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REVIEW

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Ethnomedicine and ethnopharmacology of medicinal plants used in the treatment of diabetes mellitus in Uganda

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Abstract

Diabetes mellitus (DM) is a global health problem owing to its high prevalence and increased morbidity and mortality. The prevalence of DM and impaired glucose tolerance in Uganda is approximately 4.1% and 6.6%, respectively. Medicinal plants are commonly used for the management of DM, especially in developing countries, such as Uganda. According to several ethnobotanical surveys conducted in Uganda, various medicinal plants are used in DM management. Meanwhile, ethnopharmacological studies have confirmed the anti-diabetic efficacy of various plants and plant-derived formulations from Uganda. However, these information remain highly fragmented without a single repository for plants used in the management and treatment of DM in Uganda, hindering further investigations. Therefore, this study aimed to comprehensively explore plants used for DM treatment in Uganda and retrieve relevant ethnopharmacological and ethnomedicinal information that can be used for DM therapy development. English peer-reviewed articles and books were searched in scientific databases, especially PubMed, Scopus, Google Scholar, Science Direct, SciFinder, and Medline, to retrieve information on medicinal plants used for DM treatment and management in Uganda. The databases were searched to obtain published literature on the anti-diabetic activities and safety of plants among the identified plants. The family name, plant parts used, anti-diabetic activities, dosage, and mechanisms of action of plant extracts were captured. In total, 46 species belonging to 26 families are used to treat DM in Uganda. Most species belonged to the Fabaceae (20%), Asteraceae (13%), and Solanaceae (7%) families. Anti-diabetic activities of 27 (59%) species have been scientifically investigated, whereas the rest have not been evaluated. This review indicated that various medicinal plants are used in the traditional treatment and management of DM across different regions in Uganda. Scientific investigations have revealed the anti-diabetic potential and safety of several of these plants. However, there is a need to validate the anti-diabetic potential of other unstudied plants. Additionally, isolating and characterizing active principles and elucidating the anti-diabetic mechanism of these plants and performing preclinical and clinical studies in the future could aid in the formulation of an effective and safe treatment for DM.

Keywords Antidiabetic activities, Diabetes mellitus, Medicinal plants, Herbal medicine, Uganda, Ethnomedicine, Ethnopharmacology

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Introduction

Diabetes mellitus (DM) is referred to as heterogeneous disturbances of metabolism characterized by chronic hyperglycemia, which is caused by either insufficient insulin secretion in the pancreatic β-cells (type-1 diabetes mellitus (T1D)) or impaired insulin secretion and action (type-2 diabetes mellitus (T2D)) [1]. The disease and its complications continue to be a major global health threat [2]. In 2017, DM-associated complications resulted in approximately 4 million deaths worldwide and accounted for 6.8% of total deaths in Africa [3]. Additionally, DM is predicted to be among the top seven causes of death by 2030 [4]. The prevalence of DM has increased exponentially worldwide in the last four decades [5, 6], which is mainly attributed to the growing and aging population, high energy/high fat diet, as well as sedentary lifestyle [7]. Notably, more than 90% of all DM cases are T2D [8] and according to Noubiap et al. [9], approximately 425 million DM cases were recorded in 2017 globally. The caseload is predicted to increase by 48% with an estimated 629 million affected individuals by 2045 [9]. In the African population, approximately 19.8 million DM cases are recorded, and it is estimated that 75% of them have not been diagnosed [10]. The prevalence of DM and impaired glucose tolerance is approximately 4.1% and 6.6%, respectively, in Uganda [10]. Moreover, the prevalence of DM in Uganda is projected to increase by 166.9% between 2013 and 2035, which will exceed the prevalence of DM in most other countries [11]. The management and treatment of DM are challenging as currently available conventional drugs, like acarbose are expensive, inaccessible, associated with several undesirable side effects, and have high secondary treatment failure rates [12]. Moreover, a definitive cure for DM is currently unavailable [13]. To overcome these challenges in the management and treatment of DM, there is a need to employ multiple approaches to identify alternative therapeutic strategies. Medicinal plants have been historically used to treat and manage DM in several traditional medicine systems of many cultures worldwide, especially in developing countries such as Uganda [12]. The use of medicinal plants is popular for primary health care among the general population owing to cultural acceptability, compatibility with the human body, and less side effects [14]. The World Health Organization has recommended the use of medicinal plants for managing DM and suggested increased efforts to scientifically evaluate the hypoglycemic properties of diverse plant species [13]. Ethnopharmacological studies are, by definition, scientific approaches to the study of biological activities of preparations used by humans, which possess, either beneficial or toxic or other direct pharmacological effects [15] and thus, ethnopharmacology involves investigating the relationship between humans and plants in all its complexity [15]. Accordingly, several ethnobotanical surveys conducted in Uganda have revealed that various medicinal plants are used in the management of DM [16–24]. Indeed, ethnopharmacological studies have reported the anti-diabetic efficacy of some of these plants and their derived formulations [23, 25]. However, these information remain highly fragmented without a single repository for plants used in the management and treatment of DM in Uganda, hindering further investigations. Therefore, this review aimed to explore plants used for treatment and management of DM in Uganda including relevant ethnopharmacological and ethnomedicinal information, which could provide useful information for research on DM therapy.

Methods

To get information on medicinal plants used in the management and treatment of DM in Uganda, Scientific databases namely, PubMed, Scopus, Google Scholar, Science Direct, SciFinder, and Medline were searched to retrieve relevant English peer-reviewed articles and books. Additional articles were found after tracking citations of the already accessed publications. Various attributes captured included species, family, local name, parts used, mode of preparation, habitat, and other diseases treated. Following this, the same databases were searched to obtain information on the anti-diabetic potential and safety of the identified plants. In this regard, research articles reporting anti-diabetic activities and safety of these plants were reviewed and findings recorded. During the search process, initially, the key words; ''ethnomedicine", ''ethnopharmacology", ''traditional medicine", ''herbal medicine", ''medicinal plant", ''phytomedicine", ''ethnobotany" were combined with "diabetes mellitus", "Uganda". Next, each plant name identified from the above search were paired with "phytochemicals", ''extract", ''isolation", ''efficacy", ''safety", ''toxicity", "anti-diabetic", "diabetes mellitus", "hyperglycemic", "hypoglycemic", "mechanism of action," "antihyperglycemic", ''antilipidemic". The medicinal plants were then categorized based on their anti-diabetic activity investigation status. Additionally, ethnomedicinal uses of the identified plants in other countries neighbouring Uganda namely, Kenya, Tanzania, Democratic Republic of the Congo, Rwanda, and Sudan were obtained. Thereafter, the collected data were summarized and presented accordingly.

Results and discussion

Traditional concept of DM in Uganda

Generally, the understanding of DM is associated with several misconceptions, including its prevention, causes, signs, and treatment. A large portion of the population is aware of DM, especially in urban areas. However,

nonfactual information on DM exists in the Ugandan population. For instance, DM symptoms are associated with witchcraft [26] and most people seek medical help when the symptoms of DM are severe, resulting in increased morbidity and mortality [27]. The use of traditional medicine inluding medicinal plants for treatment of DM is widespread in Uganda [28].

Plants used for treating DM in Uganda

The literature review identified 46 species of plants belonging to 26 families that are used to treat DM in Uganda (Table 1). The most commonly used species belonged to the Fabaceae (20%), Asteraceae (13%), and Solanaceae (7%) families (Fig. 1). The predominant use of plant species from these families to treat DM and its complications is attributed to a wide range of bioactive compounds, which make them largely effective in the treatment of human diseases [29, 30]. The widespread use of medicinal plants for DM treatment and management among the Ugandan population is due to low cost, easy accessibility, cultural acceptability, and the perceived less side effects [28]. This suggests that medicinal plants are key alternatives to the currently available conventional DM medicines. Consistent with our findings, several other researchers have also reported dominant use of plant species belonging to Fabaceae and Asteraceae families for treatment of DM in other countries, such as Nigeria and Tanzania [13, 31, 32]. Furthermore, studies have also shown that same plants are used similarly for DM treatment in neighboring and other countries (Table 2), for instance, the use of *Erythrina abyssinica* DC. (Fabaceae) and *Bidens pilosa* L. (Asteraceae) for treatment of DM were reported in Kenya [31]. *Vernonia amygdalina* Del., *Aspilia africana* (Pers.) C.D.Adams, and *Ageratum conyzoides* (L.) L. (all in Asteraceae) were documented to be used traditionally for treating DM in Nigeria [31, 33]. *Cajanus cajan* (L.) Huth (Fabaceae) has been used to treat DM in Tanzania [32].

Plant parts used, preparation, and mode of administration

The leaf (44%) was the most commonly used part, followed by the root (20%), fruit (12%), seed (9%), stem (8%), whole plant (3%), flowers (2%), and other unspecified parts (2%) (Fig. 2). The high use of leaves for DM treatment compared to other plant parts might be accounted to their potency associated with higher accumulation of bioactive compounds, ease of harvest, and quick ability to regenerate [30]. The extensive use of leaves for the treatment of DM corroborates with the findings of Skalli et al. [104] and Mohammed et al. [31] who also reported highest use of leaves for DM management compared to other plant parts. The most common modes of herbal preparation include decoction [17, 24] and infusion [21, 24] (Table 1). Decoctions are prepared by boiling plant materials in a specific quantity of water for 15–20 min and after, the mixtures are allowed to cool before administration. For example, *Canarium schweinfurthii* Engl. (stem barks), *Cymbopogon citratus* Stapf (leaves), *Cajanus cajan* (L.) Huth (leaves), and *Hallea rubrostipulata* (K. Schum.) J-F. Leroy (roots) are all prepared by decoction before administration. Infusion involves pouring hot or warm water onto the plant material and allowing the mixture to cool prior to administration. Plants such as *Bidens pilosa* L. (leaves, whole plant, roots) and *Schkuhria pinnata* (Lam.) Kuntze ex Thell. (leaves) are prepared through infusion for treatment of DM. Meanwhile, example of plants that are consumed directly for purposes of treating DM include *Oxalis corniculata* L. and *Carissa macrocarpa* (Eckl.) A.DC.. As observed, some medicinal plant parts are prepared through maceration; this involves crushing plant materials of a single species or a combination to extract a liquid before consumption. A case in point is *Vigna unguiculata* (L.) Walp. preparation. The common employment of decoction as a mode of preparation is attributed to the fact that boiling enables extraction of ingredients and preserves the herbal remedy longer compared to when cold water is used [30]. In some instances, other methods of preparation are more valuable because boiling leads to remarkable degradation of phytochemicals more so, aromatic compounds when done for a longer time [30]. This implies that no single mode of extraction is suitable for all medicinal plant preparation. Several other studies have reported similar modes of herbal preparation for treatment of DM [13, 31]. The solvent used for these herbal preparations is water and all prepared herbal medicines for DM treatment are orally administered (Table 1). Worth mentioning is that majority of these plants (about 63%) are obtained from the wild (Table 1). This is an indication that there is heavy dependence on wild source or natural environment in obtaining these medicinal plants; suggesting need to adopt propagation strategies (both macro and micro methods) for the plants for massive and sustainable supply of these medicinal materials. This finding is consistent with ethnobotanical study reports from other countries including Mexico [105], Ethiopia [106], and Turkey [107].

