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ARTICLE

Ethnomedicinal Uses, Antidiabetic, Antioxidant and Anti-inflammatory Activity of *Gmelina arborea* Roxb. and Its Bioactive Compounds: A Review

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Abstract: *Gmelina arborea* Roxb. (Family: Verbenaceae) is a medicinal plant that has been used in the treatment of diabetes mellitus (DM) since ancient times. Decoctions prepared from various parts of *G. arborea* are used in traditional systems of medicine as a remedy against DM and various other diseases. The present review describes the antidiabetic, antioxidant and anti-inflammatory properties of *G. arborea* extracts and their bioactive phytoconstituents that are likely to contribute to antidiabetic properties and their therapeutic importance in the management of diabetes. A comprehensive literature search was conducted using PubMed, ScienceDirect, Semantic Scholar and Google Scholar databases. Studies published from 1970 to 2021 were considered in this review. Out of the 157 results, 34 articles were excluded being duplications and 58 articles were excluded being outside the scope of this review. The remaining 65 articles were considered in this review. The *in vitro* and *in vivo* assays reveal the therapeutic potential of *G. arborea* in terms of antidiabetic, antioxidant and anti-inflammatory properties, indicating that the plant is a valuable source for developing non-toxic herbal formulations to manage DM.

Keywords: Antidiabetic activity, Anti-inflammatory activity, Antioxidant activity, Diabetes mellitus, *Gmelina arborea*.

Introduction

The prevalence of diabetes mellitus (DM) has increased globally during the last few decades. According to the International Diabetes Federation (IDF) diabetes atlas, approximately 463 million adults (20–79 years) are living with DM and of them, 79% of adults are from low- and middle-income countries[1]. DM leads to the development of complications, such as blindness, cardiovascular disease, kidney failure, lower limb amputation and eventually death; diabetes-related mortality was 3.7 million in 2019[2]. It is estimated that the number of patients with DM would increase to 700 million patients by 2045[1].

DM is a complex metabolic disorder marked by elevated blood glucose concentration (hyperglycemia) resulting from either insulin deficiency, insulin resistance or both. The three main types of diabetes are type 1, type 2 and gestational DM. Type 1 DM, which is the most common in childhood and early adulthood, results from pancreatic β-cell destruction and absolute insulin deficiency. Type 2 DM is the most prevalent type and is associated with various degrees of β-cell dysfunction and insulin resistance. Gestational DM refers to hyperglycemia diagnosed during pregnancy[3,4].

Hyperglycemia is the main clinical characteristic feature of DM and plays a key role in the development of diabetic complications[5]. Endoplasmic reticulum stress, mitochondrial dysfunction and inflammation associated with DM are closely related to β-cell dysfunction and insulin resistance[6].

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Oxidative stress plays a major role in the pathogenesis of DM[7]. Oxidative stress is generally described as the inadequate ability to fend off and detoxify reactive oxygen species (ROSs) and associated free radicals with the loss of antioxidant defenses[8]. There is a significant increase in damage to cells by ROSs and abnormalities in antioxidant defense mechanisms in patients with DM compared to healthy individuals[9]. Oxidative stress causes oxidative damage to DNA, lipid peroxidation, β-cell damage, etc.[10–12]. Antioxidants inhibit the formation of ROSs, scavenge free radicals and potentiate the activity of antioxidant enzymes[13].

Insulin resistance is a major feature of the pathogenesis and etiology of type 2 DM. Elevated levels of glucose and free fatty acids in plasma activate the c-Jun N-terminal kinase and Iβ kinase pathways. As a result, there is a translocation of nuclear factor-kappa-B plus an increased expression of inflammatory mediators interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) that trigger insulin resistance[14]. The development of insulin resistance is primarily associated with low-grade tissue-specific inflammatory responses which are induced by various oxidative stress mediators and pro-inflammatory cytokines[15].

Conventional therapies, such as oral glucose-lowering drugs and insulin, are prescribed in addition to the involvement of exercise, weight control and medical nutrition therapy in the management of DM[16]. Although oral anti-diabetic drugs respond significantly at the initial stage, their long-term use leads to side effects and other consequences that include the development of hyperinsulinemia, weight gain, fatigue, lactic acidosis, diarrhea and increased low-density lipoprotein cholesterol (LDL-C) levels[17].

Due to the problems associated with currently available oral hypoglycemic drugs and their increasing cost in the global market, attention is focused on alternative therapies that could treat DM with high efficacy along with favorable overall tolerability and safety[17,18]. The use of complementary and alternative medicines (CAMs) for the treatment of DM has increased during the last few years[19]. Alternative medicines are widely used in developing countries due to their accessibility and affordability. Even in developed countries, CAMs are gaining popularity due to the adverse side effects associated with conventional oral hypoglycemic agents over long-term exposure[20]. Examples of complementary and alternative therapies include yoga, massage, acupuncture, aromatherapy and Ayurveda[17]. According to the World Health Organization (WHO) global report on traditional and complementary medicine, 88% of its 170 member states have acknowledged the use of traditional and CAMs in combatting DM[4].

Scientists are exploring medicinal plants that are widely used in traditional medicine to develop low-cost non-toxic antidiabetic drugs. *Gmelina arborea* Roxb. (Family: Verbenaceae) (Figure 1) is a medicinal plant that is used in traditional and Ayurvedic medicine[21]. This deciduous tree could commonly be found in Sri Lanka, India, Bangladesh, Myanmar, Thailand, southern China, Laos, Cambodia and Indonesia[22]. The leaves, fruits, heartwood, bark and roots of the plant are used in the preparation of decoctions for treating DM and other diseases.

Figure 1. Photographs of branches (a), leaves (b) and flowers (c) of *Gmelina arborea.*

This review scopes *G. arborea*, focusing on its ethnomedicinal uses, antidiabetic and related biological properties, phytoconstituents and potential antidiabetic principles. An attempt is also made to associate the observed biological and medicinal properties of *G. arborea* with its potential bioactive compounds and to briefly overview the cytotoxic effects of different parts of *G. arborea*. The *in vitro* and *in vivo* assays reveal the therapeutic potential of *G. arborea* in terms of antidiabetic, antioxidant and anti-inflammatory properties, indicating that the plant is a valuable source for developing non-toxic herbal formulations to manage DM. This review will serve as a comprehensive source of literature for investigating unexplored vistas of the plant in future antidiabetic research studies.

Study Design

A comprehensive literature search was conducted using the PubMed, ScienceDirect, Semantic Scholar and Google Scholar databases. Studies published from 1970 to 2021 were considered in this review. The keywords for the search were "*Gmelina arborea*", "Biological activities of *Gmelina arborea*", "Bioactive constituents of *Gmelina arborea*" and "Ethnomedicinal uses of *Gmelina arborea*". The abstracts and the articles that met the selection criteria were reviewed. Out of the total of 157 results, 34 articles were excluded being duplications and 58 articles were excluded as being out of the scope of this review (Figure 2). The remaining pool of 65 articles is critically reviewed in this article.

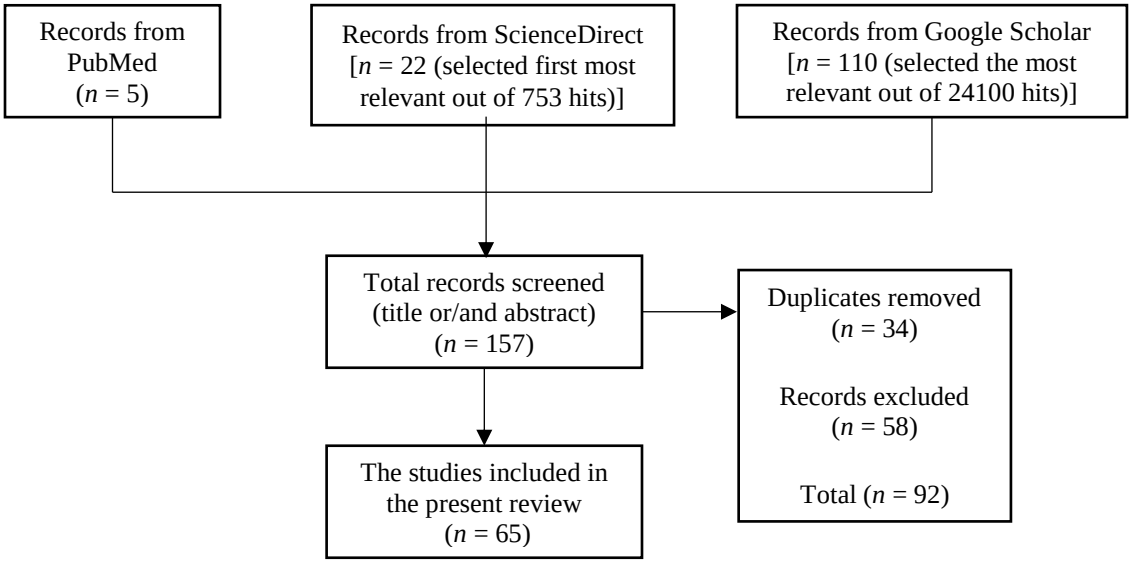


Figure 2. Flow diagram for selecting *Gmelina arborea*-based research articles for the review.

