



Review

Pharmacological reflection of plants traditionally used to manage diabetes mellitus in Tanzania

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ARTICLE INFO

Keywords:

Medicinal plants

Diabetes mellitus

Tanzania

Ethnopharmacology

ABSTRACT

Ethnopharmacological relevance: The increasing national prevalence of diabetes mellitus (DM) and its complications have overstretched the health care system in Tanzania and influenced patients to use herbal medicines as alternative therapeutic strategies. Therefore, an urgent need exists to validate the safety and efficacy of plants used locally.

Aim of the study: To identify plants used for the management of DM in Tanzania and analyses their pharmacological, phytochemistry, and safety evidence with a special focus on the mechanism of action.

Methods: Researchers searched Medline, web of science, and Scopus for published articles. Also, specialized herbarium documents of Muhimbili Institute of traditional medicine were reviewed. Articles were assessed for relevance, quality, and taxonomical accuracy before being critically reviewed.

Results: We identified 62 plant species used locally for DM management. *Moringa oleifera* Lam. and *Cymbopogon citratus* (D.C) Stapf were the most mentioned. Fifty-four phytochemicals from 13 species had DM activities. These were mainly; polyphenolics, phytosterols, and triterpenoids. Extracts, fractions, and pure compounds from 18 species had *in vitro* antidiabetic activities of which 14 had α -glucosidase and α -amylase inhibition effects. The most studied *Momordica charantia* L. increased; glucose uptake and adiponectin release in 3T3-L1 adipocytes, insulin secretion, insulin receptor substrate-1 (IRS-1), GLUT-4 translocation, and GLP-1 secretion; and inhibited protein tyrosine phosphatase 1 B (PTP1B). Preclinical studies reported 30 species that lower plasma glucose with molecular targets in the liver, skeletal muscles, adipose tissues, pancreases, and stomach. While three species; *Aspilia mossambicensis* (Oliv.) Willd, *Caesalpinia bonduc* (L.) Roxb, and *Phyllanthus amarus* Schumacher & Thonn. had mild toxicity in animals, 33 had no report of their efficacy in DM management or toxicity.

Conclusion: Local communities in Tanzania use herbal medicine for the management of DM. However, only a fraction of such species has scientific evidence. *A. mossambicensis*, *C. bonduc*, and *P. amarus* had mild toxicity in animals. Together, our findings call for future researches to focus on *in vitro*, *in vivo*, and phytochemical investigation of plant species for which their use in DM among the local communities in Tanzania have not been validated.

1. Background

Diabetes mellitus (DM) is a chronic, multifactorial metabolic

disorder characterized by persistent hyperglycemia and increased risk of microvascular and macrovascular pathology. The DM results from either insufficient insulin secretion in the pancreatic β -cells (type-1 diabetes mellitus) or impaired insulin secretion and action (type-2 diabetes

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6 Abbreviations

GPx	Glutathione peroxidase	LDL-c	Low-density lipoprotein cholesterol
INF- γ	Interferon-gamma	LPO	Lipid peroxidation
11 β -HSD1	11 β -Hydroxysteroid dehydrogenase type 1	MDA	Malondialdehyde
AMPK	Adenosine monophosphate-activated protein kinase	MoHCDGEC	Ministry of Health, Community Development, Gender, Elderly and Children
CAT	Catalase	NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
DM	Diabetes mellitus	PG	Plasma glucose
DPP-4	Dipeptidyl peptidase-4 inhibitor	PI3K	Phosphoinositide 3-kinase
FFAs	Free fat acids	PKB	Protein Kinase B
FIGR	Fasting insulin–glucose ratio	PKC- β	Protein Kinase C β isoform
FIRI	Fasting insulin resistance index	PPAR- α	Peroxisome proliferator-activated receptor alpha
FPG	Fasting plasma glucose	PPAR- δ	Peroxisome proliferator-activated receptor gamma
GLP-1	Glucagon-like peptide-1	PPG	Postprandial glucose
GLUT1	Glucose transporter type 1	PTP1B	Protein tyrosine phosphatase 1 B
GLUT-4	Glucose transporter type 4	SOD	Superoxide dismutase
GSH	Reduced glutathione	STZ	Streptozotocin
HbA1c	Glycosylated haemoglobin A1c	TC	Total cholesterol
HDL-c	High-density lipoprotein cholesterol	TGs	Triglycerides
HOMA-IR	Homeostasis model assessment of insulin resistance	TNF- α	Tumor necrosis factor- α
ICMEs	Inhibition of carbohydrate metabolizing enzymes	TP	Total protein
IL-6	Interleukin-6	VLDL-c	Very low-density lipoprotein cholesterol
IRS-1	Insulin receptor substrate-1	WHO	World Health Organization
JNK	c-Jun N-terminal kinases		

mellitus). The magnitude of type-2 diabetes mellitus affects countries worldwide, but with a growing trend in low- and middle-income countries due to a gradual demographic and socio-economic transition (WHO, 2016).

A recent STEP survey ranked Tanzania at the top in the East African region with an estimated diabetes mellitus prevalence at 9.1% among adults aged 25–64 years (WHO, 2012). This accounts for a significant increase in prevalence from the estimated 2.5% in 1984 (WHO, 2016). Such an increase in the prevalence of DM has been implicated in the occurrence of several morbidities and premature death. Studies indicated that adults with persistently high blood glucose levels have an increased risk of heart attacks and strokes, kidney failure, foot ulcers, infection, and limb amputation; and account for 2.6% of global blindness (Bourne et al., 2013; Sarwar et al., 2010).

