at concentrations of 500 and 1000 mg/kg on wistar rats was investigated. It was reported no significant changes were observed in hematological and biochemical parameters studied except for creatine kinase, with no architectural changes in organ histological data (Dél et al., 2020).

The safety of hydro-ethanol root bark extract was also assessed on Balb/c mice and male Wistar rats (Bakoma et al., 2013). Orally administered extract at 2000 and 5000 mg/kg in an acute toxicity study caused no significantly visible signs of toxicity or mortality in test animals. The extract administered to Wistar rats for 28 consecutive days at 250, 500 and 1000 mg/kg caused no mortality, with no significant differences observed in relative organ weights, biochemical and histological studied parameters when treated animals were compared to controls. The acute and sub-acute toxicity effects of the leaf of *B. ferruginea* on male wistar rats has been evaluated (Owoade et al., 2018). In the acute study, $LD_{50}$ value of >2000 mg/kg was reported. The methanolic extract administered for 28 days at 200, 400 and 600 mg/kg in a sub-acute study showed no significant changes in blood lipids, biochemical and hematological parameters, with nonlipotoxic dyslipidaemia effect observed in some vital organs. The extracts administered for 28 days at the respective doses reduced the level of cardiac cholesterol by 37.16%, 39.36% and 17.64% and pulmonary cholesterol levels by 22.17%, 28.08% and 6.24 %. Pulmonary triglyceride level was dose-dependently decreased by 16.17, 29.14 and 54.25% respectively.

The effect of wastewater treated with 2.5% (w/v) methanolic crude extract of *B. ferruginea* on rat's kidney, was assessed at different times (0–96 h). In a histological examination, the kidneys of rats given the extract-treated wastewater showed an acute pyelonephritis with oedematous infiltration of cells throughout the duration of the experiment, suggesting potential damage to the kidneys, which may be as a result of unspent tannins of the extract in the water as the contact time increases (Kolawole et al., 2009). In a study to determine acute toxicity of *B. ferruginea* aqueous stem bark extract, Ikechukwu et al. (2015), reported $LC_{50}$ of the extract at 24, 48, 72 and 96 h in *Clarias garriepinus*. The experiment was done in a semi-static bowl with the fishes being exposed to 870, 750, 625, 500, 375, 250 and 125 mg $L^{-1}$ of the aqueous stem bark

extract *of B. ferruginea*. The $LC_{50}$ values of the aqueous extract at 24, 48, 72 and 96 h were 199.72, 165.76, 149.78 and 139.09 mg/L respectively, with highest (100%) mortality at 625 mg/L and lowest mortality (50%) at 250 mg/L after 96 h of exposure.

## 7. Conclusion

*Bridelia ferruginea* has been widely used in the management of various disease conditions in traditional and folklore medicine. Pharmacological studies performed on the various parts of this plant support most of these claims with a few traditional uses yet to be proved. The study indicates the enormous potential of *B. ferruginea* with anti-inflammatory, anti-diabetic, antioxidant, antimicrobial, antipyretic, analgesic, fibroblast growth stimulation, anthelmintic, antityphoid, diuretic and natriuretic properties although some of the mechanisms involved are still unclear. Due to its wide distribution, richness of the phytochemicals present and folklore uses, *Bridelia ferruginea* can be useful in lead compound discovery. Although *B. ferruginea* has been widely studied, countless potential for further investigation still remains.

## Declarations

### *Author contribution statement*

Genevieve Naana Yeboah: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Frederick William Akuffo Owusu: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Mary-Ann Archer; Michael Odoi Kyene; Susana Oteng Mintah: Analyzed and interpreted the data; Wrote the paper.

Doris Kumadoh; Frederick Ayertey; Peter Atta-Adjei Junior: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Alfred Ampomah Appiah: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

### *Funding statement*

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### *Data availability statement*

Data included in article/supplementary material/referenced in article.

### *Declaration of interest's statement*

The authors declare no conflict of interest.

### *Additional information*

No additional information is available for this paper.

## Acknowledgements

The authors are grateful to Kwadwo Asante and Godwin Danso of the Department of Pharmaceutics and Quality Control of CPMR for their contribution.

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