Ethnomedicinal Uses

Different parts of the plant *G. arborea* are used in the management of diseases and/or disorders in traditional medicine systems (Table 1). Aqueous decoctions prepared from the stem bark and heartwood are used to treat diabetes mellitus and bark is used to manage headaches and head reeling[23]. Aqueous leaf extracts of *G. arborea* are used in the treatment of wounds, ulcers and strengthening the bones[24,25]. The *G. arborea* fruit extract, prepared by boiling a fistful of ripe fruit with one glass of milk and one glass of water, is prescribed twice a day for 10 to 15 days in the management of tuberculosis[23]. *G. arborea* roots-based decoctions are used to clean and heal septic wounds[26]. A form of crushed fruit and bark of *G. arborea* is used to treat disorders in the stomach and to purify blood[27].

Antidiabetic Properties

In vivo antidiabetic activity of different extracts derived from *G. arborea* plant has been tested on rats (Table 2). Administration of the aqueous bark extract of *G. arborea* at a daily oral dose of 1.00 g/kg for 30 days to streptozotocin-induced diabetic Wistar rats led to an increase in the average percentage area of islets (48.78%), the number of insulin-secreting cells and the mean profile diameter

Table 1. Ethnomedicinal uses of *Gmelina arborea*.

Plant part	Ethnomedicinal use	Reference
Bark	Diabetes, hallucination, piles, abdominal pain, burning sensation, fever, urinary discharges, rotten wounds, peptic ulcer, diarrhea, snake bites, scorpion stings, gonorrhea and bone fractures.	[23, 28–31]
Leaves	Headache, asthma, diabetes, bronchitis, bone fractures, cholera, acidity, colic pain, cough, gonorrhea indigestion, cephalgia, warm infection, rheumatism, smallpox and fetid discharge removal.	[24, 25, 31, 32]
Fruits	Alopecia, anemia, leprosy, renal failure, nephrotic syndrome, strangury, thirst, vaginal discharges, vomiting, burning sensations, itches constipation, diarrhea, excessive thirst dysuria and urticaria.	[27, 31, 33, 34]
Flowers	Blood disorders, leprosy and dandruff.	[23, 31]
Roots	Anthrax, bilious disorders, blood disorders, cholera, diarrhea, bitter tonic, convulsions, epilepsy, dropsy, gout, rheumatism, intoxication, urinary discharges, abdominal pain, hallucination, fever, demulcent, laxative and galactagogue.	[31, 35, 36]

(164.34±2.56 μm) of large islets by 7%[37]. Additionally, bark extract led to a significant reduction ($p < 0.05$) in blood-glucose concentration (37%) and an increase in serum insulin and C-peptide by 57% and 39%, respectively[37]. The alloxan-induced diabetic Wistar rats with an oral dose of 1.00 g/kg of *G. arborea* aqueous bark extract for 30 days showed a significant reduction in the percentage of glycated hemoglobin (HbA_{1C}%) and serum fructosamine by 31% and 25%, respectively, with a significant increment of insulin and C-peptide by 44% each[38]. Furthermore, the study findings showed a significant increment ($p < 0.05$) in the diameter of average (2%) and large (10%) islet cells. A significant reduction ($p < 0.05$) of HbA_{1C}, serum concentration of insulin, fructosamine and C-peptide by 31%, 44%, 25% and 44%, respectively, was observed upon the administration of the aqueous leaf extract of *G. arborea* (1.00 g/kg) for 30 days in alloxan-induced Wistar rats[39].

The oral administration of *G. arborea* aqueous bark extract (1.00 g/kg) in streptozotocin-induced diabetic rats for 30 days showed an increment in the insulin biosynthesis (6%) by β-cells with regenerative effects[37]. A dose-dependent improvement in glucose tolerance (29 %) was observed in alloxan-induced diabetic rats during a 4-h period after the administration of aqueous bark extract of *G. arborea* (1.00 g/kg)[40].

Administration of the ethanol extract of *G. arborea* fruit at an oral dose of 300 mg/kg for 7 days to alloxan-induced diabetic rats showed a significant reduction ($p < 0.05$) in blood-glucose concentration (23%) comparable to that of the positive control glibenclamide (5mg/kg)[41]. Administration of the aqueous bark extract (500 mg/kg) for 28 days to streptozotocin-induced diabetic Wistar rats showed a significant reduction in plasma glucose level (35%) when compared to diabetic rats[42]. Oral administration of the aqueous leaf extract of *G. arborea* (0.5 g/mL) at a daily dose of 10 mL/kg to streptozotocin-induced albino rats for 30 days showed a significant decrement ($p < 0.05$) in fasting blood-glucose level (71.21%)[43].

The stem bark and root methanolic extracts of *G. arborea* with two different concentrations (250 and 500 mg/mL) were administered orally to streptozotocin-induced Wistar rats for 21 days to evaluate their antidiabetic activity. The highest percentage of blood-glucose level (74.41%) was observed after treatment with the *G. arborea* stem bark-derived 100% methanol extract (500 mg/mL) for 21 days[44]. In a separate study, the blood glucose-lowering effect of *G. arborea* stem bark-derived 50%-methanol extract was assessed with the same oral doses (250 and 500 mg/mL) in streptozotocin-induced Wistar rats, where the 500 mg/mL extract displayed the highest percentage of blood-glucose level (54.69%) after 21 days[45].

Table 2. *In vivo* antidiabetic properties of *Gmelina arborea*-derived extracts.

Plant part	Extract (dose - mode)	Positive control (dose)	Animal model	Duration	Results	Ref.
Bark	Aqueous (1.00 g/kg - oral)	GLI (0.50 mg/kg)	STZ-induced Wistar rats	30 days	Increase in average area of insulin-secreting β-cells (48.78%) Increase in mean profile diameter: large-sized islets (164.34±2.56 µm) Reduction in blood-glucose concentration (37%) Increase in serum insulin concentration (57%) and C-peptide concentration (39%)	[37]
Bark	Aqueous (250 or 500 mg/kg - oral)	GLI (0.6 mg/kg)	STZ-induced Wistar rats	Acute assay - 30, 60, 120, 240, 360 min	Reduction in plasma-glucose concentration at a single administration; 250 mg/mL (410.97±9.66 mg/dL) and 500 mg/mL (407.98±9.87 mg/dL, maximum reduction)	[42]
Bark	Aqueous (1.00 g/kg - oral)	GLI (0.50 mg/kg)	ALX-induced Wistar rats	30 days	Reduction in HbA_{1C} percentage (31%), serum fructosamine concentration (25%) Increase in insulin concentration (44%) and C-peptide concentration (44%) Increase in diameter of islet profile: average-sized islets (129.4±0.7 µm, diameter) and large-sized islets (163.4±1.7 µm, diameter)	[38]
Bark	Aqueous (1.00 g/kg - oral)	GLI (0.50 mg/kg)	ALX-induced Wistar rats	30 days	Reduction in HbA_{1C} percentage (6.7±0.1%) Reduction of insulin concentration (8.7±0.1 µIU/mL) and C-peptide (7.7±0.1 ng/mL)	[39]
Fruit	Ethanol, *n*-butanol, petroleum ether, ethyl acetate (300 mg/kg - oral)	GLI (5 mg/kg)	ALX-induced Wistar rats	7 days	Reduction in blood-glucose concentration (92±1.21 mg/dL)	[41]
Leaf	Aqueous (200/kg - oral)	Glipside (200 ug/kg)	ALX-induced albino rats	21 days	Reduction in plasma-glucose concentration (132.50±4.72 mg/dL)	[46]
Leaf	Aqueous (decoction) (10 mL/kg - oral)	GLI (500 mg/kg)	STZ-induced albino rats	30 days	Decrease in fasting blood-glucose concentration (71.21%)	[43]
Root and stem	Methanol 250, 500/kg - oral	GLI (0.25 mg/kg)	STZ-induced Wistar rats	21 days	Decrease in blood-glucose concentration (74.41%, 500 mg/kg, stem extract) compared to the methanol stem extract (250 mg/kg) and root extracts (250, 500 mg/kg)	[44]
Root and stem	50% Methanol (250, 500 mg/kg - oral)	GLI (0.25 mg/kg)	STZ-induced Wistar rats	21 days	Decrease in blood-glucose concentration: Stem: 250 mg/kg (41.05%) 500 mg/kg (54.69%) Root: 250 mg/kg (40.57%) 500 mg/kg (45.31%)	[45]
Stem bark	Aqueous (0.25, 0.50, 1.00, 1.25, 2.00 g/kg - oral)	GLI (0.50 mg/kg)	ALX-induced Wistar rats	1, 2, 3, 4 h	Improvement in glucose tolerance (29.35%) at the optimum effective dose (1.00 g/kg)	[40]
Stem bark	Aqueous (1.00 g/kg - ip)	GLI (0.50 mg/kg)	ALX induced Wistar rats	30 days	Increase in the diameter of islet cells in average-(2%) and large (5%)-sized islets	[38]

ALX, alloxan; GLI, glibenclamide; ip, intraperitoneal; OGTT, oral glucose tolerance test; STZ, streptozotocin.