Both the high prevalence of DM and associated complications overstretched health care resources among low- and middle-income countries (WHO, 2016). For instance, studies in Tanzania revealed unprepared health care personnel and a shortage of essential medical supplies for diabetes care in some health facilities (Adinan et al., 2019; Mwangome et al., 2017). In another study, researchers found a gross unmet need for therapeutic choices for patients with DM in public health facilities while their private counterparts had wide therapeutic choices at a high cost (Justin-Temu et al., 2009).

These unmet health care challenges could likely have influenced the patients with DM to seek alternative health care to traditional healers and in particular the use of herbal medicines as reported in other studies. A study in Kilimanjaro, a northern region of Tanzania reported that 77.1% of patients with DM use herbal medicines (Lunyera et al., 2016), a similarly high prevalence (67.5%) of herbal medicine use was reported in another study in Tanzania (Kasole et al., 2019a). Along the same lines, about 76% of type 2 diabetes mellitus in Sri Lanka use herbs (Medagama et al., 2014), while Australia and the United Kingdom recorded a prevalence of 46% among diabetics (Manya et al., 2012; Thomas et al., 2001).

It follows that the resurgence of interest in herbal medicine across the globe and in Tanzania, in particular, could be attributed to perceived efficacy, few side effects, affordability, or limited access to conventional health care.

Several animal experiments and randomized clinical trials have been conducted to validate the antidiabetic effects of many plant extracts, fractions, and isolated compounds across countries. These studies provided a scientific basis to support the traditional use of the plants in the local communities. It is not clear, however, that these studies apply to plants traditionally used to manage DM in Tanzania. Thus, a critical need to provide scientific evidence to validate local therapeutic use still existed.

Therefore, we conducted a review to identify plants used traditionally to manage DM among local communities in Tanzania, and critically analyse their pharmacological, phytochemistry, and toxicological evidence with a special focus on the mechanism of action. This analysis is critical to inform the local community on potentially useful or harmful plants based on available scientific evidence and identify future research in drug lead identification and development.

2. Methods

2.1. Search strategy

Authors searched the following databases: PubMed/Medline, web of science, Scopus, Google Scholar, and OpenGrey from inception through August 2020. The databases were searched firstly, with keywords; “medicinal plant (s)”, “herbal/traditional medicine (s)/therapies”, pairing with “diabetes mellitus”, “Tanzania”, “United Republic of Tanzania”, “Zanzibar”. Secondly, with a specific plant name identified from the above search paired with “phytochemicals”, “toxicity”, “diabetes mellitus”, “anti-diabetic”, “antidiabetic”, “hyperglycemic”, “hypoglycemic”, “antihyperglycemic”, “anti-hyperglycemic”. Besides, the central library of the Muhimbili University of Health and Allied Sciences was searched for books (published or not) or theses on the topic. We also reviewed the Institute of traditional medicine’s herbarium voucher specimen. Later, reference lists of included studies were screened for additional studies. Throughout the search, no language restriction was imposed.

