Chapter

Antidiabetic Activities of *Terminalia* Species in Nigeria

Franklyn Nonso Iheagwam, Omoremime Elizabeth Dania, Happiness Chijioke Michael-Onuoha, Olubanke Olujoke Ogunlana and Shalom Nwodo Chinedu

Abstract

Terminalia species are well recognised in traditional medicine. They are known for producing fruits and nuts which are edible and possess pharmacotherapeutic properties. They also have ornamental purposes in urban areas where they are found. These species are used by traditional healers in the treatment and management of diabetes mellitus, its complications and other related ailments that are involved in the pathophysiological process of this disease. Research has been extensively done to validate these antidiabetic claims scientifically as well as understand the mechanism and mode of antidiabetic action. This chapter proposes to highlight the antidiabetic activities of *Terminalia* species found in Nigeria.

Keywords: *Terminalia* species, antidiabetic, Nigeria, diabetes mellitus, mode of action, mechanism, traditional medicine

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder that is not only affecting various populations worldwide but also poised on affecting the developing nations of the world much more than developed countries [1, 2]. The International Diabetes Foundation (IDF) reported a diagnosis of over 400 million people living with diabetes and postulated an estimated increase to over 600 million people by the year 2040 in a worldwide survey [3, 4]. The report also shows that diabetes accounts for a death every 6 seconds [3]. In a recent study, it was observed that the total reported cases of people affected by DM had increased by 10 million in the subsequent survey carried out by IDF over the next year [5].

DM is a heterogeneous metabolic disorder and is difficult to classify. However, DM has been categorised into three major types based on the pathologic process. Type 1 diabetes mellitus (T1DM), also known as childhood/early-onset diabetes or insulin-dependent DM, is characterised by insulin deficiency as a result of β-cell dysfunction, degeneration and degradation by the immune system [6]. Type 2 diabetes mellitus (T2DM), also known as adult/late-onset diabetes or non-insulin-dependent DM has insulin secretion and insulin resistance (IR) as its major characteristics [7]. Gestational diabetes mellitus (GDM) has glucose intolerance in pregnant women as its major characteristic. It is as a result of the β-cells inability to meet up with the insulin demand in pregnant women without a previous diagnosis of diabetes [8].

Diabetologists have a few other categories, such as tropical DM and Type 3 diabetes mellitus (T3DM). The former is thought to have a relationship with malnutrition [8], while the latter is a suggested mechanistic link to Alzheimer's disease via inflammatory response and other mechanisms resulting in the pathophysiologic changes relating diabetes to dementia [3]. However, there is little information on the rarer forms of diabetes, such as secondary diabetes, mitochondrial diabetes, maturity-onset diabetes of the young, and latent autoimmune diabetes of adults [9].

1.1 Risk factors

Physical inactivity or sedentary lifestyle, excessive alcohol, overweight, obesity and unhealthy diet intake are modifiable DM risk factors [10]. Family history, hypertension, history of previously impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), advancing age, history of GDM, ethnicity and genetic makeup are some unmodifiable risk factors. However, various researchers have reported that novel risk factors such as short sleep duration [11], noise pollution [12] and environmental toxins [13] contribute to the causal pathways which lead to diabetes. Trade and agricultural production policies are thought to contribute to both individual and societal level risk factors [14].

2. Diabetes mellitus in Nigeria

2.1 Epidemiology

The transition from infectious diseases to non-communicable diseases as leading causes of death is fast becoming a growing epidemiological trend and public health dichotomy in Sub-Saharan African countries [15]. In Africa, there is a 1% estimated prevalence of diabetes in rural areas while in urban areas, the range is from 5–7% [16]. Nigeria accounts for about one-sixth of Africa's population [1]. The national prevalence of diabetes, which was less than 1% between 1960 and 1990, has risen from 2.2% in 1997 to 5% in 2013 [17]. However, the current prevalence may currently be as high as between 8 and 10% [9], with 4.83% recorded for patients aged 20 and above, accounting for over 3 million people currently living with this condition [18]. This observation makes her the country with the highest number of people living with diabetes and IFG in Africa [19]. Epidemiological statistics show that Nigeria is responsible for one in every five reported sub-Saharan case of diabetes, with a steep increase in the prevalence of this disease from the rural areas to members of the high socio-economic population [9]. Continuous urbanisation, the increasing population and poor economy, will further drive the incidence and burden of diabetes upwards in Nigeria [1, 2, 20]. T2DM appears to be the majority of the DM burden in Nigeria with T1DM accounting for less than 10% of DM cases [21], while tropical DM makes up less than 1% [8]. Lifestyle factors such as sedentary lifestyle, cigarette smoking and generous consumption of alcohol are known risk factors linked to the development of T2DM. Obesity has been reported to be a major contributor to approximately 55% of diagnosed cases of T2DM, with a prevalence of 3.3 to 18% [2]. It has also been associated with several life-threatening diseases such as cardiovascular disease (CVD), several cancer types, as well as reduced quality of life [22, 23]. Diabetes-related morbidity and mortality have been reported to be high in different locations in Nigeria with 105,091 diabetes-related deaths recorded as at 2013 and most patients reported to have been suffering from T2DM [10].