Antioxidant Properties

Table 3 outlines the *in vitro* antioxidant screening studies conducted using *G. arborea*-derived extracts. An aqueous extract of *G. arborea* bark showed antioxidant activity in the following assays: 2,2′-diphenyl-2-picrylhydrazyl (DPPH) assay, radical scavenging assay of nitric oxide (NO) and ferric-reducing antioxidant potential (FRAP) assay[47]. The concentration of the aqueous bark extract that reduced 50% of the activity of the radical (IC_{50}) was 36.89±1.23 µg/mL and 139.56±4.20 µg/mL in the DPPH and NO radical scavenging assays, respectively, while the reducing power of *G. arborea* aqueous extract was 8.98±0.09 µM in the FRAP assay[47]. Aqueous extracts derived from *G. arborea* bark- and fruit-derived aqueous extracts showed potent antioxidant activity, equivalent to 1.7 and 0.9 mM ascorbic acid equivalents, respectively, in the DPPH assay[48]. In the ABTS assay, inhibition of 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid ($ABTS^{\bullet+}$) radical formation by the bark and fruit extracts of *G. arborea* occurred at 0.68 mM and 1.7 mM ascorbic acid equivalents, respectively. Both the bark and fruit aqueous extracts had the same reducing power as 1.23 mM ascorbic acid equivalents in the FRAP assay[48].

The non-aqueous extracts derived from the bark, leaves, roots, twigs and fruits of *G. arborea* were screened for antioxidant activity. Among the methanol extracts of bark, leaves, roots and twigs, the bark extract showed the highest free radical scavenging activity (71.51%) in the DPPH assay[49]. Bark, root and leaf extracts also exhibited metal-chelating properties[49]. The Fe^{3+}-reducing capacity of the extracts of ethanol, *n*-butanol, ethyl acetate and petroleum ether extracts of the *G. arborea* fruit differed in the order of ethanol > *n*-butanol > ethyl acetate > petroleum ether extracts[41]. In the DPPH assay, all the extracts, except the petroleum ether extract, showed significant free radical scavenging activities compared to the positive control[41]. According to the DPPH and total antioxidant capacity assays conducted for the 90% methanol extract of *G. arborea* leaves and its *n*-butanol, ethyl acetate, chloroform and petroleum ether fractions, the *n*-butanol fraction showed the highest radical scavenging activity (SC_{50}=14.10±1.68 µg/mL) and total antioxidant capacity (518.45±1.35 mg ascorbic acid equivalents/g of extract)[50]. The ethyl acetate and *n*-butanol fractions obtained from the 80% (v/v) ethanol extract of *G. arborea* leaves showed DPPH radical scavenging activities with a percentage reduction of 68.27±25.36 and 68.85±21.77, respectively, while the methanol extract of *G. arborea* seeds showed the highest antioxidant activity (91.99±0.46%) at 500 µg/mL[51].

G. arborea stem-derived 50% methanol extract exerted antioxidant activity in the DPPH (IC_{50} = 47.4733 µg/mL) and H_2O_2 scavenging assays. Additionally, the extract displayed a free radical scavenging activity of 85.2% at a concentration of 100 µg/mL[52]. The stem bark methanol extract of *G. arborea* showed scavenging activity on H_2O_2, nitric oxide and hydroxyl radicals with IC_{50} values of 73.6±0.03, 93.6±0.98 and 34±0.82 µg/mL, respectively[53]. In a separate study, the 70% methanol stem bark extract of *G. arborea* showed IC_{50} of 124.39 µg/mL in the DPPH assay[54].

The *in vivo* antioxidant properties of the *G. arborea* extracts are summarized in Table 4. Oral administration of the aqueous bark extract (1g/kg) for 30 days resulted in a 27% decrease in lipid peroxidation in streptozotocin-induced diabetic rats[47]. Furthermore, the results showed more effective restoration of liver antioxidant enzymes by the extract in streptozotocin-induced diabetic rats compared to the standard antidiabetic drug glibenclamide (0.5 mg/kg). In addition, aqueous bark extract was able to increase glutathione reductase, glutathione peroxidase (GPx) and glutathione S-transferase by 29, 23 and 20% in streptozotocin-induced diabetes rats, respectively[47]. Administration of the hexane leaf extract of *G. arborea* to gastric intubated Wistar rats for 52 days revealed an increase in the superoxide dismutase (SOD) enzyme activities of the liver, heart and kidney homogenates at 26.33±1.14, 81.32±2.39 and 87.79±2.13) µU/mg tissue, respectively[55]. Furthermore, the study findings showed an increase in catalase (CAT) activities as 1.4±0.13, 2.01±0.17 and 2.02±0.17 µU/mg for liver, heart and kidney homogenates, respectively[55]. Upon treatment of Wistar rats with gastric ulcers (80% ethanol-induced) with *G. arborea* stem bark-derived 70% methanol extract showed an improvement in the activities/level of reduced glutathione (GSH), GPx and SOD in a dose dependant manner[54].

Table 3. *In vitro* antioxidant properties of *Gmelina arborea*-derived extracts.

Plant part	Extract	Positive control	Antioxidant assay	Result	Ref.
Bark	Aqueous	Ascorbic acid	DPPH	IC_{50}: 36.89±1.23 µg/mL	[47]
			FRAP	Reducing power: 8.98±0.09 µM	
			NO	IC_{50}: 139.56±4.20 µg/mL	
Bark, fruit	Aqueous	Ascorbic acid	DPPH	1.7 mM (bark) and 0.9 mM (fruit) AAE	[48]
			ABTS	0.68 mM (bark) and 1.7 mM (fruit) AAE	
			FRAP	Reducing power: 1.23 mM (bark) and 1.23 mM (fruit) AAE	
Fruit	Ethanol, *n*-butanol, ethyl acetate and petroleum ether	Ascorbic acid	DPPH	IC_{50}: 60.1 µg/mL (n-butanol extract) 61.8 µg/mL (ethanol extract) 82.6 µg/mL (ethyl acetate extract)	[41]
			Fe^{3+}-reducing	Fe^{3+} reducing ability of extracts: ethanol > n-butanol > ethyl acetate > petroleum ether	
Bark, leaves, roots, twigs	Methanol	Ascorbic acid	DPPH	Highest scavenging activity: 71.51% (bark extract)	[49]
			Metal-chelating	Metal chelating activity: 88.04% (root extract)	
Leaves	Methanol and $CHCl_3$, ethyl acetate and *n*-butanol fractions	Ascorbic acid	DPPH	SC_{50}: 14.10±1.68 µg/mL (*n*-butanol fraction, highest scavenging activity)	[50]
			Total antioxidant capacity	Total antioxidant capacity: 518.45 mg AAE/g extract	
				Highest total antioxidant capacity in *n*-butanol fraction (518.45 mg AAE/g of extract)	
Leaves	ethyl acetate, *n*-butanol fractions	Ascorbic acid	DPPH	Mean percentage reduction: 68.27±25.36% (ethyl acetate fraction, highest antioxidant activity) 68.85±21.77% (butanol fraction)	[56]
Seed	Petroleum ether, chloroform, acetone and methanol	Ascorbic acid	DPPH	IC_{50}: 91.99±0.46% (500 µg/mL, methanol extract, highest antioxidant activity)	[51]
Stem	50% Methanol	Not mentioned	DPPH	IC_{50}: 47.47 µg/mL	[52]
			H_2O_2 scavenging	IC_{50}: 97.33 µg/mL	
Stem bark	Methanol	Ascorbic acid	H_2O_2 scavenging	IC_{50}: 73.6±0.03 µg/mL	[53]
Stem bark	70% Methanol	Ascorbic acid	DPPH	IC_{50}: 124.39 µg/mL	[54]

AAE, ascorbic acid equivalent; ABTS, 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid; DPPH, 2,2′-diphenyl-2-picrylhydrazyl; FRAP, ferric reducing antioxidant potential; NO, nitric oxide; IC_{50}, concentration of the inhibitor that reduces response by half; SC_{50}, concentration of the extract that reduces the DPPH concentration into half of its initial concentration.

Anti-inflammatory Properties

The anti-inflammatory activity of the different extracts of *G. arborea* has been examined *via in vitro* and *in vivo* studies. A higher *in vitro* inflammatory activity was shown by the acetone seed extract of *G. arborea* at 45.36% at 2000 µg/mL compared to the petroleum ether, chloroform and methanol extracts[51].