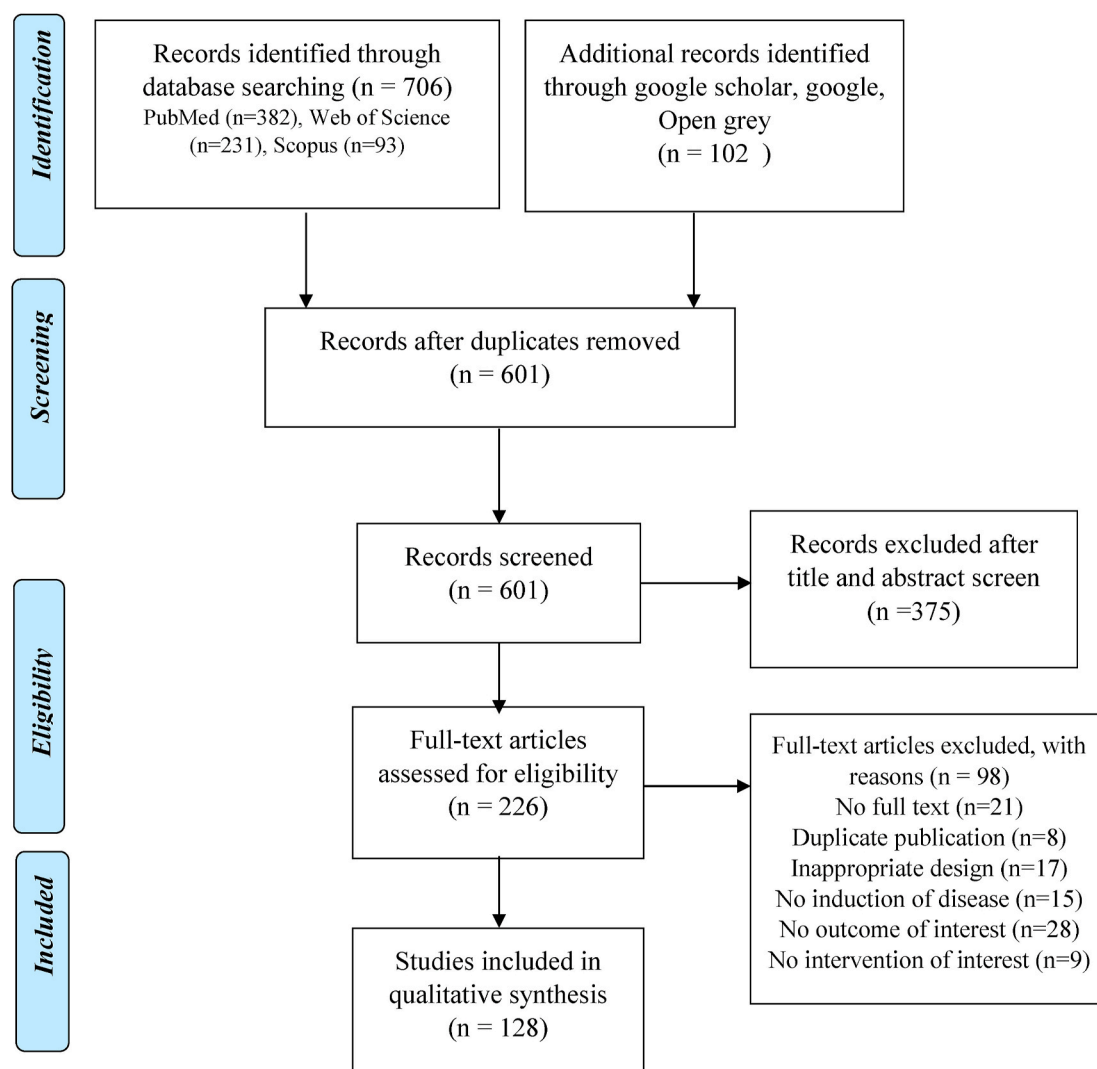


Fig. 1. Flow diagram for screened, included, and excluded studies.

2.2. Study selection and review of evidence

Information about the traditional use of plants for diabetes mellitus was obtained from published articles highlighted plants used traditionally to manage DM in Tanzania or unpublished ethnomedical field reports, herbarium voucher specimens, and experimental studies that used plants collected in Tanzania. However, scientific evidence to validate such use was based on experimental studies conducted in any part of the world. The selection of articles was based on the inclusion and exclusion criteria listed below.

Inclusion criteria.

- i. Studies of plants mentioned in traditional use for the management of diabetes mellitus
- ii. Experimental studies that were carried out *in vitro*, *ex vivo*, *in vivo*, and clinical trials investigating the antidiabetic activity of plant parts' crude extracts, fractions, isolated compounds, their derivatives, and their preparations.
- iii. Studies reported antidiabetic activities with or without a mechanism of action.

Exclusion criteria

- i. Studies reported extracts, fractions, and phytochemicals without biological activities.

- ii. *In silico* and review studies of isolated compounds, their derivatives, or preparations.
- iii. Studies that did not investigate plants of interest or without the outcome of interest, those with inadequate reported information and articles without full texts.
- iv. *In vivo* studies that were carried out without using either pre-diabetes or diabetes mellitus models.
- v. *In vitro*, *ex vivo*, or *in vivo* studies on antioxidant activity of plants of interest without clear linkage to prediabetes or diabetes mellitus.

The selected articles were critically appraised for quality and relevance. Initially, plant scientific names were extracted and accepted names verified in <http://www.plantlist.org> or <http://www.worldfloraonline.org>. Those articles originally reported plant names using synonyms; both accepted and synonyms were tabulated. Also, the family name, vernacular names, other medicinal uses, plant part(s), traditional method(s) of preparation, and geographical distribution were collected. Accordingly, scientific evidence of antidiabetic activities was assessed for extracts, fractions, or isolated pure bioactive constituent(s) from plants and their parts, dose and route of administration, animal models, possible mechanisms of action, and toxicity. For this review, Tanzania was stratified into nine geographical zones as per a recent Malaria demographic survey zones (MoHCDGEC et al., 2016). This includes

Table 1

Medicinal plants used traditionally to manage diabetes mellitus in Tanzania.