2.2 Management

Given the current DM epidemic and its projected consequences, effective population-based intervention identification has become a priority public health strategy in Sub-Saharan Africa [24]. In Nigeria, insulin, oral glucose-lowering drugs, diet and exercise are used in the management of DM. Complementary and alternative medicine such as concoctions, infusions, tinctures and herbal supplement is also used [1]. Inability to use insulin syringe, the high cost of therapy, few options in the Nigerian market and poor policies on DM management are a few challenges affecting insulin treatment [25]. The medications used in the management of diabetes become less effective over time as most patients do not achieve normal glycaemic control with their use [26], and thus have resulted to possible second-line medications to achieve the normal glycaemic target [27]. Despite the high cost of medication as well as the inability to maintain normal glycaemic control for an extended period, the use of polytherapy to achieve sufficient glucose control is a common feature in Nigeria [28]. Challenges such as needle phobia, hypoglycaemia, drug-associated side effect and cost of medication have made over 46% of diabetic patients opt for complementary and alternative medicine, with *Vernonia amygdalina* which is also known as "bitter leaf" being most utilised [29]. The school of thought that diabetics should abstain from carbohydrate rich meals has led to the intake of monotonous food like unripe plantain, beans and wheat rich diet [1, 30]. This challenge occurs due to the absence of a taste-appealing standardised diet for diabetics as well as their dietary requirements influenced by economic status, religious and cultural beliefs [1].

3. *Terminalia* species as medicinal plants

Medicinal plants (MPs) are a rich source of natural products with potential medical interest. There is an increased interest in the use of medicinal plants and their products as a result of their reported wide range application. Asides their application, they are the richest bioresource of modern medicines, nutraceuticals, food supplements, chemical entities for synthetic drugs, pharmaceutical intermediates, folk medicines and drugs of traditional systems of medicine [31]. These plants are also known to contain different plant secondary metabolites such as tannins, flavonoids, saponins alkaloids, terpenoids and phenols, which are responsible for numerous characteristics such as colour, flavour, smell and texture in various parts of these plants. These plant metabolites are also known for their pharmacological mechanism of actions in the treatment, management and prevention of diseases [32].

Terminalia genus has about 250 flowering tree species which belong to the Combretaceae family. They are found in the tropics of Australia, Asia, Africa and South America. The bark of many *Terminalia* species appear to be cracked from the stem, the branches are arranged in a stepwise manner with the leaves appearing large and leathery on the tips of shoots. The appearance of the leaves is responsible for the genus nomenclature *Terminalia* which is a derivative of the Latin word Terminus. The fruits of most *Terminalia* species are edible with deep red, yellow or black pulp colouration and hard nuts [33]. Extensive research has shown that *Terminalia* species are a rich source of phytocompounds ranging from flavonoids (gallic acid, ellagic acid, quercetin, hesperetin), steroids (β-sitosterol, terminic acid), tannins (punicallin, terchebulin, castalagin), vitamins (α-tocopherol), carotenoids (lutein) and others [33–35]. The various reported pharmacological activities

such as antimalarial, antioxidant, antibacterial, antifungal, cardiovascular effects, antidiarrhoeal, analgesic, anti-inflammatory, hypolipidaemic, hypoglycaemic, antiprotozoal, antiviral, wound healing, antimutagenic and anticancer properties have been attributed to these compounds [33].