The stem bark and fruit extracts of *G. arborea* showed potent *in vivo* anti-inflammatory activity in rats (Table 5). The stem bark methanol extract (500 mg/kg) and its butanol (50 mg/kg) and ethyl acetate (50 mg/kg) fractions showed 67, 40 and 69.5% inhibition of paw edema, respectively, in Wistar rats over 4 h[57]. The anti-inflammatory properties of *G. arborea* stem bark-derived aqueous and methanol extracts were screened *in vivo* using Wistar rats at two doses, 250 and 500 mg/kg. The results showed the maximum decrease in paw volumes as 1.35±0.04 and 1.32±0.03 mL, for the aqueous

extract at 250 and 500 mg/kg, respectively, and 1.30±0.03 mL for the methanol extract at a dose of 500 mg/kg[58].

A 70% methanol stem bark extract (250 and 500 mg/kg) was tested for its anti-inflammatory activity using carrageenan-induced acute paw edema, dextran-induced acute paw edema, formalin-induced chronic paw edema and dimethylbenz(a)anthracene (DMBA)-croton oil-induced papilloma in Swiss albino mice. The percentage inhibitions were 33.3, 41.8 and 15.34% (for 250 mg/kg) and 26.73, 18.51 and 34.07% (for 500 mg/kg), respectively. An aqueous stem bark extract (5 and 10%) inhibited DMBA-croton oil-induced papilloma by 64.55 and 77.84%, respectively[59]. The 90% methanol extracts of stem bark and fruit showed anti-inflammatory activity in Wistar rats and the stem bark extract was more potent than the fruit extract, having inhibition of 75–80% paw edema for all doses (100–400 mg/kg) of the extract administered[60].

Cytotoxic properties

Cytotoxic properties of plant-derived extracts and compounds are evaluated to establish their safety in intended pharmaceutical applications[61]. *In vitro* and *in vivo* studies on the cytotoxic properties of *G. arborea* extracts are shown in Table 6. The bark-derived ethanol extract inhibited cell proliferation of human liver hepatocellular cells (HepG2) at relatively high doses (IC_{50}: 412.88 µg/mL) and Vero cells (IC_{50}: 541.42 µg/mL)[62], indicating that the ethanol bark extract is not cytotoxic. An aqueous leaf extract of *G. arborea* (5–10 mg/mL) showed significant inhibition of cell proliferation and reduction in the number of cells in a dose-dependent manner, with the MTT and clonogenic assays, respectively. The same extract

Table 4. *In vivo* antioxidant properties of *Gmelina arborea*-derived extracts.

Plant part	Extract (dose - mode)	Positive control (dose)	Animal model	Duration	Results	Ref.
Bark	Aqueous (1 g/kg - oral)	GLI (0.5 mg/kg)	STZ-induced rats	30 days	Decrease in lipid peroxidation (27%) in the liver Decrease in activities of liver enzymes: 29% (alanine aminotransferase) 29% (alkaline phosphate) 23% (aspartate aminotransferase) Increase in activities of antioxidant enzymes: 49% (glutathione reductase) 86% (glutathione peroxidase) 57% (glutathione S-transferase)	[47]
Leaves	Hexane (150 mg/kg)	Ascorbic acid (5 mg/kg)	Gastric intubated Wistar rats	52 days	Elevation of SOD and CAT activity: (26.33±1.14, 1.4±0.13) µU/mg (liver) (81.32±2.39, 2.01±0.17) µU/mg (heart) (87.79±2.13, 2.02±0.17) µU/mg (kidney)	[55]
Stem bark	70% methanol (250, 500 mg/kg - oral)	Ranitidine (50 mg/kg)	80% ethanol induced-gastric ulcer Wistar rats	4 h	Reduction of MDA concentration: 0.822±0.048, 0.376±0.047 nmol/mg of protein (250 mg/kg and 500 mg/kg) Enhancement of antioxidant levels: 30.421±0.644, 35.000±0.668 U/mg of protein (Reduced GSH, extract: 250 mg/kg and 500 mg/kg) 30.421±0.644, 35.000±0.668 U/mg of protein (SOD, extract: 250 mg/kg and 500 mg/kg 30.421±0.644, 35.000±0.668 U/mg of protein (GPx, extract: 250 mg/kg and 500 mg/kg	[54]

CAT, catalase; GLI, glibenclamide; GPx, glutathione peroxidase; GSH, reduced glutathione; MDA, malondialdehyde; SOD, superoxide dismutase; STZ, streptozotocin.

Table 5. *In vivo* anti-inflammatory properties of *Gmelina arborea*-derived extracts.

Plant part	Extract (dose - mode)	Positive control (dose)	Animal model	Duration*	Result	Ref.
Stem bark	Methanol (500 mg/kg), BFME (50 mg/kg), EFME (50 mg/kg)	Diclofenac (10 mg/kg)	Carrageenan-induced Wistar rats paw edema	1, 2, 3, 4 h	Inhibition: 67% (methanol), 40% (BFME) 69.5% (EFME) at 4th h	[57]
Stem bark	Aqueous and methanol (250 and 500 mg/kg - subcutaneous)	Phenyl-butazone (75 mg/kg)	Carrageenan-induced Wistar rats	6 h	Maximum decrease in paw volume: 35±0.04 and 1.32±0.03 mL (aqueous, 250 and 500 mg/kg) 1.30±0.03 mL (methanol, 500 mg/kg)	[58]
Stem bark	70% methanol (250, 500 mg/kg - ip)	Diclofenac (10 mg/kg)	Swiss albino mice: carrageenan-induced acute paw edema	4 days	Inhibition of paw oedema: 33.3, 41.8% (250 and 500 mg/kg)	[59]
			dextran-induced acute paw oedema	4 days	15.34, 26.73% (250 and 500 mg/kg)	
			formalin-induced chronic paw oedema	6 days	18.51, 34.07% (250 and 500 mg/kg)	
			(DMBA)-croton oil-induced papilloma	20 weeks	inhibition of papilloma: (64.55, 77.84%) (5, 10% of extract)	
Stem bark and fruit	Methanol 90% (100, 200, 400 mg/mL - oral)	Diclofenac (100 mg/kg)	Egg-albumin-induced Wistar rats paw edema	½, 1, 2, 3, 4 h	Inhibition of paw edema by 60 and 70% (200 and 400 mg/kg, fruit extract) compared to standard at 3rd 4th h Reduction in inflammation by 75–80% (100, 200, 400 mg/kg, stem bark extract)	[60]

* BFME, butanol fraction of methanol extract; EFME, ethyl acetate fraction of methanol extract; ip, intraperitoneal.

decreased the viability of HL-60 cells more than the control after 24 and 48 h[63]. An ethanol extract derived from *G. arborea* leaves inhibited the proliferation of cancer-cell types, with the maximum inhibition of 62% (IC_{50}: 20±0.15 mg/mL, colon cancer cell-COLO 201), 80% (IC_{50}: 12±0.32 mg/mL, gastric cancer cell-HT-29) and 70% (IC_{50}: 16±0.05 mg/mL, human esophageal cancer cells TE-2)[64]. The LD_{50} values (lethal dose, 50%; the dose required to kill a half of the members of a tested population during the period of observation) of 90% methanol extract and the defatted 90% methanol extract and its *n*-butanol and ethyl acetate fractions of *G. arborea* leaves were 158.48, 125.89, 39.81 and 199.52 µg/mL, respectively, in the brine shrimp lethality assay. The defatted 90% methanol leaf extract and its *n*-butanol and ethyl acetate fractions exerted potent cytotoxic effects on HepG2 cells at doses of 22.1, 22.1 and 17.3 µg/mL, respectively. The results revealed that HepG2 cells are more sensitive to the *n*-butanol fraction than to the ethyl acetate fraction. HepG2 is a widely used cell line for *in vitro* screening of toxicity, while the brine shrimp bioassay is considered a preliminary method to screen plant extracts for cytotoxicity[50]. The cytotoxic activity of a 70% acetone leaf extract of *G. arborea* was evaluated using a 3,4,5-dimethylthiazol-2,5-diphenyltetrazolium bromide (MTT) assay using six different cell lines; namely, breast cancer stem (MDA-MB 231), skin cancer stem (MDA-MB 435 and B16F10), colon cancer stem (Caco-2) and brain cancer stem (C6 and SNB75) strains. The IC_{50} values corresponding to all the cancer-cell lines were less than 1 mg/mL. The 70% acetone extract showed cytotoxicity on C6 and MDA-MB 231 cancer cells, causing low viability (< 40% and < 50%, respectively)[65].