Knowledge dynamics of antidiabetic plants in Uganda

Through generations, knowledge of traditional medicine and medicinal plants are orally transferred from elders to young ones in Uganda [108]. Similar trend of traditional medicine knowledge transfer has been recorded in other African countries like Kenya and Ghana [109, 110]. At present, to the best of our knowledge, there are no exclusive indigenous knowledge systems or databases

Table 1 Plants used for traditionally treating diabetes mellitus in Uganda based on ethnobotanical surveys

Plant family	Scientific name	Local name	Parts used	Mode of preparation	Habitat	Anti-diabetic activity investigation status	Other diseases treated	References
Fabaceae	*Acacia constricta* A. Gray	*Muwelamanyo*	Roots and flowers	Decoction	W	Not recorded	Sinus infections and convulsions in children	[24]
Asteraceae	*Ageratum conyzoides* L	*Akaddo Kanamirembe*	Leaves	•The leaves are crushed and filtered after the addition of water • The leaves are minced, shade-dried, powdered, and reconstituted with water	W	Investigated	Not recorded	[23]
Fabaceae	*Albizia chinensis* (Osbeck) Merr	*Omugavu*	Leaves	•Leaves crushed and filtered after the addition of water • The leaves are minced, shade-dried, powdered, and reconstituted with water	W, C	Not recorded	Not recorded	[23]
Fabaceae	*Albizia coriaria* Welw. ex Oliv	*Omusisa*	Stem bark	Dried and powdered; consumption of 1 teaspoonful in 1 glass of water	W, C	Not recorded	Cough, pleurisy, allergy, sore skin, chest congestion, worm infection, stomach ache, colic pain, and toothache	[18]
Asphodelaceae	*Aloe vera* (L.) Burm.f	*Ekigaji*	Leaves	•Leaves crushed, mixed with water, and filtered. Honey can be added as a sweetener • Leaves may be minced; the jelly is drained and dried under sunshine. The dried material can be reconstituted with water	C	Investigated	Not recorded	[23]
Annonaceae	*Annona muricata* L	*Ekitafeli*	Leaves and fruits	•Fruits consumed when ripe or minced and crushed to obtain the juice • The leaves are minced, shade-dried, powdered, and reconstituted with water • Fresh leaves crushed, mixed with water, and filtered to obtain a debris-free solution	C	Investigated	Not recorded	[23]

Table 1 (continued)

Plant family	Scientific name	Local name	Parts used	Mode of preparation	Habitat	Anti-diabetic activity investigation status	Other diseases treated	References
Moraceae	*Artocarpus heterophyllus* Lam	*Ffene*	Seeds	The seeds are dried, powdered, and reconstituted with water	C	Investigated	Not recorded	[23]
Meliaceae	*Azadirachta indica* A. Juss	Neem	Leaves, roots, root bark, and seeds	Decoction and infusion	C	Investigated	Malaria, cough, syphilis, skin disease, chickenpox, vomiting, fever, obesity, and nausea	[21]
Asteraceae	*Bidens pilosa* L	*Kalala*	Leaves, whole plant, and roots	Infusion	W	Investigated	Malaria, wounds, skin diseases, pain relief, fever, inflammation, and flu	[17, 21]
Fabaceae	*Cajanus cajan* (L.) Huth	*Entondaigwa/Nkolimbo*	Leaves	Decoction	C	Investigated	Ulcer, diarrhea, pain, cough, sores, dysentery, hepatitis, measles, malaria febrifuge, and irregular menstrual cycle	[17]
Burseraceae	*Canarium schweinfurthii* Engl	*Muwafu*	Barks	Decoction	W	Investigated	High blood pressure and cough	[24]
Apocynaceae	*Carissa macrocarpa* (Eckl.) A.DC	*Amatungulu*	Fruits	Fresh fruits consumed or crushed and filtered after the addition of water to obtain a juice	C	Not recorded	Not recorded	[23]
Rutaceae	*Citrus sinensis* (L.) Osbeck	*Omucungwa*	Roots	Decoction	C	Investigated	Cough and vomiting	[21]
Lamiaceae	*Clerodendrum rotundifolium* Oliv	*Kisekeseke*	Roots/leaves	Freshly picked leaves are squeezed, and the extract is consumed	W	Not recorded	Malaria	[16]
Asteraceae	*Crassocephalum vitellinum* S. Moore	*Ekilalaakuba*	Leaves	•The leaves are minced and filtered after the addition of water • The leaves are minced, shade-dried, powdered, and reconstituted with water	W	Not recorded	Not recorded	[23]
Fabaceae	*Crotalaria ochroleuca* G.Don	*Alaju*	Leaves	Raw leaves chewed or stewed daily	W	Not recorded	Anemia, malaria, abdominal pain, chest pain, visual impairment, cough, and hypertension	[20]
Cucurbitaceae	*Cucurbita maxima* Duchesne	*Ensujju*	Fruits	Fruits minced and crushed. The juice is filtered after the addition of water	C	Investigated	Not recorded	[23]

Table 1 (continued)

Plant family	Scientific name	Local name	Parts used	Mode of preparation	Habitat	Anti-diabetic activity investigation status	Other diseases treated	References
Poaceae	*Cymbopogon citratus* Stapf	*Akisube /Kisubi/Omuteete*	Leaves	Decoction	C	Investigated	Fever, jaundice, throat and chest infections, hypertension, and obesity	[17]
Fabaceae	*Erythrina abyssinica* DC	*Ejirikiti/Lochoro*	Stem bark	Not specified	W	Investigated	Not recorded	[22]
Moraceae	*Ficus saussureana* DC	*Omuwo*	Stem bark	Not specified	W	Not recorded	Fallopian tube blockage, HIV/AIDS, male infertility, syphilis, typhoid fever, and ulcers	[22]
Clusiaceae	*Garcinia buchananii* Baker	*Musali*	Roots	Pounded and added to tea	W	Not recorded	Bone injury	[24]
Cleomaceae	*Gynandropsis gynandra* (L.) Briq	*Akeo*	Leaves	Stewed daily	C	Investigated	Malaria, abdominal pain, eye pain, hernia, and hypertension	[20]
Rubiaceae	*Hallea rubrostipulata* (K. Schum.) J-F. Leroy	*Muziku*	Roots	Decoction	W	Not recorded	Pre-hepatic jaundice, malaria, backache, and salpingitis	[34]
Fabaceae	*Indigofera arrecta* Hochst. ex A. Rich	*Akabamba maliba*	Leaves	• The leaves are crushed and filtered after the addition of water • The leaves are minced, shade-dried, powdered, and reconstituted with water	W	Investigated	Not recorded	[23]
Acanthaceae	*Justicia betonica* L	*Nalongo/Lukawa*	Leaves	Powdered and boiled for 15 min	W	Not recorded	Yellow fever and malaria	[16, 24]
Bignoniaceae	*Kigelia africana* (Lam.) Benth	*Yago/Omusa*	Not specified	Not specified	W	Investigated	Diarrhea, malaria, and cancer	[19]
Lamiaceae	*Leonotis ocymifolia* (Burm.f.) Iwarsson	*Ekifumufumu*	Leaves	•The leaves are crushed and filtered after the addition of water • The leaves are minced, shade-dried, powdered, and reconstituted with water	W	Not recorded	Not recorded	[23]

Table 1 (continued)

Plant family	Scientific name	Local name	Parts used	Mode of preparation	Habitat	Anti-diabetic activity investigation status	Other diseases treated	References
Apocynaceae	*Mondia whitei* (Hook.f.) Skeels	*Omulondo*	Roots	•The roots are crushed and filtered after the addition of water to obtain a clear solution • The roots may be chewed directly	W	Not recorded	Not recorded	[23]
Moringaceae	*Moringa oleifera* Lam	*Muringa*	Leaves	Decoction	C	Investigated	Constipation, headache, arthritis, genito-urinary diseases, hypertension, and typhoid fever	[17]
Oxalidaceae	*Oxalis corniculata* L	*Kajjampuni*	Leaves and flower	Chewing of leaves	W	Investigated	Wounds, athlete's foot, skin cancer, and high blood pressure	[24]
Lauraceae	*Persea americana* Mill	*Ovakedo*	Seeds	The seeds are dried, powdered, and reconstituted with water	C	Investigated	Not recorded	[23]
Arecaceae	*Phoenix reclinata* Jacq	*Empirivuma*	Seeds	The seeds are dried, roasted, and powdered. The powder can be reconstituted with water. Alternatively, the seeds may be crushed after drying without roasting	W	Not recorded	Not recorded	[23]
Anacardiaceae	*Pseudospondias microcarpa* Engl	*Nalongo*/quinine	Leaves and whole plant	Decoction	W	Not recorded	Hypertension and malaria	[19]
Myrtaceae	*Psidium guajava* L	*Mapera*	Leaves and root bark	Decoction	C	Investigated	Malaria, cough, wounds, typhoid, measles, diarrhea, smallpox, and dysentery	[21]
Asteraceae	*Schkuhria pinnata* (Lam.) Kuntze ex Thell	*Apunait*	Leaves	Infusion	W	Investigated	Malaria and chest pain	[21]
Fabaceae	*Sesbania sesban* (L.) Merr	*Muzimbandeya*	Roots	Not specified	W, C	Investigated	High blood pressure	[24]
Solanaceae	*Solanum aethiopicum* L	*Entula*	Fruits	The fruits are minced and cooked. The soup and fruits are consumed	C	Not recorded	Not recorded	[23]

Table 1 (continued)

Plant family	Scientific name	Local name	Parts used	Mode of preparation	Habitat	Anti-diabetic activity investigation status	Other diseases treated	References
Solanaceae	*Solanum indicum* Roxb	*Katunkuma*	Fruits	•Fruits crushed, mixed with water, and filtered •Fruits dried, powdered, reconstituted with water, and filtered • Fruits cooked and consumed	C	Investigated	Not recorded	[23]
Solanaceae	*Solanum melongena* L	*Bilinganya*	Leaves and fruits	•The fruits are minced and cooked. The soup and the fruits are consumed • The leaves are crushed and filtered after the addition of water • The leaves are minced, shade-dried, powdered, and reconstituted with water	C	Investigated	Not recorded	[23]
Apiaceae	*Steganotaenia araliacea* Hochst	*Omuwanula*	Leaves	Decoction	W	Not recorded	Not recorded	[34]
Myrtaceae	*Syzygium cumini* (L.) Skeels	*Jambula*	Fruits and seeds	•Fruits cooked and consumed without the seeds • The seeds are dried and crushed into a paste. The paste is reconstituted with water and filtered to obtain a solution	W	Investigated	Not recorded	[23]
Asteraceae	*Tithonia diversifolia* (Hemsl.) A.Gray	*Kimyula*	Leaves	Consumed after boiling	W	Investigated	Malaria	[16]
Rutaceae	*Toddalia asiatica* (L.) Lam	*Kaule*	Roots	Not specified	W, C	Investigated	Anemia, aphrodisiac, brain disorders, diarrhea, HIV/AIDS, hypertension, menstrual cramps, typhoid fever, snake bite, and ulcers	[22]

Table 1 (continued)