S/ No	Scientific name (Family)	Tanzanian local name	Voucher #	Region	Parts used	Traditional preparation and dose	Other uses	References
1	<i>Azelia quanzensis</i> Welw. (Caesalpiniaceae)	Mkola (Nyamwezi)	IMPP 002-0107	WZ	Roots	Boiled with water and decoction taken three times a day. No mention of quantity	–	Moshi et al. (2006)
2	<i>Aspilia mossambicensis</i> (Oliv.) Willd (Compositae)	–	MJM 3056	LZ	Leaves	Mixed with <i>Centella asiatica</i> and boiled. Decoction used	Malaria, Tonic	Moshi et al. (2009)
3	<i>Bridelia duvigneaudii</i> J. Léonard (Euphorbiaceae)	Msalasi (Nyamwezi)	IMPP 002-0057	WZ	Roots	Fresh or dried roots are boiled with water. One teaspoonful taken 3 times a day for one to 2 weeks	–	Moshi et al. (2006)
4	<i>Cyphomandra crassifolia</i> Kuntze (Solanaceae)	Mtomatoma/ mtomasi	MJM 3117	LZ	Seeds	Dried and powdered. Taken orally	Cardio tonic	Moshi et al. (2012)
5	<i>Cyphostemma junceum</i> (Bak.) Descoings (Vitaceae)	Mhogo mwitu	ITM3421	WZ	Roots	Whole roots added to a porridge. Taken orally	–	ITM Herbarium
6	<i>Dioscorea praehensilis</i> Benth. (Dioscoriaceae)	Amasoma	MJM 3246	LZ	Tuber	Cooked and eaten as food	Hypertension	Moshi et al. (2012)
7	<i>Ehretia amoena</i> Klotzsch (Boraginaceae)	Mkirika, Msekwa msekeseke	Mh 11403	EZ	Roots	Boiled with water. Half cupful of decoction taken orally twice a day for seven days	Stomachache, fever, Gynecological problems	Moshi and Mbwanbo (2002)
8	<i>Entada abyssinica</i> A.Rich. (Mimosaceae)	Mfutwamvula (Nyamwezi)	IMPP 002-0101	WZ	Roots	Mixed with <i>Pterocarpus tinctorius</i> , soaked in water or boiled. Taken orally	Epilepsy, Schistosomiasis	Moshi et al. (2006)
9	<i>Erythrina abyssinica</i> DC. (Fabaceae)	Mkalwanhuba	IMPP002-0054	WZ	Roots	One teaspoonful of powdered root bark mixed in tea or hot water taken orally three times a day	Increase libido, stomach pain,	ITM Herbarium
10	<i>Euclea natalensis</i> A. DC. (Ebenaceae)	Mdala	MJ25	NZ	Root bark	Grinded mixed with cold water. Taken orally three times a day	Dysmenorrhea	ITM Herbarium
11	<i>Euphorbia hirta</i> L. (Euphorbiaceae)	Mziwaziwa	KIUT1 14	EZ	Leaves	Decoction of fresh leaves. Half glass taken three times a day for three days	–	Musibha (2018)
12	<i>Ficus fischeri</i> Mildbr. & Burr. (Moraceae)	Mvila (Nyamwezi)	IMPP 002-0141	WZ	Stem bark	The powder taken with porridge or boiled with water. One cup three times a day	Stroke, paralysis	Moshi et al. (2006)
13	<i>Deinbollia borbonica</i> Scheff. (Sapindaceae)	Mmoyomoyo, mbwakabwaka, mkuyu, Muhunge	16571	NZ	Roots	Boil with maize. One cupful of the soup is taken orally	Headache, constipation, gonorrhea, Bilharzia	ITM Herbarium
14	<i>Maprounea africana</i> Müll. Arg. (Euphorbiaceae)	Mtunu (Yao)	ITM 3429	WZ	Roots	Decoction. One cupful given orally to patient	–	ITM Herbarium
15	<i>Melanthera scandens</i> (Schumacher & Thonn.) Roberty (Asteraceae)	Byabarwoya/ Eshurwa	MJM 3190	LZ	Leaves	Boiled to make thick decoction. One cupful taken orally	Ulcers	Moshi et al. (2012)
16	<i>Pseudolachnostylis maprouneifolia</i> Pax (Phyllanthaceae)	Mwana	TMRU 2290	EZ	Roots	One cupful of decoction given orally three times a day	Eye problems, stomachache	ITM Herbarium
17	<i>Sorindeia madagascariensis</i> DC. (Anacardiaceae)	Mpilipili	TMRU1690	EZ	Roots	Boiled with water and taken orally	Back ache	ITM Herbarium
18	<i>Uvariopsis bisexualis</i> Verdc. (Annonaceae)	Ntaka	ITM3412	EZ	Roots/ leaves	One cupful of decoction taken orally three times a day	Aphrodisiac	ITM Herbarium
19	<i>Vangueria apiculata</i> K. Schum (Rubiaceae)	Kirongomani/ Mtigunda	MJM 3048	LZ	Stem bark, leaves	A decoction is made mixed with leaves of <i>Dracaena steudneri</i> . Taken orally	–	Moshi et al. (2009)
20	<i>Vangueria infausta</i> Burch (Rubiaceae)	Amabungo/ Mabungo	MJM 3139	LZ	Stem bark, leaves, fruits, seeds	The fruits and seeds are burnt and eaten. Leaves mixed with <i>Dracaena steudneri</i> ; decoction. One cup taken once a day	Malaria	Moshi et al. (2009)
21	<i>Withania somnifera</i> (L.) Dunal (Solanaceae)	Mkubya (Nyamwezi)	IMPP 002-0115	WZ	Roots	Fresh roots boiled with water. One cup taken twice a day.	–	Moshi et al. (2006)
22	<i>Cassia abbreviata</i> Oliv. (Fabaceae)	Mkundekunde	KWB 22	EZ	roots	–	Epilepsy, malaria and asthma	ITM Herbarium
23	<i>Cassia abbreviata</i> Oliv. (Fabaceae)	Singwai, mkundekunde	SH36	EZ	Root, bark	–	Malaria, stomach ache, amoebiasis, STIs, infertility, dysmenorrhoea	Hilonga et al. (2019)
24	<i>Centella asiatica</i> (L.) Urb. (Apiaceae)	–	TMRU 3314	NZ	leaves	–	Hernia	ITM Herbarium

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Table 1 (continued)