Acute toxicity is an adverse change that occurs immediately or in a short period following exposure to a substance or an adverse effect due to the administration of single or multiple doses of a substance within 24 h[66]. Administration of the aqueous bark extract of *G. arborea* orally to Swiss albino mice at doses 300, 2000 and 5000 mg/kg did not show any sign of adverse effects after 14 days[67]. The acute toxicity of petroleum ether, *n*-butanol,

ethyl acetate and ethanol extracts of *G. arborea* fruits was evaluated on Swiss albino mice at oral doses of 100, 300, 600, 1000, 2000 and 3000 mg/kg, and the results indicated an LD_{50} value of 1300 mg/kg of body weight[33]. An aqueous leaf extract of *G. arborea* was screened for subchronic oral toxicity using healthy Wistar albino rats by oral administration of 15.62, 62.5 and 250 mg/L of the aqueous extract for 90 days. The results revealed that the extract had no impact on the behavioral pattern of the rats. Significant changes ($p > 0.05$) in the relative weights of the kidneys, lungs, heart and spleen were not observed in *G. arborea* treated rats compared to the untreated healthy control rats[68].

Table 6. *In vitro* cytotoxic properties of *Gmelina arborea*-derived extracts.

Plant part	Extract	Bioassay (Positive control)	Cytotoxicity	Ref.
Bark	Ethanol	MTT assay	IC_{50}: 412.88 µg/mL (HepG2 cells) IC_{50}: 541.42 µg/mL (Vero cells)	[62]
Leaves	Aqueous	MTT assay	Cell viability: 97.40±0.17, 65.60±0.05, 6.30±0.11 and 11.50±0.23% (HL-60 cells at 5, 10, 15, and 20 mg/mL)	[63]
		Trypan blue exclusion assay	Cell viability: 82.33±0.20, 70.53±0.43, 19.44±0.51 and 41.60±0.28% after 48 h (HL-60 cells at 5, 10, 15 and 20 mg/mL)	
		Clonogenic assay	Number of colonies: 140.00±11.54, 860.00±13.85, 420.00±4.61 and 290.00±5.19 (HL-60 colony formation at 5, 10, 15, and 20 mg/mL)	
Leaves	Acetone 70% (hydroacetonic) (v/v)	MTT assay	IC_{50}: 0.246 mg/mL (MDA-MB 231 cell line) IC_{50}: 0.379 mg/mL (MDA-MB 435 cell line) IC_{50}: 0.246 mg/mL (B16F10 cell line) IC_{50}: 0.250 mg/mL (Caco-2 cell line) IC_{50}: 0.304 mg/mL (C6 cell line) IC_{50}: 0.404 mg/mL (SNB75 cell line)	[65]
Leaves	Ethanol	MTT assay	IC_{50}: 20±0.15 mg/mL (COLO 201 cell line) IC_{50}: 12±0.32 mg/mL (HT 29 cell line) IC_{50}: 16±0.05 mg/mL (TE 2 cell line)	[64]
Leaves	Methanol 90%, defatted methanolic extract, ethyl acetate, *n*-butanol fractions of 90% methanol	*In vivo* Brine shrimp lethality bioassay (K_2CrO_4)	LC_{50}: 39.81 µg/mL (*n*-butanol fraction) 125.89 µg/mL (defatted methanolic extract), 158.48 µg/mL (90% methanol extract) 199.52 µg/mL (ethyl acetate fraction)	[50]
		In vitro Liver carcinoma cell line HepG2 (doxorubicin)	IC_{50}: 17.3 µg/mL (n-butanol fraction) 22.1 µg/mL (defatted methanolic extract) 22.1 µg/mL (ethyl acetate fraction)	

B16F10, skin cancer stem; Caco-2, colon cancer stem; COLO 201, colon cancer cells; C6, brain cancer stem; HT 29, gastric cancer cells; IC_{50}, concentration of the inhibitor which reduces the response by a half; LDH, lactate dehydrogenase; MDA-MB 231, breast cancer stem; MDA-MB 435, skin cancer stem; MTT assay, 3,4,5-dimethylthiazol-2,5-diphenyltetrazolium bromide: SNB75, brain cancer stem; TE 2, esophageal cancer cells.

Other Therapeutic/Biological Properties

Extracts of *G. arborea* have shown anti-microbial, anti-nociceptive, gastroprotective, antiulcer, diuretic, vasorelaxant, anticonvulsant, anthelmintic, antihyperlipidemic and antipyretic properties. Aqueous extracts derived from leaves and stem bark of *G. arborea* at 12.5 mg/mL inhibited the growth of recalcitrant pathogenic bacteria, such as *Escherichia coli*, *Klebsiella pneumonia*, *Proteus mirabilis*, *Shigella dysenteria* and *Salmonella typhi* of above-average resistance, in the broth dilution assay. However, the activity was less than that of chloramphenicol standard at 12.5 mg/mL[35]. The hexane leaf extract of *G. arborea* showed vasorelaxant effects on isolated Wistar rats' thoracic aorta, indicating antihypertensive properties of the plant. The vasorelaxant effects of the hexane extract were suggested to mediate through the release of nitric oxide and prostacyclin from the vascular endothelium and by activating the ATP-sensitive potassium channels present in the vascular smooth muscle[55].

The antinociceptive properties of the *G. arborea*-derived aqueous and methanol extracts were studied using the acetic acid-induced writhing method and hot-plate method. The central analgesic activity was examined by the hot-plate method. Wistar albino rats showed a significant increment in paw licking with 8.8±0.97 and 8.2±1.24 after 30 min of administering the aqueous and methanol extracts at a dose of 500 mg/kg in separate. The writhing response induced by acetic acid included abdominal muscle contractions along with hind limb stretching ultimately perceiving peripheral analgesia. The aqueous extract (500 mg/kg) exerted an inhibition (84.3%) of writhes during 20 min in Wistar albino rats compared to the standard drug, salicylic acid (81.1%). The methanol extract caused a significant inhibition ($p < 0.01$) of writhes by 70% and 77.9% at 250 and 500 mg/kg, respectively[58].

A 70% methanol stem bark extract of *G. arborea* significantly inhibited ulcer formation in a dose-dependent manner after 4 h of administration in Wistar rats ($p < 0.01$). The extract at 500 mg/mL caused slightly superior inhibition compared to standard ranitidine. A significant reduction in cell atrophy in mucosal gland lining, leukocyte infiltration, vacuolation, necrosis and considerable inflammatory changes in histology was observed in rats treated with ranitidine and *G. arborea* methanol extract (500 mg/mL), indicating gastroprotective activity of the extract against ethanol-induced injury[54].

The anticonvulsant activity of *G. arborea* stem-derived 50% methanol extract was examined in healthy adult albino mice. The oral administration of the methanol extract (250 and 500 mg/kg) caused a dose-dependent delay in the onset of convolution after 1 h on pentylenetetrazole (PTZ)- and strychnine (STR)-induced seizure models. The methanol extract (500 mg/kg) significantly delayed ($p < 0.0001$) the onset of convolution (8.188 min) in PTZ-induced rats than the standard drug diazepam (3.494 min)[52].

Aqueous, ethanol and acetone leaf extracts of *G. arborea* showed promising anthelmintic activity[69]. The nonparasitic nematode *Caenorhabditis elegans* was used for the screening of compounds. The activity of *C. elegans* was substantially restricted to 126±20, 34±9 and 39±5% by the aqueous, ethanol and acetone extracts at 10 mg/mL in separate[69].

G. arborea leaf-derived ethanol extract exerted antihyperlipidemic activity. The extract showed higher hypoglycemic activity at a dose of 150 mg/kg compared to STZ-induced diabetic Wistar albino rats (disease control group). The levels of triglycerides (102±48 mg/dL), total cholesterol (170.0±11.5 mg/dL) and low-density lipoprotein (167.0±3.3 mg/dL) were reduced in extract-fed rats compared to the rats in the control group[70].

The aqueous and ethanolic bark extracts of *G. arborea* showed antipyretic properties in a rat model. The aqueous and ethanol bark extracts (420 mg/kg) caused a higher reduction of yeast-induced pyrexia in Wistar albino rats compared to the paracetamol (50 mg/kg) administered group after 1 h of administration[71].

G. arborea fruit-derived *n*-butanol extract (300 mg/kg) exerted a potent diuretic effect with a diuretic index of 1.798 in adult Wistar male rats after 5 h of the oral administration, while standard (urea) had a diuretic index of 1.344 at the dose of 1g/kg [33].

Secondary Metabolites and Potential Bioactive Compounds present in *G. arborea*

Several secondary metabolites (**1**–**58**, Tables 7 and 8, Figures 3–5) have been isolated from the heartwood, aerial parts, roots, fruits and leaves of *G. arborea* using a variety of chromatographic techniques and the isolated compounds were characterized by advanced spectroscopic methods. These compounds belong to several structural classes, such as lignan, iridoid glycoside, steroid, flavonoid, flavonoid glycoside, phenylethanoid, phenylethanoid glycoside, quinone, phenol, fatty alcohol, long-chain ester and carboxylic acid. Most of the compounds isolated from *G. arborea* are yet to be screened for bioactivity although some secondary metabolites of *G. arborea* have displayed antioxidant properties (**1**–**13**, Table 7, Figure 3). Some compounds isolated from other plants, which are also present in *G. arborea*, have shown a variety of important biological properties, including antioxidant, anti-inflammatory, antidiabetic, antiviral and anticancer activities, indicating that *G. arborea* is potentially a valuable source of bioactive compounds.