Plant family	Scientific name	Local name	Parts used	Mode of preparation	Habitat	Anti-diabetic activity investigation status	Other diseases treated	References
Asteraceae	*Vernonia amygdalina* Del	*Omululuza*	Leaves	•Fresh leaves mixed with water and squeezed to obtain the juice • Leaves shade-dried, powdered, and reconstituted	W	Investigated	Not recorded	[23]
Fabaceae	*Vigna unguiculata* (L.) Walp	*Bojo*	Leaves	Mixed with acacia (Garcia) and crushed to extract the juice. The juice is consumed twice a month stewed (+ paste) once daily or raw leaves chopped and consumed daily	C	Investigated	Malaria, abdominal pain, chest pain, visual impairment, hernia, ulcers, and cancer	[20]
Canellaceae	*Warburgia ugandensis* Sprague	*Abasi*	Leaves and stem bark	Fresh leaf boiled or bark dried and consumed (1 teaspoonful)	W, C	Not recorded	Colic pain, worm infection, allergy, malaria, general body weakness, stomach ache, erectile dysfunction, cough, and snakebite	[18]

Habitat C cultivated, *W* wild; *HIV* human immunodeficiency virus; *AIDS* acquired immunodeficiency syndrome

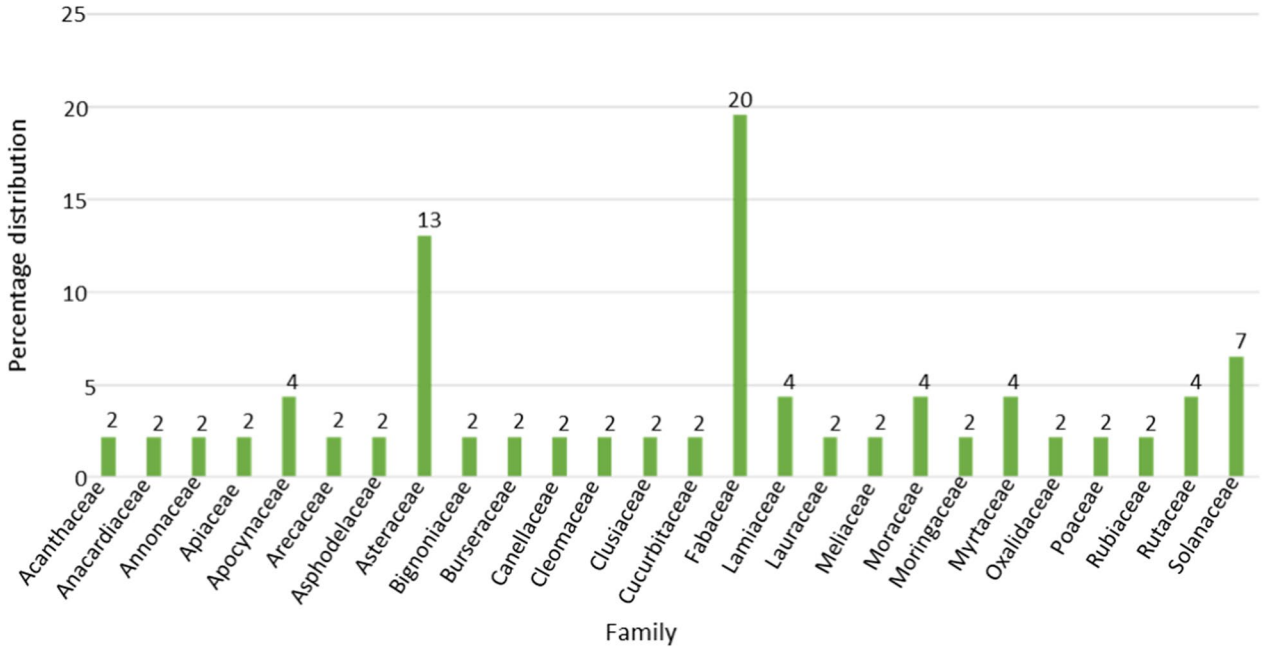

Fig. 1 Distribution of medicinal plant families used for treating diabetes mellitus in Uganda

for Ugandan traditional medicines, except the highly fragmented reports of ethnobotanical studies conducted in Uganda. However, at African level, some active databases for African traditional medicine are available with non being specific to DM or any other disease (Table 3). Consequently, due to a wide range of biodiversity among countries, antidiabetic use of most plants registered in this study are not found in these general databases; although some plants are available with similar uses. For example, use of *Acacia constricta* for treatment of DM and other ailments is documented in PRELUDE database while use of *Albizia chinensis* for treatment of DM in the same database is not found currently. Considering the biodiversity difference among countries, development of comprehensive indigenous knowledge systems for African traditional medicine requires more efforts towards documenting these knowledge at country and subsequently regional (East, North, West, and South African) levels. The unavailability of Ugandan and limited African traditional medicine databases or records may be attributed to several factors among others, difficulty associated with language translation as most countries are made of diverse population with various languages, lack of funds for establishment and maintenance, and issues of intellectual property right [111]. In fact, insufficient or lack of funding has made several indigenous knowledge systems for traditional medicine become less updated or/and inactive online. For instance, a database known as NTRAP (Website: http://www.ippc.orst.edu/ipmafrica/db/index.html) that contained traditional medicine indigenous knowledge for East Africa (Uganda inclusive) is currently inactive [111].

Ethnopharmacological activities of medicinal plants used for treating DM in Uganda based on global scientific investigations

In vitro and in vivo studies

According to the WHO Traditional Medicine Strategy objectives, experimental validation with specified doses is the only way for proper understanding of the safety and efficacy of herbal medicines despite their long traditional use [114]. With respect to DM, the typical clinical target is to reduce blood sugar [115]. Therefore, the in vivo evaluation of blood sugar lowering effect of medicinal plants is for inferring potential clinical efficacy. In vitro studies are useful in the establishment or verification of the mechanisms of action of substances with potential therapeutic effects including medicinal plants [115]. Twenty seven (59%) out of the forty six medicinal plants in this review have been evaluated for their pharmacological activities against DM in several in vitro and in vivo studies worldwide (Table 4). Indeed, these plants have shown significant pharmacological activities including anti-hyperglycemic, anti-lipidemic, and antioxidative properties.

Taken together, these ethnopharmacological activities were exerted through various mechanisms of action. The mechanisms of action included decreasing blood sugar

Table 2 Ethnomedicinal uses of the identified plants in other countries neighbouring Uganda

Plant name	Country	Diseases treated	Part used	Reference
Ageratum conyzoides L	Kenya	Wounds, malaria, and asthma	Roots	[35]
	Tanzania	Malaria, cough, constipation, and peptic ulcers	Roots and leaves	[36, 37]
	DR Congo	DM, hypertension, poisoning, and malaria	Aerial parts and leaves	[38–40]
Albizia coriaria Welw. ex Oliv	Kenya	Malaria, inflammatory disorders, toothache, cough, and cancers	Stem bark	[41–43]
Aloe vera (L.) Burm.f	Kenya	DM, malaria, wound, low immunity, cryptococcal meningitis, HIV/AIDS, and skin infections	Leaf exudate/aerial parts	[44–46]
	Tanzania	DM, kidney diseases, and syphilis	Leaf exudate	[47–49]
	DR Congo	DM, abscess, burns, cancer, cough, and hepatitis	Leaves	[39]
Annona muricata L	Kenya	Cancers (Breast and cervical)	Fruits	[50]
	Tanzania	DM	Leaves	[32]
Azadirachta indica A. Juss	Kenya,	DM, malaria, skin rashes, and HIV/AIDS	Leaves, fruits, and stem bark	[44, 51]
	Tanzania	Head ache, back ache, malaria, fever, and stomachache	Leaves, stem bark, and seeds	[52]
	DR Congo	DM, malaria, and tuberculosis	Leaves	[39]
	Sudan	Malarial, fever, jaundice, helminthiasis, and skin diseases	Roots and leaves	[53]
Bidens pilosa L	Kenya	DM, malaria, and pneumonia	Leaves	[31, 54]
	Tanzania	Induce abortion and wound	Roots and whole plant	[55, 56]
	Rwanda	Pneumonia, yaws, and antiseptic	Leaves	[57]
	DR Congo	DM, abscess, cancer (prostate), cough, diarrhea, hemorrhage, urinary tract infections, wounds, and hypertension	Leaves, roots, seeds, and aerial parts	[39, 40]
Cajanus cajan (L.) Huth	Tanzania	DM, poisoning, nausea, and swelling of legs	Leaves, seeds, and aerial parts	[32, 37]
	Kenya	Chronic joint pains and allergies	Leaves and seeds	[58, 59]
	Rwanda	Pneumonia, gonorrhea, and asthama	Leaves	[57, 60]
Canarium schweinfurthii Engl	Tanzania	Malaria and syphilis	Stem bark	[36]
	DR Congo	DM, dysentery, hemorrhoids, and tuberculosis	Leaves	[39]
Citrus sinensis (L.) Osbeck	Kenya	Contraceptive and infertility	Roots and stem bark	[61]
	Tanzania	Induce abortion	Roots	[56]
	DR Congo	DM, cough, dysmenorrhea, fever, gonorrhea, malaria, and otitis	Leaves, roots, and fruits	[39]
Clerodendrum rotundifolium Oliv	Kenya	Pneumonia and malaria	Leaves and roots	[62, 63]
	Tanzania	Stomach ache and diarrhoea	Stem bark	[64]
Crassocephalum vitellinum S. Moore	Kenya	Stomach complications, malaria, and mouth infection in babies	Leaves	[65]
	Tanzania	Gonorrhea and the urinary tract infection	Leaves and stem	[66]
	Rwanda	liver diseases	Not recorded	[67]
	DR Congo	Swelling of leg	Leaves	[68]
Cucurbita maxima Duchesne	Tanzania	Epixstasis and excessive menstrual bleeding	Fruits	[37]
	Kenya	Diarrhoea	Seeds, leaves, and fruits	[69]
	DR Congo	Kidney disease	Not recorded	[70]
Cymbopogon citratus Stapf	Kenya	Colorectal cancer	Leaves	[41]
	Tanzania	DM	Leaves	[32]
	DR Congo	DM, malaria, measles, and premature delivery	Leaves	[39]

Table 2 (continued)