3.1 *Terminalia* species in Nigeria

There are about ten species of *Terminalia* found in Nigeria, namely; *Terminalia altissima* (Synonym: *superba*), *Terminalia avicennioides, Terminalia brownii, Terminalia catappa, Terminalia glaucescens, Terminalia ivorensis, Terminalia laxiflora, Terminalia macroptera, Terminalia mollis and Terminalia schimperiana* [33, 36, 37]. These species have been reported to be pharmacologically active with antimicrobial, antimycobacterial, wound healing, gastroprotective, antimalarial, antioxidant, antifungal, anthelmintic, antibacterial, antifungal, antiviral, analgesic, radical scavenging, hepatoprotective, anticancer, antimutagenic, antiaging, aldose inhibitory, antiplasmodial, cytotoxic, antipsychotic, sedative, analgesic, anti-inflammatory, trypanocidal, hypolipidaemic, antioxidant, antimycoplasmal and androgenic, properties as shown in **Table 1** [34, 35, 38–42].

Terminalia species in Nigeria, have numerous application in the treatment and management of ailments among the various traditional medicine systems of different ethnic groups. Different parts are utilised by traditional healers to treat cholera, malaria, typhoid, hepatitis, stomach ache, tuberculosis, leprosy, diarrhoea, skin diseases, gastritis, hyperglycaemia, diabetes, gonorrhoea, wounds, epilepsy and catarrh [56–58]. They are also used as tonic, laxative and chewing sticks [26, 59, 60].

Several reports have highlighted some pharmacological properties of *Terminalia* species in Nigeria, such as its antimicrobial properties, antibacterial property, anti-inflammatory action, anti-HIV, hypoglycaemic, modulatory properties, analgesic, wound healing, antioxidant and radical scavenging activity, hepatoprotective, anticancer, anti-trypanocidal, antimutagenic and antiaging properties.

Nigeria's vegetation is made up of forests, savannahs and montane land. All others but the latter are further divided into three parts which have ensured the wide distribution of these species across the country. This variation in the country's vegetation has not only made these *Terminalia* species specific to Nigeria and West Africa, but accounts for the difference in their evolutionary relationship, development and pharmacologic activity. Upon assessment of the phylogenetic relationship on www.phylogeny.fr [61], using the available nucleic acid sequence of the *Terminalia* species that were deposited in National Center for Biotechnology Information (NCBI) GenBank, it was observed that species that were closely related such as *T. catappa* and *T. glaucescens* as well as *T. superba* and *T. avicennioides* were located in the same vegetative region of the country (**Figure 1**). Irrespective of their evolutionary differences, it was observed that there were conserved regions that were similar in the deposited genetic sequence of the *Terminalia* species in Nigeria showing over 94% sequence similarity (**Figure 2**).

3.2 Pharmacologic antidiabetic activities of Nigerian *Terminalia* species

The pharmacologic antidiabetic activity of *Terminalia* species have been reported in different climes using various *in vitro, in vivo* and *in silico* techniques in mice, rat, rabbit and humans to elucidate them. Nonetheless, in Nigeria, there is a paucity of data on the antidiabetic mode of action and mechanisms of *Terminalia* spp. despite its abundance. However, there are antidiabetic reports of these species from neighbouring countries with similar vegetation.

Name of specie	Location in Africa	Common name	Pharmacological activity	References
Terminalia altissima (Synonym: *superba*)	Tropical west Africa, Sierra Leone, Congo, Nigeria, Cameroon	White afara, Limba	Antimicrobial, α-glucosidase inhibitory properties	[37, 43, 44]
Terminalia avicennioides	West Africa	Kpace, Kpayi, Baushe, Idi	Antimycobacterial, wound healing, gastroprotective, antimalarial, antioxidant, antifungal, anthelmentic activities	[45, 46]
Terminalia brownii	Nigeria, Congo, Sudan, Tanzania, Kenya, and Sudano-Sahelian Africa	Different names based on location	Antibacterial, antifungal, antiviral activities	[47]
Terminalia catappa	Africa	Indian almond, Tropical almond	Analgesic, wound healing, antioxidant, radical scavenging, hepatoprotective, anticancer, antimutagenic, antiaging properties	[41]
Terminalia glaucescens	Tropical Africa	Different names based on location	Antimicrobial, aldose inhibitory, antiplasmodial, cytotoxic properties	[48, 49]
Terminalia ivorensis	Western Africa	Idigbo, Black Afara, Blackbark	Antibacterial, antipsychotic, sedative, analgesic, anti-inflammatory, trypanocidal properties	[50, 51]
Terminalia laxiflora	Sudano-Sahelian Africa	Idi, Baushe	Antimycoplasmal activitiy	[37]
Terminalia macroptera	Tropical West Africa	Orin idi, kwandare	Antimicrobial, antimalarial, hypolipidaemic, antioxidant, antimycoplasmal properties	[52, 53]
Terminalia mollis	Tropical Africa	Bush willow, baúshin giíwaá	Antimycoplasmal, antimalaria activitiy	[33, 54]
Terminalia schimperiana	Tropical West Africa, Uganda, Ethiopia	Idi, Tuit plant, Kwuegh, Buashe	Androgenic, antioxidant, antimicrobial properties	[55]