Among the isolated compounds of *G. arborea* (**1**–**13**, Table 7, Figure 3), isoquercetin (**4**) was reported to exert the highest activity

(SC_{50} = 5.70±1.20 µg/mL) (Table 7) and it was higher than that of ascorbic acid (SC_{50} = 8.0±1.30 µg/mL); SC_{50} refers to the concentration of the sample that reduces the concentration of DPPH to a half of its value[22].

5,7-Dihydroxy-4′-methoxyflavone (**14**) (Figure 4) isolated from the ethanol extract of *G. arborea* fruit showed *in vivo* anti-inflammatory activity on carrageenan-induced rat paw edema model; the inhibitory paw thickness was 1.11±1.14% and 1.01±0.97% at doses of 5 and 10 mg/kg, respectively, after 6 h, while the corresponding value for diclofenac was 1.05±1.03% at 5 mg/kg[73].

Table 7. Secondary metabolites (1–13) isolated from *Gmelina arborea* showing antioxidant properties.

Secondary metabolite	Plant part	Antioxidant assay (Positive control)	Antioxidant activity	Ref
luteolin (**1**) luteolin-4′-*O*-β-D-$^4C_1$-galactoside (**2**) kaempferol (**3**) isoquercetin (**4**) rutin (**5**) luteolin-7-*O*-β-D-$^4C_1$-galactoside (**6**) quercetin-3-*O*-robinobioside (**7**)	Leaves	DPPH (ascorbic acid)	SC_{50} = 9.20±2.0 µg/mL SC_{50} = 14.40±1.50 µg/mL SC_{50} = 10.25±3.45 µg/mL SC_{50} = 5.70±1.20 µg/mL SC_{50} = 8.35±2.15 µg/mL SC_{50} = 10.65±1.55 µg/mL SC_{50} = 9.40±2.65 µg/mL	[22]
3,4,5-trimethoxyphenol (**8**)	Bark	DPPH (trolox)	Moderate antioxidant activity	[72]
2-(4-hydroxyphenyl)ethanol (**9**) (+)-balanophonin (**10**) gmelinol (**11**) 2,6-dimethoxy-*p*-benzoquinone (**12**) (–)-*p*-hydroxyphenylethyl[5‴-*O*-(3,4-dimethoxycinnamoyl)-β-D-apiofurano-syl(1‴→6′)]-β-D- glucopyranoside (**13**)	Bark	DPPH (trolox)	Weak antioxidant activity	

DPPH, 2,2′-diphenyl-2-picrylhydrazyl; $SC_{50,}$ 50% reduction of DPPH concentration.

Table 8. Secondary metabolites (15–58) isolated from *Gmelina arborea*, which have not been screened for their antidiabetic, antioxidant and anti-inflammatory activity.

Plant part	Extract	Secondary metabolites	Ref.
Heartwood	Sequential extracts of hexane and methanol, methylated spirit	arboreol (**15**), isoarboreol (**16**), 2-*O*-methylarboreol (**17**), gmelanone (**18**), gummadiol (**19**), 7-oxo-dihydrogmelinol (**20**), β-sitosterol (**21**), paulowin (**22**), 2-*O*-ethylarboreol (**23**), campesterol (**24**), stigmastanol (**25**), stigmasterol (**26**) (Figure 5a)	[74-77]
Aerial parts	Methanol	6-*O*-(3″-*O*-*trans*-cinnamoyl)-α-L-rhamnopyranosylcatalpol (**27**), 6-*O*-(3″-*O*-*cis*-cinnamoyl)-α-L-rhamnopyranosylcatalpol (**28**) and 6-*O*-(3″-*O*-benzoyl)-α-L-rhamnopyranosylcatalpol (**29**) (Figure 5b)	[78]
Root	Light petroleum extract	hentriacontanol (**30**), 1-hexacosanol (**31**), octacosanol (**32**), 4,8-dihydroxysesamin (**33**), 4-hydroxysesamin (**34**) and 6″-bromoisoarboreol (**35**) (Figure 5c), cluytylferulate (**36**) (Figure 5d), β-sitosterol (**21**) (Figure 5a)	[77, 79, 80]
Fruit	Ethanol	apigenin (**37**), quercetagenin (**38**), quercetin (**39**), tartaric acid (**40**), arborone (**41**) and tannic acid (**42**) (Figure 5d), β- sitosterol (**21**) (Figure 5a), hentriacontanol (**30**) and 1-hexacosanol (**31**) (Figure 5c)	[57, 73, 77]
Leaf	Methanol, 90% Methanol	6-*O*-(2″-*O*-acetyl-3″,4″-*O*-di-*trans*-cinnamoyl)-α-L-rhamnopyranosylcatpol (**43**), 6-*O*-(3″-*O*-*trans*-feruloyl)-α-L-rhamnopyranosylcatpol (**44**), 6-*O*-α-L-rhamnopyranosylcatalpol (**45**) and twelve acylated iridoid glycosides, i.e. gmelinosides (**46**–**58**) (Figure 5e)	[22, 81]

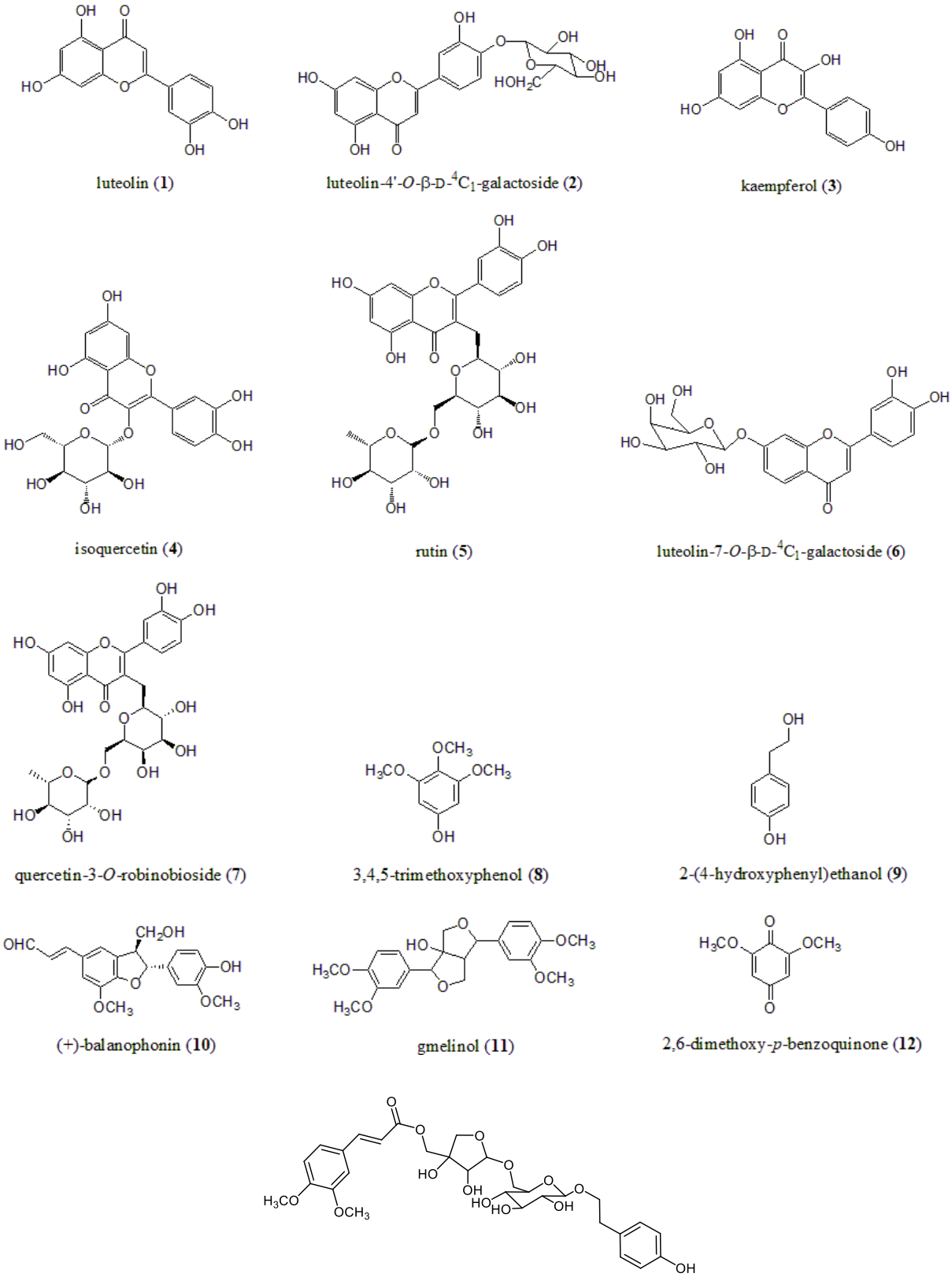
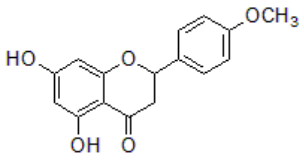
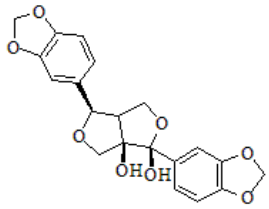


Figure 3. Structures of antioxidant compounds (1–13) derived from G. arborea (Table 7).