Plant name	Country	Diseases treated	Part used	Reference
Erythrina abyssinica DC	Kenya	DM	Stem bark	[31]
	Tanzania	DM, increase libido, and stomach pain	Roots	[32]
	DR Congo	DM, cancer, hepatitis, hernia, and sinusitis	Roots, stem bark, and leaves	[39]
	Sudan	Antimicrobial, jaundice, and rheumatic pain	Bark and seeds	[53]
Garcinia buchananii Baker	Kenya	DM and aphrodisiac	Stem bark	[44]
	Tanzania	Venereal diseases, dysentery, HIV/AIDS, and malaria	Stem bark or roots	[36]
Gynandropsis gynandra (L.) Briq	Kenya	Recuperating pregnant and lactating mothers and circumcised boys	Leaves	[71]
	Tanzania	Headache	Roots and leaves	[72]
	DR Congo	Lymphoadenitis, otitis, mumps, bronchitis, and elephantiasis	Leaves and flowers	[73]
Hallea rubrostipulata (K. Schum.) J-F. Leroy	Tanzania	Respiratory tract infections	Stem bark and leaves	[74]
	Rwanda	Liver diseases	Not recorded	[67]
Indigofera arrecta Hochst. ex A. Rich	Kenya	Stomach disorders	Roots	[58]
	Tanzania	Increase virility	Roots	[75]
	DR Congo	DM, fractures, and malaria	Roots	[39]
Justicia betonica L	Kenya	Inflammation	Whole plant	[76]
	Tanzania	stomach ache	Whole plant	[77]
Kigelia africana (Lam.) Benth	Kenya	Measles	Fruits	[58]
	Tanzania	DM and mental illness	Fruits	[32]
	DR Congo	DM, male impotence, and vaginal infections	Stem bark	[78]
	Sudan	DM	Fruits	[79]
Leonotis ocymifolia (Burm.f.) Iwarsson	Kenya	DM, coughing, and asthma	Roots	[80]
Mondia whitei (Hook.f.) Skeels	Kenya	Aphrodisiac, ringworms, skin diseases, stomach worms, heart diseases, and asthma	Roots	[58, 81]
	Tanzania	Abdominal pain and facilitate child birth	Roots	[82]
	DR Congo	Erectile dysfunction	Leaves and roots	[83]
Moringa oleifera Lam	Kenya	Arthritis/gouts, loss of memory, prostate cancer, and high blood pressure	Seeds and leaves	[84]
	Tanzania	DM	Flowers, Pods, seeds, roots, and leaves	[32]
	DR Congo	DM, cataract eye, conjunctivitis, and malaria	Leaves and flowers	[39]
Oxalis corniculata L	Kenya	Skin infections	Leaves	[85]
	Tanzania	Stomach upset, rusts, and wounds	Leaves	[86]
	Rwanda	Asthama	Aerial parts	[60]
Persea americana Mill	Kenya	DM	Leaves	[87]
	Tanzania	DM	Seeds and whole plant	[32]
	Rwanda	Liver diseases	Not recorded	[67]
	DR Congo	DM, anemia, constipation, diarrhea, fever, pain, and sickle cell	Leaves, stem bark, and fruits	[39]
Phoenix reclinata Jacq	Kenya	Male reproductive dysfunctions	Roots	[61]
	Tanzania	Epilepsy, eye troubles, stomach aches, pleuritic pains and pleurisy	Roots, leaves, and thorn	[88]
Pseudospondias microcarpa Engl	Tanzania	Peptic ulcers and malaria	Stem bark	[36, 89]
	DR Congo	Malaria	Stem bark and root bark	[89]

Table 2 (continued)

Plant name	Country	Diseases treated	Part used	Reference
Psidium guajava L	Kenya	Diarrhea and stomachache	Leaves	[90]
	Tanzania	Yellow fever, dysentery, and mucoid diarrhea	Not recorded	[36]
	DR Congo	DM, amoebiasis, diarrhea, dysentery, and female infertility	Roots and leaves	[39]
Schkuhria pinnata (Lam.) Kuntze ex Thell	Kenya	Malaria	Whole plant	[91]
	Tanzania	Gastrointestinal remedies	Whole plant	[92]
Sesbania sesban (L.) Merr	Kenya	Throat/stomach/oesophageal cancer	Whole plant	[41]
	Tanzania	Venereal diseases	Leaves	[93]
	Rwanda	Gonorrhea, syphilis, and conjunctivitis	Leaves	[57]
Solanum aethiopicum L	DR Congo	DM and abdominal pain	Roots, fruits, leaves, and seeds	[39]
Solanum melongena L	DR Congo	DM	Fruits	[94]
Steganotaenia araliacea Hochst	Kenya	DM	Leaves	[44]
	Tanzania	Herpes zoster and HIV/AIDS	Areal parts	[36]
	DR Congo	DM	Not recorded	[95]
Syzygium cumini (L.) Skeels	Tanzania	DM	Stem bark	[32]
	DR Congo	DM	Fruits	[39]
Tithonia diversifolia (Hemsl.) A.Gray	Kenya	Stomach pains and typhoid	Leaves	[96]
	Tanzania	Skin infections, stomach problem	Leaves	[93]
	DR Congo	DM, amoebiasis, anorexia, asthenia, constipation, and splenomegaly	Leaves	[39]
Toddalia asiatica (L.) Lam	Kenya	Abdominal pains, gynaecologic disorders such as infertility, common colds, cancer, and renal disorders	Roots and leaves	[97]
	Tanzania	Stomach problems and malaria	Root bark, stem bark, leaves, and fruits	[98]
Vernonia amygdalina Del	Kenya	Abdominal pains in infants and in pregnancy, arthritis, meningitis, malaria, typhoid, and epilepsy	Roots	[97]
	Tanzania	Febrile convulsions, fever, and malaria	Roots and leaves	[36]
	Rwanda	Gastroenteritis	Leaves	[57]
	DR Congo	DM, dysentery, gallstone, gastritis, helminthiasis, headache, hepatitis, malaria, poisoning antidote, rashes with itching, scabies, and tuberculosis	Leaves	[39]
Vigna unguiculata (L.) Walp	Kenya	Obesity	Leaves	[99]
	Tanzania	Anemia	Leaves and seeds	[100]
	DR Congo	Sickle cell	Leaves	[101]
Warburgia ugandensis Sprague	Kenya	DM, malaria, and pneumonia	Leaves	[102]
	Tanzania	Toothache, cough, fever, general body pains, anthelmintic, and malaria	Roots and stem bark	[103]

DR Congo Democratic Republic of the Congo; *DM* Diabetes mellitus; *HIV* human immunodeficiency virus; *AIDS* acquired immunodeficiency syndrome

via stimulation of pancreatic β-cells [116, 117], inhibition of α-amylase, α-glucosidase, DPP-IV, insulinase, and aldose reductase enzymes activities [118–121], increasing expression of glucose transporters [122, 123], and enhancement of the affinity as well as sensitivity of insulin receptors [124]. Additionally, the plants acted through increase of glucose utilization within several tissues and organs [125], resistance of lipid peroxidation [126–128], clearance of free radical [127], and correction of lipid as well as protein metabolic disorders [129–131]. The observed mechanisms of action are comparable to those of current drugs used in DM treatment. For example, plants such as *Syzygium cumini* (L.) Skeels and *Kigelia africana* (Lam.) Benth., with α-amylase and α-glucosidase inhibitory effects are similar in action to acarbose [132]. Stimulators of pancreatic β-cells, for instance *Tithonia diversifolia* (Hemsl.) A.Gray and *Bidens pilosa* L. function as sulfonylureas or non-sulfonylureas secretagogues

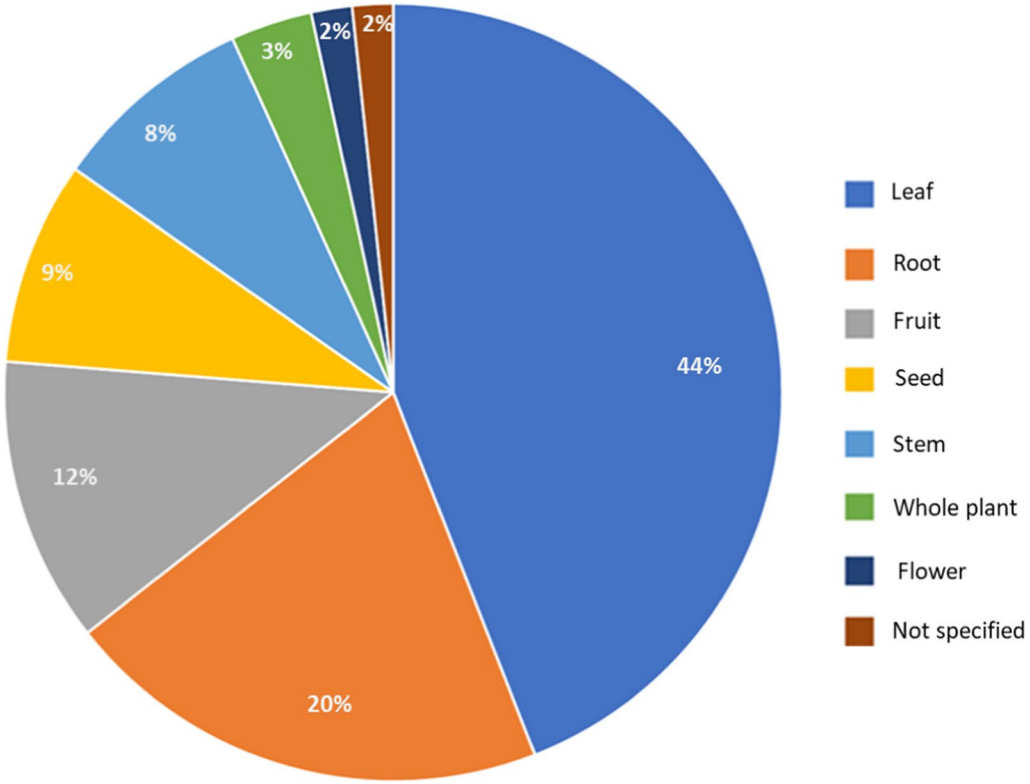

Fig. 2 Percentage use of different plant parts for treatment of diabetes mellitus in Uganda

Table 3 List of some active African Traditional Medicine Databases

Name of database	Compiler/ publisher	Country	Language	Website	References
PRELUDE	Jean Lehmann Universite de Louvain	Sub-Saharan Africa/ Belgium	English/French	http://www.africamuseum.be/collections/external/prelude	[111]
Botanica Ethiopia	Elizabeth d'Avigdor	Ethiopia	English/Amharic	https://botanicaethiopia.com/herbs	[112]
PlantZAfrica	South African National Biodiversity Institute (SANBI)	South Africa	English	http://pza.sanbi.org	[113]
PROTAbase	Wageningen University (WU)	International	English	https://www.prota4u.org/database/	[111]

PROTAbase Plant Resources of Tropical Africa Database

classes of drugs [115]. Plants like *Schkuhria pinnata* (Lam.) Kuntze ex Thell. which increase glucose utilization within tissues and organs are comparable to the biguanides drugs [115]. Agonists of PPARγ, for instance, *Tithonian diversifolia* (Hemsl.) A.Gray are similar in action with thiazolidinediones class of hypoglycemic agents [132]. Thus, the known mechanisms of action of the antidiabetic medicinal plants provide prospective therapeutic benefits of the plants, which may be utilized in the development of DM therapy. Medicinal plants studied elsewhere such as *Chiliadenus iphionoides* (Boiss. & C.I.Blanche) Brullo, *Prunus africana* (Hook.f.) Kalkman, *Aspilia africana* (Pers.) C.D.Adams, *Cassia fistula* L., and *Ocimum gratissimum* L. were reported to exhibit similar mechanisms of action against DM [33, 104, 132–134].