S/ No	Scientific name (Family)	Tanzanian local name	Voucher #	Region	Parts used	Traditional preparation and dose	Other uses	References
25	<i>Chassalia umbraticola</i> Vatke (Rubiaceae)	Mkangaa	KWB23	EZ	–	–	Asthma, ulcers	ITM Herbarium
25	<i>Crossopteryx febrifuga</i> (Afzel. ex G.Don) Benth. (Rubiaceae)	Nakasabuni	ITM3406	WZ	Bark	–	Aphrodisiac	ITM Herbarium
26	<i>Dichrostachys cinerea</i> (L.) Wight & Arn.(Fabaceae)	Mkalala (Hehe)	TMRU 765	SHZ	Roots	–	Dysentery, headaches, toothaches, elephantiasis	ITM Herbarium
28	<i>Kigelia africana</i> (Lamarck) Benth.(Bignoniaceae)	Mwegea	ITM 3706	WZ	Fruits	–	Mental illness	ITM Herbarium
29	<i>Phyllanthus amarus</i> Schumach. & Thonn. (Phyllanthaceae)	Mzalia nyuma (Zaramo)	TMRU 3156	NZ	Leaves	–	Coughs, Stomachaches,	Moshi et al. (1997)
30	<i>Ochna confusa</i> Burt Davy & Greenway (Ochnaceae)	Mnungamo	ITM 3407	WZ	Root/bark	–	–	ITM Herbarium
31	<i>Phyllanthus amarus</i> Schumach. & Thonn. (Phyllanthaceae)	Mturuka	SH227	LZ	Leaves	–	–	Hilonga et al. (2019)
32	<i>Warburgia stuhlmannii</i> Engl. (Canellaceae)	Sokono	SH93	EZ	Root and bark	–	–	Hilonga et al. (2019)
33	<i>Terminalia mollis</i> M. Laws. (Combretaceae)	Mkelenge	IMPP002- 0067	WZ	Stem bark	–	Heart problems	ITM Herbarium
34	<i>Solanum americanum</i> Mill. (Solanaceae)	shwiga	SH206	LZ	Leaves	–	–	Hilonga et al. (2019)
35	<i>Zanthoxylum acanthopodium</i> DC. (Rutaceae)	Mjafari, oloisuki,	SH10	EZ	Root and bark	–	–	Hilonga et al. (2019)
36	<i>Aloe vera</i> (L.) Burm.f. (Xanthorrhoeaceae)	Aloe, Alovera	–	NZ	leaves	Gel extract	–	Lunyera et al. (2016)
37	<i>Annona muricata</i> L. (Annonaceae)	Soursop	–	NZ	leaves	Small quantity of juice is taken orally	–	Kasole et al. (2019b)
38	<i>Momordica charantia</i> L. (Cucurbitaceae)	Bitter melon	–	NZ	Fruits	Drinking as a juice, eating while cooked, or cooked and mixed with other vegetables. Eaten once daily	–	Ludwig et al. (2012)
39	<i>Moringa oleifera</i> Lam. (Moringaceae)	Mlonge	–	NZ	Flowers Pods, seeds, roots, leaves	Grounded into powder and mixed	–	Lunyera et al. (2016)
40	<i>Terminalia sericea</i> Burch. ex DC (Combretaceae)	–	–	NZ	Stem bark, roots, leaves	The powdered bark is taken with mealie meal	Gonorrhea, bilharzia, stomach troubles. purgative	Hedberg et al. (1982)
41	<i>Abelmoschus esculentus</i> (L.) Moench (Malvaceae)	Okra pods, Bamia	–	NZ	Fruits	–	–	Kasole et al. (2019)
42	<i>Acacia kirkii</i> Oliv. (Mimosaceae)	Mgunga	–	NZ	–	–	Malaria	Moshi et al. (2004)
43	<i>Acacia tortilis</i> (Forsk) Hayne (Mimosaceae)	Kikwesa/chikwesa	–	EZ	Roots	–	–	Moshi and Mbwambo (2002)
44	<i>Albizia anthelmintica</i> Brogn. (Mimosaceae)	Mkutani	–	EZ	Roots	–	–	Moshi and Mbwambo (2002)
45	<i>Artemisia afra</i> Jacq. ex Willd. (Asteraceae)	Fivi, Majani mapana, artemisia	–	NZ	Roots, stems, leaves	–	–	Lunyera et al. (2016)
46	<i>Bridelia micrantha</i> Bertol (Euphorbiaceae)	Kitovutovu	–	EZ	Roots	–	–	Moshi and Mbwambo (2002)
47	<i>Caesalpinia bonducella</i> (L.) Flem. (Caesalpinaceae) Accepted: (<i>Caesalpinia bonduc</i> (L.) Roxb)	Msoro/mkomve	–	NZ	–	–	–	Moshi et al. (2004)
48	<i>Cajanus cajan</i> (L.) Millsp. (Fabaceae)	Majani ya mbaazi	–	NZ	Leaves, Seeds	–	–	Lunyera et al. (2016)
49	<i>Clausena anisata</i> (Willd) Hook.f. ex Benth. (Rutaceae)	Mjafari	–	NZ	Leaf, stem, roots	extracts	–	Lunyera et al. (2016)
50	<i>Commiphora africana</i> (A. Rich.) Endl.(Burseraceae)	–	–	EZ	–	–	–	Moshi and Mbwambo (2002)
51	<i>Croton macrostachyus</i> Hochst. ex Delile (Euphorbiaceae)	Mhulugu, mbiha	–	NZ	–	–	–	Moshi et al. (2004)
52	<i>Cyanoglossum lanceolatum</i> Forsk (Boraginaceae)	Kifasa	–	EZ	Roots	–	–	–

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Table 1 (continued)

S/ No	Scientific name (Family)	Tanzanian local name	Voucher #	Region	Parts used	Traditional preparation and dose	Other uses	References
53	<i>Cymbopogon citratus</i> (DC.) Stapf. (Poaceae)	Mchaichai	–	NZ	Leaves Stem	–	–	Moshi and Mbwambo (2002)
54	<i>Cymbopogon citratus</i> (DC.) Stapf. (Poaceae)	Majani ya chai	–	EZ	Leaves	–	–	Lunyera et al. (2016)
55	<i>Cymbopogon citratus</i> (DC.) Stapf. (Poaceae)	lemongrass	–	NZ	–	–	–	Moshi and Mbwambo (2002)
56	<i>Cyphostemma buchananii</i> (Planch.) Desc. ex Wild & R. B.Drumm. (Vitaceae)	Kigugire/kigugile kidogo	–	EZ	Roots and leaves	–	–	Kasole et al. (2019)
57	<i>Diospyros loureiroana</i> G.Don (Ebenaceae)	Mgoto Syn. <i>Diospyros usambarensis</i> F.White	–	EZ	Roots	–	–	Moshi and Mbwambo (2002)
58	<i>Hagenia abyssinica</i> (Bruce ex Steud.) J.F.Gmel. (Rosaceae)	Enjani engashe (Maasai)	–	NZ	–	–	–	Moshi et al. (2016)
59	<i>Lannea schimperi</i> (A.Rich.) (Anacardiaceae)	Mbumbu nyika	–	EZ	Stem bark	–	–	Lunyera et al. (2016)
60	<i>Markhamia obtusifolia</i> Bak Spragne (Bignoniaceae)	Myuyu	–	NZ	–	–	–	Moshi and Mbwambo (2002)
61	<i>Moringa oleifera</i> Lam. (Moringaceae)	Mlong'e	–	EZ	Roots	–	–	Moshi et al. (2004)
62	<i>Moringa oleifera</i> Lam. (Moringaceae)	Moringa	–	NZ	Leaves, Seeds	–	–	Moshi and Mbwambo (2002)
63	<i>Mormodica calantha</i> Gilg (Cucurbitaceae)	Mtundwa	–	NZ	–	–	–	Kasole et al. (2019)
64	<i>Persea americana</i> Mill. (Lauraceae)	Avocado, Mparachichi	–	NZ	Seeds	–	–	Moshi et al. (2004)
65	<i>Persea americana</i> Mill. (Lauraceae)	Mparachichi	–	NZ	Whole plant	–	–	Kasole et al. (2019)
66	<i>Piliostigma tortuosum</i> (Collett & Hemsl.) Thothathri (Leguminosae)	Syn: <i>P. thorningii</i> (Schumacher) Milne- edh	–	–	–	–	Pruritus	Lunyera et al. (2016)
67	<i>Syzygium guineense</i> (Willd.) DC (Myrtaceae)	Muvengi	–	–	–	–	–	Moshi et al. (2004)
68	<i>Syzygium cumini</i> (L.) Skeels (Myrtaceae)	Black plum, Mzambarau	–	NZ	Stem bark	–	–	Moshi et al. (2004)
69	<i>Vangueria infausta</i> Burch. (Rubiaceae)	Mvilu	–	–	–	–	–	Kasole et al. (2019)
70	<i>Vitex mombassae</i> Vatke (Lamiaceae)	Mutalali, Masumgwi	–	WZ	Roots	–	–	Ruffo (1991)