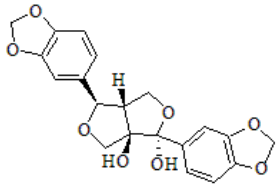


5,7-dihydroxy-4'-methoxyflavone (**14**)

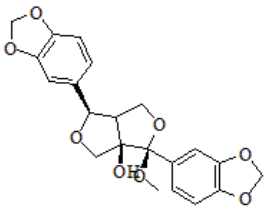
Figure 4. Structure of anti-inflammatory compound (14) derived from *G. arborea*.



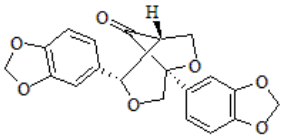
arboreol (**15**)



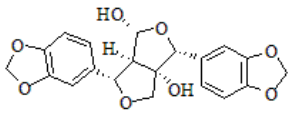
isoarboreol (**16**)



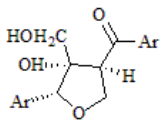
2-*O*-methyl arboreol (**17**)



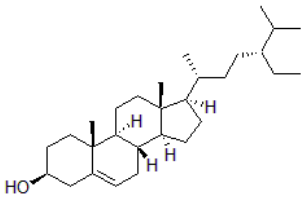
gmelanone (**18**)



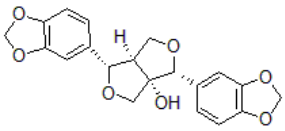
gummadiol (**19**)



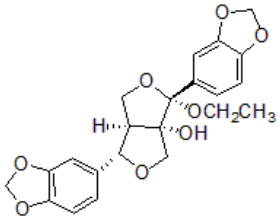
7-oxo-dihydrogmelinol (**20**)
Ar = veratryl



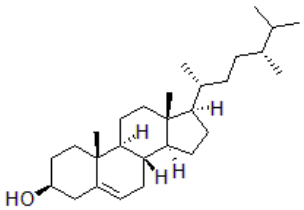
β-sitosterol (**21**)



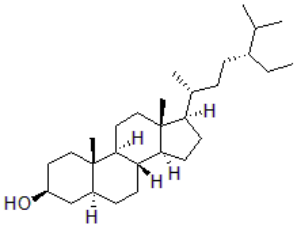
paulownin (**22**)



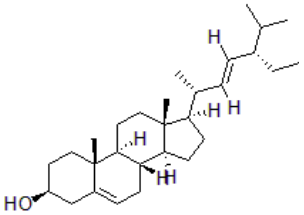
2-*O*-ethylarboreol (**23**)



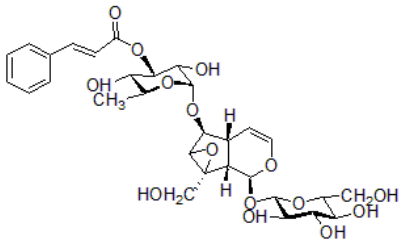
campesterol (**24**)



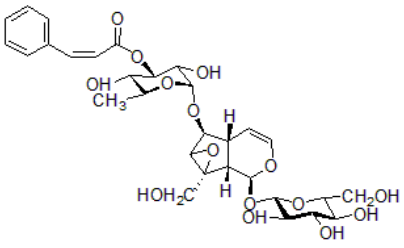
stigmastanol (**25**)



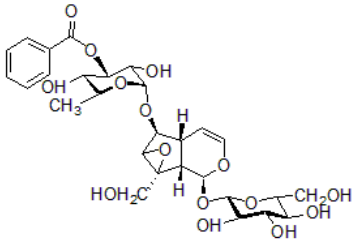
stigmasterol (**26**)



6-*O*-(3"-*O*-*trans*-cinnamoyl)- α–L rhamnopyranosylcatalpol (**27**)



6-*O*-(3"-*O*-*cis*-cinnamoyl)-α-L-rhamnopyranosylcatalpol (**28**)



6-*O*-(3"-*O*-benzoyl)-α-L-rhamnopyranosylcatalpol (**29**)

Figure 5a. Structures of compounds derived from *Gmelina arborea*: 15–26 (heartwood), 27–29 (aerial parts).

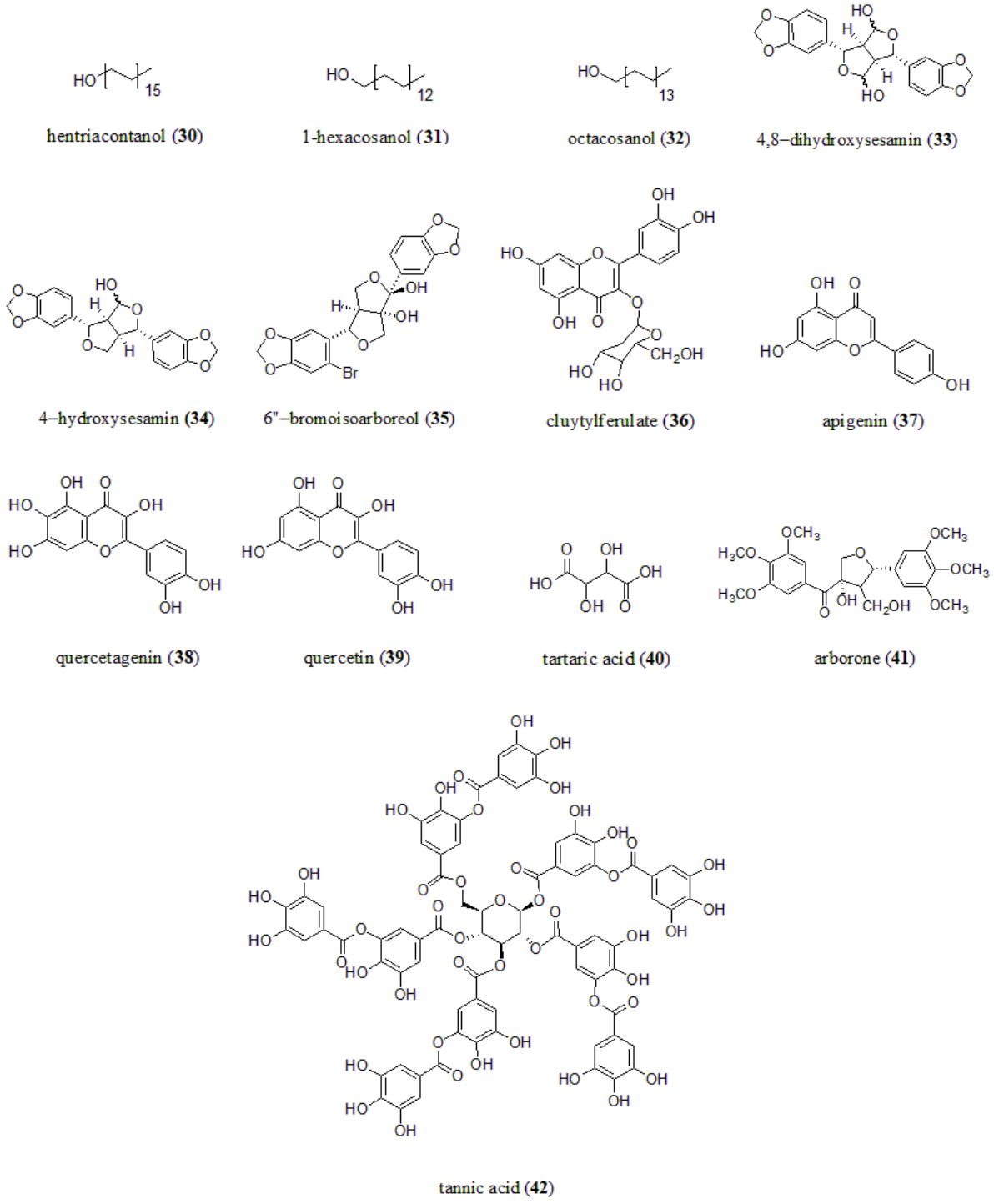
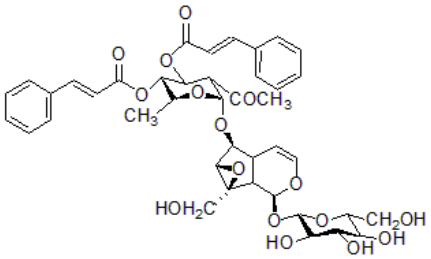
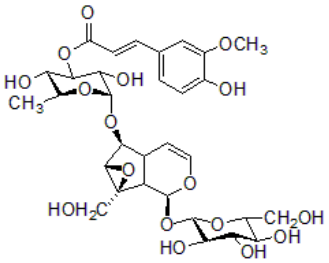


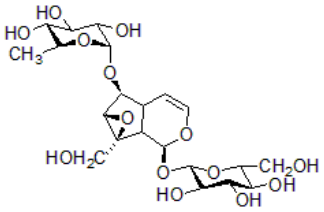
Figure 5b. Structures of compounds derived from *Gmelina arborea*: 30–36 (root), 37–42 (fruit).