Phytochemicals in these plants either singly or in combination have been implicated for their antidiabetic

Table 4 Anti-diabetic, anti-lipidemic, and antioxidative properties of medicinal plants used for treating DM in Uganda based on global scientific investigations

Plant	Part used	Extracts/ formulation	Dose and route of administration	Test modal	Activity	Result	Active phytochemicals and toxicity information	References
Tithonia diversifolia (Hemsl.) A.Gray	Leaf	Ethanol	25, 50, and 100 mg/ kg body weight (p.o)	STZ rat	Anti-hyperglycemic	↓ Blood glucose and ↓polyphagia		[156]
	Leaf	Aqueous fraction	200 and 300 mg/kg body weight (p.o)	Alloxan rat	Anti-hyperglycemic and antioxidant	↓ Blood glucose, ↑ serum insulin, ↓ oxidative damage of β-cells, and ↑ Immunoexpression of GLUT2		[157]
	Aerial part	Isolates	10 µg/mL	In vitro	Anti-hyperglycemic	↑ glucose uptake in 3T3-L1 adipocytes	Monoterpene (1S,2R,3R,5S)-2-hydroxymethyl-6,6-dimethylbicyclo [3.1.1] heptane-2,3- diol and sobrerol	[125]
	Leaf	Aqueous and n-butanol extracts	100, 200, and 300 mg/kg body weight	Alloxan mice and In vitro	Anti-hyperglycemic and antioxidant	↓ Blood glucose, ↑ serum insulin, ↓ the liver and pancreatic injuries, showed antioxidant and free radicals scavenging activities		[158]
		Isolates		In vitro	Anti-hyperglycemic	↓ Insulin resistance and ↑ PPARγ activity	Sesquiterpene lactone, thyrotundin, and tagitinin A; aerial parts exhibited cytotoxicity against cells from the human fetal lung fibroblast cell line; aerial part ethanol extract showed dose and time dependent toxic effect on the kidney and liver morphology in rats with $LD_{50} > 1600$ mg/ kg/ day	[140, 159, 160]
Erythrina abyssinica DC	Stem bark	Aqueous	500 mg/kg body weight	Guinea pigs administered glucose solution	Anti-hyperglycemic	↓ Postprandial plasma glucose levels		[161]
	Stem bark	Aqueous	50, 100, and 150 mg/ kg body weight (i.p)	Alloxan Wistar rats	Anti-hyperglycemic	↓ Blood glucose levels		[162]

Table 4 (continued)

Plant	Part used	Extracts/ formulation	Dose and route of administration	Test modal	Activity	Result	Active phytochemicals and toxicity information	References
	Stem bark	Isolates		In vitro	Anti-hyperglycemic	Inhibited PTP1B activity	Flavanones	[163]
	Stem bark	Isolates	10 µM	In vitro	Anti-hyperglycemic and anti-hyperlipidemic	↑ AMPK activation by stimulating the phosphorylation	Erythribyssin N and three other unnamed compounds; seed is reported to be poisonous; root extract produced oral LD_{50} of 776.2 mg/kg in mice and showed dose dependent acute toxicity	[141, 164, 165]
Moringa oleifera Lam	Seed	Powder	50 and 100 mg/kg body weight (p.o)	STZ Albino rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ FBG, ↓ lipid peroxide lipid, ↓ HbA1c, ↓ antioxidant enzymes, alleviated the pathological changes in the kidney and pancreas tissues to physiological levels		[166]
	Leaf	Aqueous	200 mg/kg body weight (p.o)	STZ Sprague–Dawley rats	Antioxidant	↓ FBG, ↓ glutathione, ↓ ROS, ↓ malondialdehyde, and alleviated the pathological changes in the kidney	Intake is safe at levels ≤ 1000 mg/kg body weight	[167, 168]
	Seed	Oil	2.0 mL/kg body weight (p.o)	Alloxan Wistar rats	Anti-hyperlipidemic	↓ Cholesterol, ↓ LDL, ↓ TG, ↓ serum total bilirubin, ↓ TP, ↓urea, and ↓ creatinine		[169]
	Leaf	Methanol	250 and 500 mg/kg body weight (p.o)	STZ Wister rats	Anti-hyperglycemic	↓ FBG, ↓ bodyweight gain, ↓ plasma albumin, and ↑ glucose tolerance		[170]
	Leaf	Aqueous	50 µl and 100 µl	In vitro	anti-hyperglycemic and antioxidant	Inhibited α-amylase and α-glucosidase activities, and radical scavenging activities,	Phenolics	[171]

Table 4 (continued)

Plant	Part used	Extracts/ formulation	Dose and route of administration	Test modal	Activity	Result	Active phytochemicals and toxicity information	References
	Leaf		1 g and 2 g (p.o)	Pilot clinical study	Anti-hyperglycemic	↓ Postprandial glycemia		[172]
	Leaf	Powder	p.o	Clinical	Anti-hyperglycemic	↓ Serum glucose and ↓ LDL		[173]
Persea americana Mill	fruit	Juice	1,264 and 1,896 mg/kg body weight (p.o)	STZ Wister rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ bodyweight, ↓ FBG, and ↓ LDL, and ↑ HDL		[174]
	Fruit	Oil	5–20% (p.o)	Glucose tolerance and insulin resistance Wistar rats	Anti-hyperglycemic	↓ blood glucose levels and ↓ insulin resistance		[175]
	Seed	Methanol	300 and 600 mg/kg body weight	Alloxan Wistar rats	Anti-hyperglycemic	↓ FBG, ↑ insulin, ↑ c-peptide, and ↑ β-cell function, and ↓ insulin resistance	Seed ethanol extract showed no genotoxic activity in micronucleus test. Acute toxicity study revealed a relatively low LD_{50} for seed extract of 751.6 mg/kg body weight	[176–178]
	Seed	Aqueous	20, 30, 40 g/L (p.o)	Alloxan Wister rats	Anti-hyperglycemic and organ protective effect	↓ Blood glucose and exerted protective effects on kidneys, pancreas, and liver		[179]
	Seed	Powder	500 mg (p.o)	Fructose- fed insulin resistance Wister rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ LDL, ↑ HDL, ↓ ALT, ↓ bilirubin, ↓ FBG, ↓ HbA1c, improved coronary risk index and fasting insulin resistance index		[131]
	Leaf	Hydroalcohol	0.15 and 0.3 g/kg bodyweight/day (p.o)	STZ Wister rats	Anti-hyperglycemic	↓ Blood glucose levels and mitigated the dysregulated metabolism, and activated serine-threonine kinase Akt	Leaf chloroform–methanol extract of 1900 and 2600 mg/Kg body weight showed no obvious sign of toxicity in mice	[180, 181]
	Leaf	Hydroalcohol	100 mg/kg body weight (p.o)	STZ Wister rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ Blood glucose, ↑ total cholesterol, and ↑ HDL		[182]

Table 4 (continued)

Plant	Part used	Extracts/ formulation	Dose and route of administration	Test modal	Activity	Result	Active phytochemicals and toxicity information	References
	Leaf	Methanol	10 µL	In vitro	anti-hyperglycemic	Inhibited α-glucosidase, aldose reductase, maltase-glucoamylase, and aldehyde reductase activities		[120]
	Leaf	Aqueous	125–500 mg/kg body weight (p.o)	Alloxan Wistar rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ FBG, ↓ hyperlipidaemia, ↓ AST, ↓ urea, ↓ TP, ↓ ALB, ↓ ALT, and ↓ ALP		[183]
Vernonia amygdalina Del	Leaf	Methanol	200 and 400 mg/kg body weight (p.o)	Alloxan Wistar rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ Blood glucose, ↓ LDL, and ↑ body weight		[184]
	Leaf	Aqueous	15, 30, 60, 120, and 240 µg/ml	In vitro	anti-hyperglycemic and anti-hyperlipidemic	Inhibited α-glucosidase and pancreatic lipase activities, and ↑ muscle glucose uptake	Aqueous leaf extract showed no acute hepatotoxicity in rats with LD_{50} of 500 mg/kg; No toxicity signs and mortality observed at up to 5000 mg/kg body weight in rats	[185–187]
	Leaf	Ethanol	400 mg/kg body weight (p.o)	Alloxan rats	anti-hyperglycemic	Inhibited α-amylase activity and regeneration of pancreatic beta cells		[188]
	Root	Ethanol	500 mg/kg body weight (p.o)	Alloxan Wistar rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ Blood glucose, ↓ the cholesterol, ↓ serum protein, and ↓ total lipid		[130]
	Leaf	Ethanol	400 mg/kg body weight (p.o)	STZ rats	Anti-hyperglycemic and anti-hyperlipidemic	↑ Glucose tolerance, ↓ FBG, ↓ TG, ↓total cholesterol, protective effect on pancreatic β-cells, ↑ GLUT 4 translocation, and inhibited hepatic G6Pase activity		[122]

Table 4 (continued)

Plant	Part used	Extracts/ formulation	Dose and route of administration	Test modal	Activity	Result	Active phytochemicals and toxicity information	References
	Leaf	Chloroform	1 g/kg (p.o)	STZ Sprague Dawley rats	Anti-hyperglycemic	↓ Serum glucose, suppression of gluconeogenesis, and ↑ glucose oxidation through the pentose phosphate pathway in the liver	Fatty acids (linoleic acid and α-linolenic acid) and phytols	[189]
Artocarpus heterophyllus Lam	stem bark	Acetone and ethyl acetate	400 mg/kg body weight (p.o)	In vitro and STZ Wister rats	Anti-hyperglycemic and anti-hyperlipidemic	Inhibited the α-amylase and α-glucosidase activities, ↑ insulin, ↑ glycogen, ↑ hexokinase activities, ↑ pancreatic β-cell scores, ↑ antioxidant enzymes, and ↑ glucose transporter concentration, ↓ FBG, ↓ lipid peroxidation, and ↓ glucose-6-phosphatase	Free and bound phenols	[126]
	Stem bark	Ethanol	50, 100 and 150 mg/kg body weight (p.o)	Alloxan rats	anti-hyperglycemic	↓ Weight reduction, ↓ LD, ↓ creatinine, ↓ bilirubin, ↓ urea, and ↑ albumin		[118]
	Leaf	Aqueous	250 mg/kg body weight (p.o)	STZ Wister rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ Serum glucose, ↓ total cholesterol, and ↑ HDL	Aqueous leaf extract showed no adverse effects on liver function, haematological parameters, reproductive ability, and histology of the heart, lung, kidney, intestines and pancreas in rats	[190, 191]
	Leaf	ethanol and n-butanol	200 mg/kg body weight (p.o)	STZ Wister rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ FBG, ↓ TC, ↓ lipid peroxides, ↓ HbA1c, ↓ LDL, ↑ insulin, ↑ total protein, and ↑ HDL		[192]

Table 4 (continued)

Plant	Part used	Extracts/ formulation	Dose and route of administration	Test modal	Activity	Result	Active phytochemicals and toxicity information	References
	Leaf	Decoction	96 mL (p.o)	Clinical study	Anti-hyperglycemic and anti-hyperlipidemic	↓ Post-prandial blood glucose, ↓ FBS, and ↓ TC, mitigated symptoms including polyphagia, polydipsia, joint pain, polyuria, lassitude, excessive sweating, and dryness of the mouth		[193]
Azadirachta indica A. Juss	Leaf	Ethanol	200 mg/kg body weight (p.o)	STZ Wister rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ Blood glucose, ↓ TC, ↓ LDL, ↓ TG, and ↑ HDL	Neem extracts/ subproducts are nontoxic or less toxic when orally administered in rats; animals only show acute toxicity when treated by intramuscular injection or the i.p route. Extracts show dose dependent subacute and subchronic toxicity at high doses thus safe at lower doses	[194, 195]
	Leaf and seed oil	Aqueous	500 (Leaf extract) and 5 mL/kg (seed oil) (p.o)	Normal rabbits and alloxan diabetic rabbits	Antidiabetic and anti-hyperglycemic	Protected against the development of DM in pre-treated rabbits and ↓ blood glucose	Neem oil produced different pharmacotoxic effects (LD_{50} of 14 and 24 ml/kg) in rats and rabbits respectively; suggesting a narrow margin of safety when used therapeutically	[196, 197]
	Root	Ethanol	800 mg/kg body weight (p.o)	Alloxan Wistar rats	Anti-hyperglycemic	↓ Blood glucose		[198]
	Leaf, seed, root, and stem back	Isolates		In vitro	Anti-hyperglycemic	Inhibited α-glucosidase and α-amylase activities	Limonoids, meliacinolin 1, and nimbidiol	[119, 142, 199]