Table 1.
List of Terminalia *species found in Nigeria and their reported ethnopharmacological activity.*

3.2.1 In vitro assessments

The crude aqueous and hydroethanolic leaf extracts of *T. catappa* from Nigeria have been reported to inhibit both α-glucosidase and α-amylase effectively. Mixed and non-competitive mode of inhibition were the mechanisms of action elucidated for the extracts [35]. This finding was further corroborated by *in silico* studies, in which the identified bioactives showed preferential binding to the active site than the allosteric site of α-glucosidase and α-amylase [35]. The α-amylase inhibitory property of crude methanol extract and solvent fractions of *T. brownii* stem bark was lower than that of acarbose as reported in [62]. When compared with some

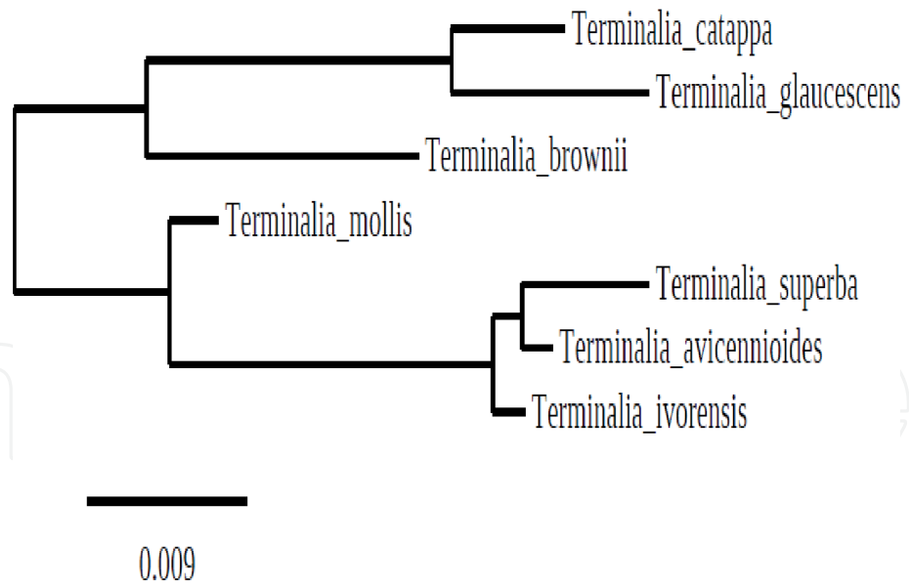

Figure 1.
Phylogenetic tree of some selected Terminalia *species in Nigeria.*

other medicinal plants, crude ethanol, aqueous and hydroethanolic extracts of *T. superba* root exhibited better inhibitory action on α-amylase activity than their respective counterparts [63]. For α-glucosidase and lipoxygenase inhibitory activity, the potency of dichloromethane, methanol and solvent fractions of *T. macroptera* leaves have been established to be more potent than acarbose and quercetin respectively [40].

High-throughput techniques were used to identify isolated bioactive compounds (gallic acid and methyl gallate) from *T. superba* stem bark dichloromethane extract, which exhibited very high inhibitory property on α-glucosidase activity [64]. Other isolates such as arjunic acid and glaucinoic acid from *T. glaucescens* stem barks and chebulagic acid, corilagin and narcissin from *T. macroptera* leaves are reported to exhibit significant β-glucuronidase, α-glucosidase and 15-lipoxygenase inhibitory activity respectively [40, 65].