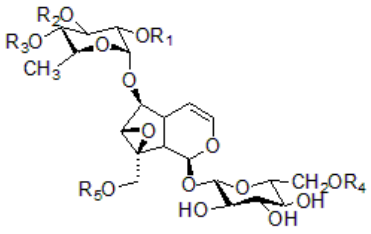
6-*O*-(2"-*O*-acetyl-3",4"-*O*-di-*trans*-cinnamoyl)-α-L- rhamnopyranosylcatpol (**43**)



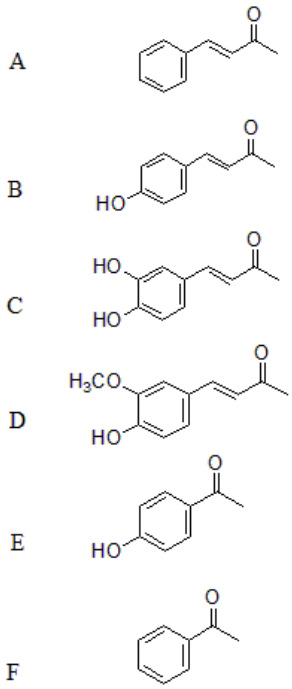
6-*O*-(3"-*O*-*trans*-feruloyl)-α-L-rhamnopyranosylcatpol (**44**)



6-*O*-α-L-rhamnopyranosylcatalpol (**45**)



gmelinosides (**46-58**)



	R_1	R_2	R_3	R_4	R_5
46	H	H	H	H	H
47	H	H	H	H	A
48	Ac	Ac	H	H	A
49	H	H	H	H	B
50	H	H	H	H	C
51	Ac	H	Ac	H	D
52	H	H	H	Ac	E
53	D	D	H	H	H
54	D	D	Ac	H	H
55	B	H	B	H	H
56	F	H	F	H	H
57	H	F	F	H	H
58	H	Ac	A	H	H

Figure 5c. Structures of compounds derived from the leaf of *Gmelina arborea*: 43–58.

Several compounds present in *G. arborea*, which are also found in other plants, showed antidiabetic, antioxidant and anti-inflammatory activities. As mentioned above, although most phytoconstituents derived from *G. arborea* have not been screened for antidiabetic, antioxidant and anti-inflammatory properties, the same compounds isolated from other plants demonstrated bioactive properties in a variety of assays. Those reported bioactivities are mentioned in this section, to emphasize the therapeutic value of *G. arborea* for future studies.

β-Sitosterol (**21**) present in *Dillenia indica* L. (Family: Dilleniaceae) potently inhibited α-glucosidase and α-amylase, the key enzymes that digest carbohydrates, leading to postprandial hyperglycemia in patients with diabetes mellitus[82].

Apigenin (**37**) isolated from *Cephalotaxus sinesis* (Family: Taxaceae) increased GLUT4 translocation in 3T3-L1 cells, leading to

increased glucose uptake[83]. Apigenin (**37**) isolated from *Teucrium polium* L. (Family: Lamiaceae) facilitated insulin release and decreased the accumulation in the pancreas of diabetic rats[84]. Luteolin (**1**) isolated from *Hydnocarpus wightiana* Blume (Family: Achariaceae) showed α-glucosidase and α-amylase inhibitory activities.[85]. Quercetin (**39**) isolated from *Cyclocarya paliurus* (Batal.) (Family: Juglandaceae) showed *in vitro* inhibitory activity on glycogen phosphorylase and protein tyrosine phosphatase-1B (PTP1B)[86]. Kaempferol (**3**), quercetin (**39**) and rutin (**5**) showed α-glucosidase inhibitory activity[87]. The inhibitory kinetics of α-glucosidase revealed that quercetin (**39**), isoquercetin (**4**) and rutin (**5**) are effective α-glucosidase enzyme inhibitors of -glucosidase enzymes [88].

Quercetin (**39**) possessed antioxidant activity, which was evident through the oxygen radical absorption capacity (ORAC) assay[89,90].

The structurally similar flavonols kaempferol (**3**) and quercetin **(39)** enhanced anti-inflammatory activity through modulation of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2) and reactive C-protein (CRP)[91]. The flavones luteolin (**1**) and apigenin (**37**) showed anti-inflammatory activity in microglia [92].

In addition to antidiabetic, antioxidant and anti-inflammatory properties, apigenin (**37**) and quercetin (**39**) showed antiviral and anticancer activities[93–95]. Apigenin (**37**) inhibited TNF-α- and IL-1β-induced activation of NF-κB in humanTHP-1 monotypic cells, while quercetin (**39**) prevented β-cell death by the mitochondrial pathway and signaling of nuclear factor kappa B (NF-κB) in RINm5F β-cells[96,97]. Luteolin (**1**) displayed bioactivities, such as antioxidant, anti-inflammatory and antiapoptosis[98–100]. Tartaric acid (**40**) showed antioxidant properties in cadmium-spiked calcareous soil[101].

Alkaloids exert potent anti-inflammatory activity, while flavonoids express their potential through the regulation of cellular activities in mast cells, macrophages, lymphocytes and neutrophils[102–105]. Quercetin (**39**) is a ubiquitous flavonoid that exerts an anti-inflammatory action by inhibiting mast cell degranulation[106,107]. Flavonoids possess anti-inflammatory activity by inducing nitric oxide synthase and by inhibiting cyclooxygenase (COX) and lipoxygenase (LOX). Enzyme inhibition results in reduced production of crucial mediators of inflammation, such as arachidonic acid, prostaglandins, leukotrienes and nitric oxide[57].

Conclusions

This paper reviews the ethnomedicinal uses and the biological properties that are important in managing diabetes mellitus and the potential antidiabetic principles of *G. arborea*. This plant has antihyperglycemic, antioxidant and anti-inflammatory properties. Secondary metabolites found in *G. arborea* are attributed to biological activities that have been identified. Different extracts of *G. arborea* exerted *in vitro* and *in vivo* antidiabetic properties and their ability to regenerate β-cells in the pancreas of rat models. Luteolin (**1**), kaempferol (**3**), isoquercetin (**4),** rutin **(5)**, β-sitosterol (**21**), apigenin (**37**) and quercetin **(39**) were the potential antidiabetic compounds of the plant. *In vitro* and *in vivo* assays revealed that the aqueous, methanol and hexane extracts had promising antioxidant properties, where the following antioxidant compounds contributed to the activity: luteolin (**1**), 3,4,5-trimethoxyphenol **(8)**, 2-(4-hydroxyphenyl)-ethanol (**9**), (+)-balanophonin (**10**), 2,6-di-methoxy-*p*-benzoquinone (**12**)(−)-p-hydroxy-phenylethyl[5‴-*O*-(3,4-dimethoxycin-namoyl)-β-D-apiofuranosyl(1‴→6′)]-β-D-gluco-pyranoside (**13**), β-sitosterol (**21**), stigmastanol (**25**), apigenin (**37**)), quercetin (**39**) and tartaric acid (**40**). The methanolic extracts of the bark and fruit possessed anti-inflammatory activity. 5,7-Dihydroxy-4′-methoxyflavone (**14**), while the compound isolated from the ethanolic extract of the fruit exerted significant anti-inflammatory activity *in vivo*. Cytotoxicity studies of different extracts of *G. arborea* revealed a significant decrease in LDH release and a reduction in cell proliferation. Toxicity studies confirmed that *G. arborea* at or below a dose of 1300 mg/kg was not toxic *in vivo*. The *in vitro* and *in vivo* assays revealed the therapeutic potential of *G. arborea* in terms of antidiabetic, antioxidant and anti-inflammatory properties, indicating that the plant was found to be a valuable source for developing non-toxic herbal formulations to manage diabetes mellitus and its complications. Detailed cellular and molecular studies and in-depth *in vivo* investigations on antidiabetic, anti-inflammatory and antioxidant principles of *G. arborea* are warranted.

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