WZ = Western zone; NZ = Northern zone; CZ = Central zone; SHZ = Southern Highlands zone; SZ = Southern zone; SWHZ = South West Highlands zone; LZ = Lake zone; EZ = Eastern zone; Zanzibar.

Western, Northern, Central, Southern Highlands, Southern, West Highlands, Lake, Eastern zones, and Zanzibar.

3. Results

3.1. Summary of studies included

A total of 808 articles were retrieved through database and hand search. These articles were assessed for relevance and screened against the predetermined inclusion criteria. Consequently, 128 were finally included (Fig. 1). The majority (71) of these articles were *in vivo* studies of plant extracts, fractions, or pure compounds; and only 40 articles investigated *in vitro* anti-diabetic activities. The remaining (17 articles) were either reported ethnomedical, toxicological, or phytochemical aspects of plant species.

3.2. Traditional use of plants for diabetes mellitus

A total of sixty-two plant species were reported in the traditional management of diabetes mellitus among local communities in Tanzania.

Among them, 46 (74.2%) were obtained from ethnomedical studies conducted in Tanzania, 3 (4.8%) from the *in vitro* or *in vivo* studies that used plant samples from Tanzania, and 13 (21%) from the review of specialized herbarium documentation.

The most-reported plant species were *Moringa oleifera* Lam. and *Cymbopogon citratus* (D.C.) stapf. with 3 use reports each. The 62 plant species were distributed in thirty-four plant families. The Euphorbiaceae family had the most species 5 (8.1%), this was followed closely by Fabaceae, Mimosaceae, and Rubiaceae families each with 4 (6.5%) as shown in Table 1.

Of 62 plant species distributed in five geographical regions, the majority 23 (37.1%) were reported in the northern zone and Eastern zone 19 (30.6%). On the other hand, Western, Lake, and Southern highland zone had fewer plant species; 13 (21%), 8 (12.9%), and 1 (1.6%) respectively (Table 1). While the use of plant species for DM in Central, West highland, Southern, and Zanzibar zones remain unknown, one study did not report the region of the two species *Piliostigma tortuosum* (Collett & Hemsl.) Thothathri and *Syzygium guineense* (Willd.) DC investigated (Moshi et al., 2004).

There were 26 (41.9%) plant species with complete taxonomical

Table 2
In vitro anti-diabetic activities of plants traditionally used in Tanzania.