3.2.2 In vivo assessments

The pre-administration of methanol-methylene chloride extract of *T. glaucescens* leaves have been reported to confer protective properties in mice against streptozotocin-induced diabetes effects [66]. *T. schimperiana* root bark extracts have been reported to be effective in reducing blood glucose and excess body lipids in alloxan-induced diabetic rats [67, 68]. The hypoglycaemic activity of *T. catappa* leaves has also been recorded [69]. The leaves have also been associated with a significant decrease of C-reactive protein, interleukin-6, fibrinogen and inflammatory markers associated with diabetes in rats when compared with other non-steroidal anti-inflammatory drugs [70]. In male rats fed with *T. catappa* drupe and seeds supplemented-diets for fourteen days, they were found to have exhibited enhanced sexual behaviour and biomarkers relevant to erectile dysfunction that were initially suppressed by streptozotocin-induced diabetic state [71]. Most research on the antidiabetic assessment of *Terminalia* species in Nigeria have reported the beneficial effect in rats and mice. Interestingly, in Ref. [72], *T. catappa* intake was found to illicit negative herb-drug effect by increasing the activity of transaminases concomitantly enhancing the adverse hepatic effects of antidiabetic drugs such as pioglitazone and atorvastatin.

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T.glaucesc      GCACGTCTGCCTGGGTGTCACGCATCGCGTTGCCTCCAAACCCTTCACCCTTCGTTCGTT
T.brownii       GCACGTCTGCCTGGGTGTCACGCATCGCGTTGCCTCCAAACCCTTCACCCTTCGGACGTT
T.mollis        GCACGTCTGCCTGGGTGTCACGCATCGCGTTGCATCCAAACCCTTCACCCTTCGGACGTT
T.superba       GCACGTCTGCCTGGGTGTCACGCATCGCGTTGCATCCAAACCCTTCACCCTTCGGACGTT
T.ivorensi      GCACGTCTGCCTGGGTGTCACGCATCGCGTTGCATCCAAACCCTTCACCCTTCGGACGTT
T.avicenni      GCACGTCTGCCTGGGTGTCACGCATCGCGTTGCATCCAAACCCTTCACCCTTCGGACGTT
T.catappa       GCACGTCTGCCTGGGTGTCACGCATCGCGTTGCCTCCAAACCCTTCACCCTTCGTTCGTT
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T.glaucesc      GCGGTGATGGTCTGGATGCGGAAGCTGGCCTCCCGCGGCCACGAGCCACGGATGGCCCAA
T.brownii       GCGGTGATGGTCTGGATGCGGAAGCTGGCCTCCCGCGGCCGCGAGCCACGGATGGCCCAA
T.mollis        GCGGTGATGGTCTGGATGCGGAAGCTGGCCTCCCGYGGCCACGAGCCACGGATGGCCCAA
T.superba       GCGGTGATGGTCTGGATGCGGAAGCTGGCCTCCCGCGGCCGCGAGCCACGGATGGCCCAA
T.ivorensi      GCGGTGATGGTCTGGATGCGGAAGCTGGCCTCCCGCGGCCGCGAGCCACGGATGGCCCAA
T.avicenni      GCGGTGACGGTCTGGATGCGGAAGCTGGCCTCCCGCGGCCGCGAGCCACGGATGGCCCAA
T.catappa       GCGGTGATGGTCTGGATGCGGAAGTTGGCCTCCCGCGGCCACGAGCCACGGATGGCCCAA
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T.glaucesc      ACACGTGCTAGGGAAGCGAAGCGCCACGGCATTCGGTGGTTGATCCAAGCCCCAGAAGC-
T.brownii       ACACGTGCTAGGGAAGCGAAGCGCCACGGCATTCGGTGGTTGATCCAAGCCCCAGAAGC-
T.mollis        ACACGTGCTAGGGAAGCGAAGCGCCACGGCATTCGGTGGTTGATCCAAGCCCCAGAAGC-
T.superba       ACACGTGCTAGGGGAGCGAAGCGCCACGGCATTCGGTGGTTGATCCAAGCCCCAGAAGCC
T.ivorensi      ACACGTGCTAGGGGAGCGAAGCGCCACGGCATTCGGTGGTTGATCCAAGCCCCAGAAGC-