Table 4 (continued)

Plant	Part used	Extracts/ formulation	Dose and route of administration	Test modal	Activity	Result	Active phytochemicals and toxicity information	References
	Seed	Powder	6 g daily (p.o)	Clinical study	Anti-hyperglycemic	↓ FBG and ↓ postprandial blood glucose		[200]
	leaf and twig	Aqueous	125, 250, and 500 mg twice a day (p.o)	Clinical study	Anti-hyperglycemic	↓ FBG, ↓ postprandial blood glucose, ↓ HbA1c, and ↓ insulin resistance		[201]
	Leaf	Powder	2 g/ day (p.o)	Clinical study	Antidiabetic	alleviated the symptoms of polydipsia, polyphagia, and headache by 33%, 35%, and 38%, respectively		[202]
	Leaf	Aqueous	400 mg/kg body weight (p.o)	High-fat and fructose Wister rats	Anti-hyperglycemic	↓ blood glucose, ↑ serum insulin, ↑ insulin signaling molecules, and ↑ GLUT4		[203]
Psidium guajava L.	Leaf	Ethyl acetate fraction	25 and 50 mg/kg body weight (intragastric)	STZ Sprague–Dawley rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ Blood glucose, ↓ fructosamine, ↓ HbA1c, and did not affect the levels of toxicity markers, including serum glutamate oxaloacetate transaminase and serum glutamate pyruvic transaminase		[204]
	Fruit		125 and 250 mg/kg body weight (p.o)	STZ Sprague–Dawley rats	Anti-hyperglycemic	↓ Bodyweight loss, ↓blood glucose, and ↑ insulin concentration		[205]
	Fruit peel	Aqueous	400 mg/kg body weight (p.o)	STZ Wister rats	Anti-hyperglycemic	↓ FBG, ↓ postprandial glucose, and ↓ urinary glucose		[206]
	Stem bark	Ethanol	250 mg/kg body weight (p.o)	Alloxan Wistar rats	Anti-hyperglycemic	↓ Blood glucose		[207]
	Leaf	Methanol, aqueous, and ethanol	50 g plant extract/l	In vitro	Anti-hyperglycemic	Inhibited α-glucosidase and α-amylase activities		[208, 209]

Table 4 (continued)

Plant	Part used	Extracts/ formulation	Dose and route of administration	Test modal	Activity	Result	Active phytochemicals and toxicity information	References
	Leaf		200 mg/kg/d (p.o)	STZ Kunming mice	Anti-hyperglycemic	↓ FBG, ↑ glucose tolerance, ↓ insulin resistance index, ↓ serum total cholesterol, and ↓ LDL	Flavonoids	[210]
	Leaf		60, 120, and 240 mg/kg body weight		Anti-hyperglycemic and anti-oxidant	↓ FBG, ↑ serum insulin and insulin sensitivity index, protected the pancreatic cells such as islet β-cells, against lipid peroxidation	Total triterpenoids	[211]
	Leaf	Aqueous	200 and 400 µg/mL	In vitro	Anti-hyperglycemic	↑ glucose uptake		[212]
Cucurbita maxima Duchesne	Pulp	Powder	5 g (p.o)	Clinical study	Anti-hyperglycemic	↓ average glucose		[213]
	Seed	petroleum ether, ethyl acetate, alcohol, and aqueous	200 mg/kg body weight (p.o)	STZ Wister rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ FBG, ↓ blood glucose, ↓ serum total cholesterol, ↓ LDL, ↓ VLDL, ↓ TG, ↑ insulin, and ↑ HDL	Hydroalcoholic extract of seeds exhibited no acute and subacute toxicity at 5000 mg/kg and 1000 mg/kg, respectively in mice	[214, 215]
	Seed	Oil	100 mg/kg body weight (p.o)	High-fat diet-induced obesity rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ Body weight gain, ↓ glucose, and ↑ insulin, and ↓ LDL		[216, 217]
	Leaf	Methanol		In vitro	Anti-hyperglycemic	Inhibited α-amylase activity		[218]
	Pulp	Methanol	200 and 400 mg/kg body weight (p.o)	STZ rats	Anti-hyperglycemic and antioxidant	↓ Serum levels of hepatic enzyme activities and oxidative stress markers, ↓ blood glucose, restored serum proteins and lipid profile		[129]
Citrus sinensis (L.) Osbeck	Fruit	Juice	2, 5, and 8 mL/kg (p.o)	Alloxan Wistar rats	Anti-hyperglycemic	↓ Blood glucose and ↑ plasma insulin		[219]

Table 4 (continued)

Plant	Part used	Extracts/ formulation	Dose and route of administration	Test modal	Activity	Result	Active phytochemicals and toxicity information	References
	Fruit peel	Methanol	50 and 100 mg/kg body weight (p.o)	STZ Wister rats	Anti-hyperglycemic	↓ FBG, ↑ PPARγ in adipose tissues, ↑ GLUT 4, and ↑ insulin receptors		[124]
	Fruit peel	Ethanol and acetone	125, 250, and 500 mg/kg body weight	Alloxan rats	Anti-hyperglycemic and anti-hypercho-lesterolemic	↓ Blood glucose and ↓ blood cholesterol		[220]
	Leaf	Essential oil	110 mg/kg body weight (i.p)	Alloxan rats	Anti-hyperglycemic	↓ FBG and ↓ hepatic glucose, and ↑ hepatic glycogen		[221]
	Stem bark	Aqueous	400 mg/kg body weight (p.o)	Wistar rats	Anti-hyperglycemic	↓ Postprandial glucose		[222]
	Seed	Oil	1000 mg/kg body weight	Alloxan Wistar rats	Anti-hyperglycemic	↓ Blood glucose		[223]
Bidens pilosa L	Leaf	Methanol and Polyacetylenes	10, 50, or 250 0.5 for Polyacety-lenes mg/kg body weight (p.o)	db/db mice	Anti-hyperglycemic	↓ Postprandial glu-cose, ↑ serum insulin, and ↓ glycosylated HbA1c	Polyacetylenes	[224]
	Whole plant	Aqueous	50 mg/kg body weight (p.o)	Alloxan db/db mice	Anti-hyperglycemic	↓ Postprandial glucose and ↑ serum insulin	Showed no adverse effects in mice and chickens at dose 5% or less of food	[225, 226]
	Whole plant	butanol fraction	10 mg/kg body weight (i.p.)	NOD mice	Anti-hyperglycemic	Regeration of pancreatic β islets, inhibited β-cell death and leukocyte infiltration		[117]
	Formulation (probetacell)		400 mg (p.o)	Pilot clinical study	Anti-hyperglycemic	↓ FBG, ↓ glycosylated HbA1c, ↑ β-cell function		[25]

Table 4 (continued)

Plant	Part used	Extracts/ formulation	Dose and route of administration	Test modal	Activity	Result	Active phytochemicals and toxicity information	References
Aloe vera (L.) Burm.f	Leaf pulp	phosphate buffered saline	500 mg/kg body weight (p.o)	STZ Wister rats	Anti-hyperglycemic	↓ Blood glucose	Observed acute and subacute toxicity, cytotoxicity, and mutagenicity associated with constituent anthraquinones of whole leaf extract; produced LC_{50} of 3.59 µg/ml in brine shrimp and LD_{50} of 120.65 mg/kg in mice; LD_{50} of 250 mg/kg in rats; HeLa and HepG2 cells with CC_{50} of 413.9 and 439.0 mg/ml, respectively, after 4-h	[227–231]
	Leaf pulp	Aqueous	150 mg/kg body weight (p.o)	Alloxan Wistar rats	Anti-hyperglycemic and anti-hypercholesterolemic	↓ Bodyweight loss, ↓ ALP, ↓ AST, ↓ ALT, ↓ cholesterol, and ↓ LDL		[232]
	Leaf pulp	Juice	One tables spoonful, twice a day for 2 weeks (p.o)	Clinical study	Anti-hyperglycemic	↓ Blood glucose and ↓ TG		[233]
	Leaf pulp	Phosphate buffered saline	500 for leaf pulp and 63 for leaf gel mg/kg body weight (p.o)	STZ Wister rats	Protective effect	Mitigated hepatic damages		[234]
	Leaf pulp	Chloroform and methanol, and isolation	1 µg/mouse/d of compounds 25 µg /mouse/d of extract (p.o)	T2D db/db mice	Anti-hyperglycemic	↓ FBG and ↓ HbA1c	Phytosterols (lophenol, 24-ethyl-lophenol, 24-methyl-lophenol, cycloartanol, and 24-methylene-cycloartanol)	[235]

Table 4 (continued)

Plant	Part used	Extracts/ formulation	Dose and route of administration	Test modal	Activity	Result	Active phytochemicals and toxicity information	References
Annona muricata L	Leaf	Aqueous	100 and 200 mg/kg body weight (p.o)	STZ Wister rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ Blood glucose, ↓ serum creatinine, ↓ AST, ↓ MDA, ↓ ALT, ↓ LDL, restored the levels of total cholesterol, TG, and SOD activity	Aqueous (LD_{50} > 5 g/kg), ethanol, and methanol (LD_{50} of > 2 g/kg) of leaves, flowers and pulp showed no acute toxicity in rats	[236–238]
	Leaf	Aqueous	100 mg/kg body weight (p.o)	STZ Wister rats	Anti-hyperglycemic, anti-hyperlipidemic, and anti-oxidant	↓ Blood glucose, ↓ TGs, ↓ ROS, ↓ TC, and ↓ LDL, ↑ antioxidant enzymes activities, ↑ serum insulin, ↓ lipid peroxidation		[239]
	Leaf	Aqueous	100 mg/kg body weight (i.p)	STZ Wister rats	anti-hyperlipidemic	↓ Serum TC, ↓ TG, ↓LDL, ↑ serum HDL levels and ↑ antiatherogenic index		[240]
		Purchased Annona liquid extract	100 mg/kg body weight (p.o)	STZ Wister rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ Blood glucose, ↑ insulin, ↓ insulin resistance, ↓ HbA1c, ↑ total proteins, and improved activities of liver function enzymes		[241]
	Fruit-pulp, leaf, stem-bark and root-bark	Methanol	100, 200, 400, 600, and 800 mg/kg body weight (p.o)	In vitro and Wister rats	Anti-hyperglycemic	Inhibited α-glucosidase and α-amylase activities	Fruits (dichloromethylenic extracts), leaves (aqueous extracts), exhibited acute neurotoxicity in rats associated with constituent annonacin and reticuline which are Acetogenins and alkaloid, respectively	[237, 242, 243]
Schkuhria pinnata (Lam.) Kuntze ex Thell	Leaf	Ethanol and acetone	50 g/mL	In vitro	Anti-hyperglycemic	↓ Blood glucose		[244]
	Leaf	Methanol, acetone, and hexane	100 µg/mL	In vitro	Anti-hyperglycemic	↑ Glucose utilization		[245]

Table 4 (continued)