Plant species	Extract/fraction(s) or compounds	Mechanism of action	System/model	Outcomes	References
<i>Abelmoschus esculentus</i> (L.) Moench ^a	Quercetin from seeds; concentration 1.0 mg/mL and acarbose	Inhibition of carbohydrate metabolizing enzymes (ICMEs)	Baker' yeast and rat intestine's α -glucosidase, maltase, and sucrase	Baker's yeast α -glucosidase [IC ₅₀ 62.8 $\pm$ 2.1 μ M], acarbose [403.9 $\pm$ 0.4]; rat intestinal maltase and sucrase inhibition [IC ₅₀ ; 12.3 $\pm$ 0.6 and 31.7 $\pm$ 1.5 μ M] respectively	Thanakosai and Phuwapraisirisan (2013)
	Methanol and ethanol fruit extracts and acarbose; conc. 50–250 μ g/mL	ICMEs	α -glucosidase and α -amylase enzymes	α -glucosidase and α -amylase inhibition in a dose-dependent manner. Standard had a stronger effect. No IC ₅₀ reported	Ahmed and Kumar (2016)
<i>Acacia tortilis</i> (Forsk) Hayne ^b	Gum polysaccharides (0.1–25 mg/mL) and acarbose (1–100 mM)	ICMEs	Rats small intestine's α -glucosidase	α -glucosidase inhibition [IC ₅₀ 0.7 mg/mL; 4 mM acarbose]. Concentration-dependent	Bisht et al. (2013)
<i>Aloe vera</i> (L.) Burm.f. ^a	Gel polysaccharides (APs) conc.10 mg/mL	β -cells protection	Hamster pancreatic β -cell line HIT-T15	Prevent β -cells death through JNK alleviation	Kim et al. (2018)
<i>Annona muricata</i> L. ^b	Aqueous extracts of pericarp; conc. 0.20, 0.40, 0.6, and 0.80 mg/mL and acarbose at 10, 30, and 40 μ g/mL	ICMEs	Hog pancreatic α -amylase and α -glucosidase.	α -amylase inhibition [IC ₅₀ 0.46 mg/mL] and α -glucosidase inhibition [IC ₅₀ 0.37 mg/mL]; inferior to standard.	Adefegha et al. (2015)
	Ethanol and butanol leaf fractions at doses of 0.15, 1.5, and 15 μ g/mL. Acarbose standard	ICMEs and formation of advanced glycation end products	BSA-fructose, BSA-methylglyoxal, Arginine-methylglyoxal models and α -amylase (HSA-f), rat intestinal α -glucosidase	Inhibited glycation in BSA-fructose AP-methylglyoxal and arginine-methylglyoxal α -amylase inhibition [IC ₅₀ 9.2 $\pm$ 2.3 and 6.1 $\pm$ 1.6 μ g/mL], α -glucosidase inhibition [IC ₅₀ 413.1 $\pm$ 121.1 and 817.4 $\pm$ 87.9 μ g/mL] respectively	Justino et al. (2018)
<i>Caesalpinia bonduc</i> (L.) Roxb ^b	Hydro-ethanol whole plant extract; Conc. 3.90–500 μ g/mL and acarbose standard	ICMEs	α -amylase and α -glucosidase	α -amylase inhibition [IC ₅₀ 9.81 μ g/mL], superior to standard; α -glucosidase inhibition [IC ₅₀ 480.25 μ g/mL], inferior to standard	Sachan et al. (2019)
<i>Cassia abbreviata</i> Oliv. ^b	Ethanol bark extract range 0.5–3.5 mg/mL	ICMEs and glucose uptake	Rat small intestine and hemi-diaphragms	α -glucosidase inhibition [IC ₅₀ 1.4 mg/mL] in dose-dependent response; $\uparrow$ glucose uptake	(Bati et al., 2017)
	Aqueous stem bark extract at conc. 10–100 μ g/L	Glucose uptake	C2C12 muscle cells	$\uparrow$ Glucose uptake in cells; $\uparrow$ GLUT4 translocation in muscle cells; $\uparrow$ GLUT1 gene expression	Seabi et al. (2016)
<i>Centella asiatica</i> (L.) Urb. ^b	Ethanol extract of edible part; conc. 25 μ L and 50 μ L; and acarbose standard	ICMEs and lipid metabolizing enzymes	Yeast α -glucosidase, α -amylase, and pancreatic lipase	α -glucosidase inhibition [IC ₅₀ 42.27 $\pm$ 1.66 μ g/mL], acarbose [34.07 $\pm$ 3.69]; α -amylase inhibition [IC ₅₀ 536.51 $\pm$ 8.80 μ g/mL], acarbose [113.25 $\pm$ 2.72]; pancreatic lipase inhibition [IC ₅₀ 759.14 $\pm$ 3.63 μ g/mL]	Supkamonseni et al. (2014)
	Aqueous extract of the herb; conc. 500 μ g/mL	Glucose uptake, transport, anti-inflammation	3T3-L1 adipocytes and RAW 264.7 cells macrophages	$\uparrow$ glucose uptake in adipocyte, induction of GLUT-4 and IRS-1 mRNA expression; $\downarrow$ IL-6 mRNA	Kusumastuti et al. (2019)
<i>Clausena anisata</i> (Willd) Hook.f. ex Benth. ^b	Aqueous, methanol, acetone, hexane extract; conc. 10 mg/mL	ICMEs	Human urinary α -amylase, <i>B. steartothermophilus</i> α -glucosidase	Not effective in α -glucosidase and α -amylase inhibition	Mogale et al. (2012)
<i>Cymbopogon citratus</i> (DC.) Stapf ^b	Acetone, methanol, hexane, and ethyl acetate whole plant extracts; conc. 0.2, 0.4, 0.6, 0.8, and 1 mg/mL and acarbose standard	ICMEs	Porcine pancreatic α -amylase and Rat small intestine' α -glucosidase	α -amylase inhibition [IC ₅₀ 0.31 mg/mL], acarbose [0.50 mg/mL] α -glucosidase inhibition (99%) at 1 mg/mL	Boaduo et al. (2014)
<i>Euphorbia hirta</i> L. ^b	Compounds Quercetin, Dimethoxy quercetin, Hirtacoumaroflavonoside, Hirtaflavonoside-B from whole plant and acarbose; conc. range of 0.012, 0.025, 0.05, 0.1 and 0.2 Mm	ICMEs	α -glucosidase solution	α -glucosidase inhibition [IC ₅₀ 0.022 mM for Hirtacoumaroflavonoside] and [IC ₅₀ 0.071 mM for Hirtaflavonoside-B] acarbose [IC ₅₀ 0.092 mM]. Showed a dose-dependent, non-competitive inhibition	Sheliya et al. (2015)
	Aqueous, water: methanol (1:1) %v/v and methanol whole plant fractions and acarbose; conc. of 50 μ L	ICMEs	α -amylase and α -glucosidase	α -glucosidase inhibition [IC ₅₀ 213.63 μ g/mL, 146.9 μ g/mL and 78.88 μ g/mL] respectively; acarbose had 8.07 μ g/mL α -amylase inhibition [IC ₅₀ 180.09 μ g/mL, 202.24 μ g/mL 280.71 μ g/mL] respectively; acarbose had 7.46 μ g/mL α -glucosidase and α -amylase inhibition in a dose-dependent manner. IC ₅₀ not reported	Sheliya et al. (2016)
<i>Momordica charantia</i> L. ^a	Polypeptide K and seeds oil; conc. 0.267–2 mg/kg	ICMEs	α -glucosidase and α -amylase	α -glucosidase and α -amylase inhibition in a dose-dependent manner. IC ₅₀ not reported	Ahmad et al. (2012)
	Aqueous and ethanol extracts of fruits and seeds; doses 0.2, 0.3, and 0.4 mg/mL	Glucose uptake	3T3-L1 adipocytes	$\downarrow$ glucose uptake (Both extracts); $\uparrow$ adiponectin release	Roffey et al. (2007)
	Paste like dried fruit extract (capsule). Conc. 5–50 μ L	11 β -Hydroxysteroid dehydrogenase type 1 (HSD1) inhibition	Human liver microsomes and purified human 11 β -HSD1	11 β -HSD1 inhibition [IC ₅₀ log –2.58 $\pm$ 0.077 g/mL]	Blum et al. (2012)