T.avicenni      ACACGTGCTAGGGGAGCGAAGCGCCACGGCATTCGGTGGTTGATCCAAGCCCCAGAAGC-
T.catappa       ACACGTGCTAGGGAAGCGAAGCGCCACGGCATTCGGTGGTTGATCCAAGCCCCAGAAGC-
                ************* ******************************************

T.glaucesc      AGTGCCGGCGGTGGCCGCGTCTGTCCTTAGCCCACGACCCTAAACGTTAACCAACGCGAC
T.brownii       AGTGCCGGCGGTGGCCGCGTCCGTCCCTAGCCCACGACCCTAATCGTTAACCAACGCGAC
T.mollis        AGTGCCGGCGGTGGCCGCATCTGTCCCTAGCCGACGACCCTAAACGTTAACCAACGCGAC
T.superba       AGTGCCGGCGGTGGCCGCACCCGTCCCTAGCCGACGACCCTAAACGTTAACCAACGCGAC
T.ivorensi      AGTGCCGGCGGTGGCCGCACCCGTCCCTAGCCGACGACCCTAAACGTTAACCAACGCGAC
T.avicenni      AGTGCCGGCGGTGGCCGCACCCGTCCCTAGCCGACGACCCTAAACGTTAACCAACGCGAC
T.catappa       AGTGCCGGCGGTGGCCGCGTCTGTCCTTAGCCTACGACCCTAAACGTTAACCAACGCGAC
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T.glaucesc      CTCAGGTCAGGCGGGGCTACCCGCTGAGTTTAAGCATATCAATAAGCGGAGG--------
T.brownii       CTCAGGTCAGGCGGGGCTACCCGCTGAGTTTAAGCATATCAATAAGCGGAGG--------
T.mollis        CTCAGGTCAGGCGGGGCTACCCGCTGAGTTTAAGCATATCAATAAGCGGAGG--------
T.superba       CTCAGGTCAGGCGGGGCTACCCGCTGAGTTTAAGCATATCAATAA---------------
T.ivorensi      CTCAGGTCAGGCGGGGCTACCCGCTGAGTTTAAGCATATCAATAAGCGGAGGAAAAGAAA
T.avicenni      CTCAGGTCAGGCGGGGCTACCCGCTGAGTTTAAGCATATCAATAAGCGGAGGA-------
T.catappa       CTCAGGTCAGGCGGGGCTACCCGCTGAGTTTAAGCATATCAATAAGCGGAGGA-------
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T.glaucesc      ------------------------------
T.brownii       ------------------------------
T.mollis        ------------------------------
T.superba       ------------------------------
T.ivorensi      CTAACAAGGATTCCCCTAGTAACGGCGAGCG
T.avicenni      ------------------------------
T.catappa       ------------------------------
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Figure 2.
Multiple sequence alignment of some selected Terminalia *species in Nigeria.*

4. Conclusion

The Nigerian *Terminalia* genus is made up of species that possess antidiabetic principles. This activity has been related to the presence and synergistic action of phytochemicals such as tannins, phenolics, terpenoids, flavonoids and other active bioconstituents. The species of this genus in Nigeria can provide great medicinal value to the country and its populace. However, most of the antidiabetic

pharmacological assessment has been done only on *Terminalia catappa, Terminalia glaucescens* and *Terminalia schimperiana.* Moreso, high throughput analytical techniques and equipment can be utilised to identify and isolate novel phytocompounds that may be of therapeutic value in the management and treatment of diabetes. It is also imperative to identify the sequence of all Nigerian *Terminalia* species to understand better the genetic relationship, genetic variability, intraspecific variability and traits heritability in vegetative and floral characters of these species.

It was also observed that the majority of antidiabetic assessments of these *Terminalia* species were done *in vitro*, in rats and mice. Nonetheless, more *in vivo* studies should be carried out to identify the molecular mechanisms involved in its antidiabetic activity. Nigeria is the most challenged sub-Saharan nation with diabetes, a public health issue that needs to be tackled urgently. Hence, there is a need to increase translational research and explore the antidiabetic assessment of these *Terminalia* species directly on patients to extrapolate results that will be beneficial to the Nigerian public health system.

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Conflict of interest

The authors declare no conflict of interest.

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