Plant	Part used	Extracts/ formulation	Dose and route of administration	Test modal	Activity	Result	Active phytochemicals and toxicity information	References
	Leaf	Aqueous and butanone		In vitro	Anti-hyperglycemic	Upregulated the expression levels of insulin receptor, GLUT-4, glycogen synthase, pyruvate carboxylase, and pyruvate kinase in C2C12 muscle cells, ↑ AMPK	2-(2–4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl) prop-2- enoic acid; Schkuhrin I and schkuhrin II; methanol extract showed low cytotoxicity against human cells; aqueous extracts showed no toxicity in mice	[123, 246]
Solanum melongena L	Skin and pulp	Aqueous	500 µl	In vitro	Anti-hyperglycemic and antioxidant	Inhibited α-glucosidase activities and showed radical scavenging activity	Aqueous fruit extract showed no acute toxicity in rats (LD_{50} > 3000 mg/kg/oral). However, the extract exhibited relative acute toxicity in guinea pigs [LD_{50}: 1098] and relative toxicity in rabbits under repeat dose evaluations	[247, 248]
	Skin	Ethanol	25, 50, and 100 mg/kg body weight		Anti-hyperglycemic	↓ Blood glucose levels and promoted pancreatic β cell regeneration		[249]
	Cap	Ethanol	100 and 200 mg/kg body weight (i.p)	STZ Wister rats	Anti-hyperglycemic and anti-oxidant	↓ FBG, ↓ NO, ↓ ALT, ↓ ALP, ↓ AST, ↑ TP, and ↑ total antioxidant capacity		[250]
	Peels	Phenolic compounds	100 mg/kg body weight	Alloxan rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ Blood glucose, ↓ TG, ↓ TC, ↓ LDL, ↑ HDL, ↓ SGOT, and ↓ SGPT	Phenol	[139]
Toddalia asiatica (L.) Lam	Leaf	Ethyl acetate	250 and 500 mg/kg body weight (p.o)	STZ Wister rats	Anti-hyperglycemic	↓ Blood glucose and ↑ insulin	Leaves ethyl acetate extract showed no acute toxicity	[251]

Table 4 (continued)

Plant	Part used	Extracts/ formulation	Dose and route of administration	Test modal	Activity	Result	Active phytochemicals and toxicity information	References
	Leaf	Methanol and petroleum ether	400 mg/kg body weight (p.o)	STZ Wister rats	Anti-hyperglycemic	↓ Blood glucose		[252]
	Stem	Isolate		In vitro	Anti-hyperlipidemic	Promoted the differentiation and lipolysis of adipocytes	Aculeatin	[143]
Cajanus cajan (L.) Huth	Leaf	Methanol	400 and 600 mg/kg body weight (p.o)	Alloxan Swiss albino rats	Anti-hyperglycemic	↓ FBG	Aqueous and ethanol leaf extract showed no acute and sub-chronic toxicity	[253, 254]
	Leaf	Ethanol	200, 400 and 800 mg/kg body weight (p.o)	Alloxan rats	Anti-hyperglycemic	↓ Blood glucose		[255]
	Germinated pigeon pea	Acetone	p.o	STZ Wister rats	Anti-hyperglycemic and antioxidant	↓ FBG and ↓ lipid peroxidation		[256]
	Pigeon pea beverage diet		2.7 g/kg body weight (p.o)	Alloxan Sprague Dawley rats	Anti-hyperglycemic and hypocholesterolemic	↓ Blood glucose and ↓cholesterol		[257]
Kigelia africana (Lam.) Benth	Fruit	Aqueous	500 and 1000 mg/kg body weight (p.o)	Alloxan mice	Anti-hyperglycemic	↓ Blood glucose	Exhibited genotoxicity in the micronucleus of human WBCs, in the form of structural and numerical chromosome aberrations	[258, 259]
	Fruit	Hexane fraction	100, 200 and 400 mg/kg body weight (p.o)	STZ Wister rats and in vitro	Anti-hyperglycemic and anti-hyperlipidemic	Alleviated oxidative stress, ↓ FBG, ↓ hyperlipidemic biomarkers, promoted pancreatic β-cell regeneration and ↑ glucose uptake in 3T3 L1 adipocytes	Aqueous fruit extract at low doses showed no acute and chronic toxicity in rats but high doses may cause hepatorenal toxicity in rats; methanol fruit leaf, and stembark extract showed no sub-acute toxicity at 1000 mg/ kg body weight in rats	[260, 261]

Table 4 (continued)

Plant	Part used	Extracts/ formulation	Dose and route of administration	Test modal	Activity	Result	Active phytochemicals and toxicity information	References
	Fruit	Powder	0.5 mL fruit powder filtered solution and 1 mL fruit powder solution	Dexamethasone rats	Anti-hyperglycemic	↓ Blood glucose		[262]
	Stem	Aqueous	1 mL	In vitro	Anti-hyperglycemic	Inhibited α-amylase activity	Flavonoids;	[263]
	Stem bark and leaf	Ethanol and methanol	300 mg/kg body weight (p.o)	Alloxan rats	Anti-hyperglycemic	↓ FBS, ↓ creatinine, and ↓ ALT	Stembark aqueous extract showed acute toxicity in *Oreochromis niloticus* (L.) (fish)	[264, 265]
	Leaf and fruit	Methanol	200 and 500 mg/kg body weight (p.o)	Alloxan Wistar rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ Blood glucose and ↓ lipid levels		[264]
Cymbopogon citratus Stapf	Leaf	Tea	0.25% or 0.5% (p.o)	STZ rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ Serum glucose, ↓ lipids, ↓ insulin resistance index, ↑ serum insulin, ↑ β-cell function, and ↑ liver glycogen		[266]
	leaf sheath	Essential oil	400 and 800 mg/kg body weight	Poloxamer-407 Wistar rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ Glycemia, ↓ lipid dysmetabolism, ↓ insulinemia, ↑ GLP-1, ↑ β-cell number, and ↑ islet number	Essential oils at doses less than 1,500 mg/kg body weight showed no acute and subacute toxicity in rats and also dose 2000 mg/kg body weight showed no acute and subacute toxicity in rats	[267–269]
	Leaf	Ethanol and aqueous	200 mg/kg body weight (p.o)	Wistar rats	Anti-hyperglycemic	↓ Blood glucose		[270]
Gynandropsis gynandra (L.) Briq	Root	Aqueous	100, 200, and 400 mg/kg body weight (p.o)		Anti-hyperglycemic	↓ Blood glucose		[271]
	Root	Methanol	100, 250, and 500 mg/kg body weight (p.o)	Alloxan Wistar rats	Anti-hyperglycemic	↓ Blood glucose		[272]

Table 4 (continued)

Plant	Part used	Extracts/ formulation	Dose and route of administration	Test modal	Activity	Result	Active phytochemicals and toxicity information	References
	Whole plant	Ethanol	5 mg/ml	In vitro	Anti-hyperglycemic	Suppressed the inhibition of glucose diffusion		[273]
Syzygium cumini (L.) Skeels	Seed	Chloroform, aqueous, and methanol		In vitro	Anti-hyperglycemic	Inhibited α-amylase and α-glucosidase activities		[274]
	Leaf	Ethanol	200 and 400 mg/kg body weight (p.o)	Alloxan mice	Anti-hyperglycemic	↓ Blood glucose, ↑ insulin secretion, ↑ glucose tolerance, ↓ creatinine kinase, ↓ lactate dehydrogenase, and ↓ HbA1c	Hydroalcoholic leaves extract exerted no acute and chronic toxicity in rats (p.o); additionally, methanol, aqueous, ethanol extracts of leaf, seed, stem bark, and root exhibited no acute toxicity in rats	[275–277]
	Seed	Powder & ethanol	1.25 mg/kg body weight (p.o)	STZ Long-Evans rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ FBG, ↓ LDL-cholesterol, and ↓ atherogenic lipids		[278]
	Stem	Beverage	4 mg/mL (p.o)	STZ Wister rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ Blood glucose and ↓ lipid		[279]
Sesbania sesban (L.) Merr	Leaf	Aqueous	250 and 500 mg/kg body weight (p.o)	STZ Wister rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ blood glucose, ↓ HbA1c, ↓ total cholesterol, ↓ serum TG, ↑ hepatic glycogen and ↑serum insulin		[280]
	Root	Petroleum ether	250, 500, and 1000 mg/kg body weight (p.o)	STZ Swiss mice	Anti-hyperglycemic and anti-hyperlipidemic	↓ FBG, ↓ cholesterol, ↓ urea, ↓ TG, and ↓ creatinine		[281]
Ageratum conyzoides L	Leaf	Aqueous	500 mg/kg body weight (p.o)	Alloxan Wister rats	Anti-hyperglycemic	↓ FBG		[282]

Table 4 (continued)

Plant	Part used	Extracts/ formulation	Dose and route of administration	Test modal	Activity	Result	Active phytochemicals and toxicity information	References
	Leaf, stem, and root	Ethanol	100 mg/kg body weight (p.o)	STZ rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ FBG, ↓ total cholesterol and ↓TG	Hydroalcoholic leaf extract showed no chronic hepatotoxicity in rats. The extract also showed relative safety in acute and sub-chronic toxicity tests (p.o)	[283–285]
	Leaf	Aqueous	150, 300, 450 and 600 mg/kg body weight (p.o)	Rats	Anti-hyperglycemic	↓ Blood glucose and ↓ creatinine		[286, 287]
	Leaf	Aqueous	200 and 300 mg/kg body weight (p.o)	STZ rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ BLOOD glucose, ↑ serum insulin and ↑ protein, ↑ HDL, ↓ LDL, and ↓ TG		[286, 287]
	shoot	Ethanol	100, 200, and 400 mg/kg body weight (p.o)	Alloxan rats	Anti-hyperglycemic	↓ FBG		[137]
Vigna unguiculata (L.) Walp	Leaf	Ethanol	50 and 25 mg/mL	In vitro	Anti-hyperglycemic	Inhibited α-glucosidase and α-amylase activities, and ↑ GLUT4		[288]
	Seed	Peptides	0.1, 1, 10, and 100 ng	In vitro	Anti-hyperglycemic	Promoted Akt phosphorylation in rat skeletal muscles	Peptides	[289]
	Seed	Oil	200 mg/kg body weight (p.o)	Alloxan rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ Blood glucose, ↓ AST, ↓ LDL, ↓ TG, ↓ total cholesterol, ↓ ALT, and ↑ HDL		[290]
	sprouted	Isolates	50, 100, 200, and 400 mg/kg body weight (p.o)	Alloxan Sprague Dawley rats	Anti-hyperglycemic and anti-hyperlipidemic	↓ Blood total cholesterol, ↓ TG, and ↓ LDL	Proteins	[291]
	Seeds	Methanol	50, 100, 200 and 400 mg/kg body weight (p.o)	Swiss mice	Anti-hyperglycemic	↓ Blood glucose		[292]
Indigofera arrecta Hochst. ex A. Rich	Leaf	Aqueous	3.75–120 mg/kg body weight (p.o & i.p)	STZ Fischer rats	Anti-hyperglycemic	↓ Blood glucose and ↑ insulin	No acute and subchronic toxic effects recorded in mice	[293]

Table 4 (continued)

Plant	Part used	Extracts/ formulation	Dose and route of administration	Test modal	Activity	Result	Active phytochemicals and toxicity information	References
	Leaf	Aqueous	7 mL/day (p.o)	db/db mice	Anti-hyperglycemic	Mitigated the development of obesity-associated hyperglycemia		[294]
	Leaf	Aqueous	p.o	Clinical study	Anti-hyperglycemic	↓ Blood glucose, ↓ TG and ↓ aspartate aminotransferase, ↓ blood creatinine	No effects of nephrotoxicity recorded in humans	[295]
Oxalis corniculata L				Sprague Dawley rats	Antioxidant	Exhibited a protective effect and ↓ oxidative stress	Aqueous, methanol and ethanol whole plant extracts showed relatively mild cytotoxic activity on brine shrimp larvae (LC_{50} of 156 µg/ml)	[86, 144]
Solanum indicum Roxb	Fruit	Ethanol	100 mg/kg body weight (p.o)	Alloxan rats	Protective effect	Exhibited renoprotective properties		[145]

i.p Intraperitoneal route, *p.o* oral route,↑ increase,↓decrease, *STZ* streptozotocin, *FBG* fasting blood glucose, *HbA1c* glycosylated haemoglobin, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *VLDL* very low density lipoprotein, *SOD* superoxide dismutase, *PPARγ* peroxisome proliferator-activated receptor-gamma, *GLUT2* glucosetransporter2, *GLUT4* glucosetransporter4, *PTP1B* protein tyrosine phosphatase 1 B, *AMPK* AMP protein kinase, *ROS* reactive oxygen species, *AST* aspartate transaminase, *TP* total protein, *ALB* albumin, *ALT* alanine transaminase, *ALP* alkaline phosphatase, *TG* triglyceride, *GLP1* glucagonlikepeptide1, *MDA* malondialdehyde, *SGOT* serum glutamate oxaloacetate transaminase, *SGPT* serum glutamate pyruvic transaminase, LD_{50} the median lethal dose, LC_{50} the median lethal concentration, CC_{50} half-maximal cytotoxic concentration

properties [135, 136]. In fact, antidiabetic effects of plants are attributed to several classes of compounds namely, alkaloids, phenolic acids, saponins, tannins, and terpenoids [127, 137, 138]. A case in point is Jassim et al. [139] who reported that phenol extracts of *Solanum melongena* L. peels decreased blood glucose, triglyceride, blood total cholesterol, and low-density lipoprotein levels alongside increased serum high density lipoprotein levels in diabetic rats. Furthermore, the extract promoted hepatic detoxification by decreasing levels of serum glutamate oxaloacetate transaminase (SGOT) and serum glutamate pyruvic transaminase (SGPT) in alloxanised diabetic albino rats [139]. Interestingly, successful isolation, characterization, and purification of some antidiabetic phytoconstituents from a few plants have been achieved [119, 125, 140–142] (Table 4). For example, thyrotundin and tagitinin A were isolated from *Tithonian diversifolia* (Hemsl.) A.Gray with confirmed effect of decreasing insulin resistance via upregulating PPARγ activity [140]. In another study, Watanabe et al. [143] reported that aculeatin isolated from *Toddalia asiatica* (L.) Lam. promoted the differentiation and lipolysis of 3T3-L1 adipocytes along with increased glucose uptake, which are critical for treatment of DM and associated conditions. This implies that these phytochemical compounds could be potential antidiabetic agents.

Essentially, bioactive compounds of some of the investigated plants in this study have produced antidiabetic effects by acting on specific targets (For example, agonists of PPARγ such as *Citrus sinensis* (L.) Osbeck) [124], while other researchers only reported antidiabetic activities without definite pharmaceutical targets [144, 145]. For successful drug development, it is pivotal to identify and select targets of therapeutic compounds. Accordingly, the bioactive principles bind selectively to the receptor on the target and trigger the desired functional response [146]. In this way, molecular interactions associated with the products are understood, enabling gain of knowledge on the mechanisms of action, a key feature in a drug discovery process. Therefore, it is crucial to establish pharmaceutical targets of these herb bioactive compounds for improved outcome and development.

Regarding medicinal plants with unspecified mechanism of action such as *Solanum indicum* Roxb., their mechanisms of action in the DM pathway could possibly be linked to constituent phytochemicals [146]. In this case, plants with flavonoids as major bioactive compounds decrease level of blood glucose, cholesterol, and triglycerides by increasing activity of hepatic glucokinase and enhancement of insulin release from pancreatic islets [147]. Ibrahim et al. [148] isolated luteolin (3′,4′,5,7-tetrahydroxy flavone) along with other flavonoids from *Oxalis corniculata* L. and this compound has been reported to possess appreciable antidiabetic potential [149, 150]. Indeed, the underlying antidiabetic mechanisms and signalling pathways of luteolin include improving the sensitivity of body cells to insulin, antioxidative effect, inhibition of enzymes like PTP1B among others [149, 150]. Luteolin exerts its antioxidant properties by scavenging ROS and inhibiting enzymes responsible for ROS generation; this protects the pancreas and promotes insulin secretion [150]. Furthermore, luteolin enhances insulin sensitivity through influencing the Akt2 kinase [151]. Accordingly, Akt2 prevents the dephosphorylation of the insulin receptor and in this way, attenuation of insulin-signaling process is prevented [151]. On the other hand, plants with alkaloids as lead compounds show inhibition of α-glucosidase and decrease glucose transport through the intestinal epithelium [146]. Based on this, antidiabetic activities of plants containing high content of alkaloids in this review for instance, *Ageratum conyzoides* L. [152], may possibly be via lowering blood glucose and α-glucosidase inhibition. Additionally, quinolizidine alkaloids like multiflorine and sparteine have been reported to have insulinotropic effects on isolated pancreatic islets, besides their blood glucose-lowering role [153]. In fact, Wiedenfeld and Röder [154] isolated and identified multiflorine from *A. conyzoides*, therefore, the plant may act in the DM pathway via mechanisms related to that of multiflorine. Antidiabetic plants with bioactive principles in the classes of saponin (For example, *Solanum indicum* Roxb.), polysaccharides, and ferulic acid may trigger insulin secretion by stimulating pancreatic β-cells [147]. Particularly, hypoglycemic action of saponin is realised through various pathways including improvement of insulin signalling, activation of glycogen synthesis, restoration of insulin response, gluconeogenesis inhibition, among others [153, 155]. Likewise, coumarins have hypoglycemic characteristics and inhibit aldose reductase enzyme as well as aggregation of platelet [153]. Relatedly, antidiabetic plants containing high content of dietary fibers such as *Cajanus cajan* (L.) Huth could act by inhibiting α-amylase and delaying glucose diffusion, which in turn cause decrease in glucose absorption rate and postprandial serum glucose [146]. However, these suggested mechanisms of action can only be validated through further scientific investigations.

Meanwhile, to the best of our knowledge, 19 (41%) of the reported medicinal plant species in this study such as *Justicia betonica* L., *Warburgia ugandensis* Sprague, and *Garcinia buchananii* Baker remain scientifically uninvestigated for their antidiabetic effects, yet used traditionally for DM treatment. Such plants could be potential sources of active ingredients for therapy of DM and its complications, hence need for evaluation of their antidiabetic properties.

Clinical studies

Clinical trials with medicinal plants on human subjects is a critical step in drug discovery [115]. Currently, no clinical study using standardized extracts, bioactive compounds, and preparations of medicinal plants against DM has been reported in Uganda. Globally, seven medicinal plants in this review have been subjected to clinical studies involving human subjects. These plants include *Moringa oleifera* Lam., *Artocarpus heterophyllus* Lam., *Bidens pilosa* L., and *Indigofera arrecta* Hochst. ex A. Rich. among others [25, 172, 193, 295] (Table 4). Accordingly, all the tested plants showed the desired clinical effects [25, 172, 193, 295]. These therapeutic effects justify the use of the plants traditionally to treat DM across different communities in Uganda [17, 23]. However, the clinical trials were preliminary in nature aimed at assessing therapeutic effect of these plants in human subjects with none being a randomized, controlled trial. In Uganda, the absence of clinical trials on DM with traditionally used preparations may be attributed to insufficient data generated from preclinical studies, huge financial and strict regulatory requirements associated with clinical studies [296]. This means, clinical safety and efficacy of preparations from plants traditionally used to treat DM in Uganda are yet to be unlocked. The observed therapeutic effects of the evaluated plants, indicate the need to further investigate the traditionally used preparations in DM therapy for drug discovery and development.

Other ethnomedicinal uses and toxicity of the reported antidiabetic plants

Most of the plants in this review are used to treat several other diseases apart from DM (Table 1). A classic example is *Kigelia africana* (Lam.) Benth. which is recorded to be used for treating various health problems such as diarrhea, malaria, and cancer across different communities [19]. As such, pharmacological efficacy of *K. africana* against cancer has also been reported, for instance, its seed oil suppressed human embryonic kidney (HEK-293) cell and human colon adenocarcinoma (Caco-2) cell dose dependently [297]. Several active phytochemicals of *K. africana* have been identified and some isolated, namely, *β*-sitosterol, specioside, lapachol, verminoside, 3-(2′-hydroxyethyl)-5-(2″-hydroxypropyl) dihydrofuran-2-(3H) one, kigelin minecoside, ferulic acid, and 1,3-dimethylkigelin [296]. Therefore, the diverse bioactive compounds in these plants may explain their multipurpose use in treatment of diseases [115].

Besides exerting pharmacological activity that can be utilized for therapeutic purposes, constituent phytochemicals of medicinal plants are known to interact with same or other receptors and consequently produce harmful toxic effects [298]. Toxic compounds from plants may affect vital human organs and key body functional systems such as the central nervous system resulting in altered coordination of nerve functions [299]. Most of the recapitulated plants in this review have exhibited no adverse toxic effect as per respective toxicity reports (Table 4). For instance, aqueous leaf extract of *Indigofera arrecta* Hochst. ex A. Rich. showed no acute (up to 10 g/kg body weight, orally administered) and subchronic toxicity (2 g/kg body weight, orally administered daily for 30 days) in mice [300]. Furthermore, the extract never altered the glutathione and hepatic cytochrome P450 (CYP) isozymes whose modulation can consequently lead to interactions of components in a multiple drug treatment [300]. In another study, oral administration of leaf aqueous extract of *Indigofera arrecta* did not exert nephrotoxicity in humans [295]. However, some of the plants in this review have shown potential toxicity properties. Notably, *Annona muricata* L. fruit and leaf extracts (106 mg/kg body weight, infused intravenously for 28 days) exhibited acute neurotoxicity in rats [243]. The degree of plant toxicity depends on several factors including route of administration, method of extraction/preparation, plant growth stage or part, victim susceptibility, species, and dosage [298]. Some phytochemicals in these plants such as anthraquinones and annonacin in *Aloe vera* (L.) Burm.f. and *Annona muricata*, respectively have been implicated for their toxicity [228, 229, 237, 243]. In cases where toxic effects are exerted at high doses, administration of preparations should be within known safe dose ranges to minimize side effects. High-risk patients like children, the elderly, pregnant women, and people with congestive heart failure ought to be more cautious when using these herbal medicines. Many other researchers around the world have provided useful information including dosages and toxicity from preclinical and clinical studies of medicinal plants, which may be relevant for development of DM therapeutic products [31, 32, 132]. It is worth noting that there is paucity of information regarding safety/toxicity profiles of the plants in this review. Moreover, most of the reported toxicity studies tested only acute toxicity either in vitro or in vivo yet this may not reflect toxicity condition experienced when taking herbal preparation for a long time as is the case in chronic diseases like DM [301]. Therefore, there is need to conduct comprehensive (acute, sub-chronic, and chronic) safety/toxicity studies on most of these potential medicinal plants to ascertain possible toxic effects to humans [302].

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Author contributions
RG conceptualized the review article, performed all the literature search based on the methodology, conducted data analysis, and wrote the original draft of the article. MM reviewed and edited the manuscript after due conceptualization of the review. DO reviewed and edited the manuscript. YK supervised the whole research work, reviewed and edited the manuscript. All authors read and approved the final manuscript.

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