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Table 2 (continued)

Plant species	Extract/fraction(s) or compounds	Mechanism of action	System/model	Outcomes	References
	Aqueous and chloroform fruit extracts at conc. 6 µg/mL	Glucose transport/uptake	L6 myotubes	↑mRNA expression of GLUT4, PPARδ, and PI3K; comparable to insulin and rosiglitazone	Kumar et al. (2009)
	25-O-methylkaraviagein D (1); karaviloside II (2); (19R,23E)-5b,19-epoxy-19,25-dimethoxycucurbita-6,23-dien-3b-ol (3); conc. 10 µL	ICMEs and PTP1B inhibition	α-amylase, α-glucosidase and protein tyrosine phosphatase 1 B (PTP1B)	α-glucosidase inhibitory activity [IC ₅₀ 10.19, 28.55, and 20.20 µM] respectively. Compound 1 had PTP1B and α-amylase inhibition	Yue et al. (2017)
	Cucurbitane-type triterpenoids from fruits (C1, C3, and C4; doses 2.5, 5, and 10 µmol/L) and C2; 1.25, 2.5, and 5 µmol/L	Glucose uptake, transport, and insulin receptor	C2C12 myotubes	↑insulin receptor substrate-1 (IRS-1); ↑basal and insulin-stimulated glucose uptake; ↑Glut-4 translocation	Han et al. (2018)
	<i>Momordica charantia</i> insulin receptor (IR)- binding protein (mcIRBP) from fruit; conc. 1 µM and 5 µM	Glucose uptake, insulin signaling pathway	3T3- L1 cells	↑: kinase activity of IR, phosphorylation-IR, phosphoinositide-3-kinase/Akt pathways. ↑ glucose uptake	Lo et al. (2014)
	Aqueous fruits extract, 9-nor-cucurbita-5 (10), 6,8,22-(E), 24-pentaen-3 β -ol, and Karavilagenine E. conc. 1000 µg/mL, 246 µM, 440 µM respectively	GLP-1 stimulation	Murine enteroendocrine cell line	↑ GLP-1 secretion dose-dependently	Huang et al. (2013)
	Momordicin (M2) and Charantin (M1) from fruits. Conc. 10–100 µg/mL each	ICMEs	α-amylase	α-amylase inhibition [IC ₅₀ 15.86 l g/mL] for M2 and [IC ₅₀ 16.17 l g/mL] for M1	Kulkarni et al. (2019)
	Saponin-rich fraction, momordicine II, kuguaglycoside G from whole fruits; conc. 125, 10, 15 µg/mL respectively	Insulin secretion	MIN6 β-cells	Insulin secretagogue activity	Keller et al. (2011)
	Protein extract from fruits (10 mg/mL)	Insulin secretion, glucose uptake	rat pancreas, C2C12 myocytes, and 3T3-L1 adipocytes	↑ insulin secretion, glucose uptake	Yibchok-anun et al. (2006)
<i>Moringa oleifera</i> Lam ^a	Aqueous leaf; conc. of extract not available	ICMEs	Pancreatic α- amylase and α- glucosidase	α- Amylase inhibition [IC ₅₀ 64.29 ± 0.52]; α-glucosidase inhibition [IC ₅₀ 38.12 ± 0.71]	Ademiluyi et al. (2018)
	Aqueous leaf extract at conc. of 50–500 µg/mL	Glucose uptake	Baker's yeast, rat hemidiaphragm, and rat skeletal muscles	↑ glucose uptake by Yeast's cell; ↓glucose uptake through the intestinal membrane; ↑ glucose uptake in muscles in a dose-dependent manner	Khan et al. (2017)
<i>Persea americana</i> Mill. ^b	Aqueous leaf extract 0.01–300 µg/mL	PTP1B inhibition	PTP1B (human, recombinant)	PTP1B inhibition; in a concentration-dependent manner.	Marrero-Faz et al. (2014)
	Methanol:1M HCL (1:1) leaf extract; up to conc. 200 µL	ICMEs	α- amylase and α- glucosidase	α- amylase inhibition [IC ₅₀ 0.219 ± 0.012 mg/mL] and α- glucosidase inhibition [IC ₅₀ 0.067 ± 0.001 mg/mL]	Obboh et al. (2014)
<i>Phyllanthus amarus</i> Schumacher & Thonn. ^b	Triacantanol (1), dotriacontanyl docosanoate (2), an isomeric mixture of oleanolic acid and ursolic acid in a ratio of 2:1 (3); conc. 0.25, 2.5 and 5 µg/mL	ICMEs	Porcine pancreatic α-amylase	α- amylase inhibition (3) [IC ₅₀ 2.01 µg/mL] -No inhibition for (1) and (2)	Ali et al. (2006)
<i>Syzygium cumini</i> (L.) Skeels ^a	Valoneic acid dilactone, rubuphenol, and ellagic acid from seeds; conc. 100 µg/mL	PTP1B inhibition	PTP 1B inhibition assays	PTP1B inhibition [IC ₅₀ : 9.37, 28.14, and 25.96 µg/mL, respectively]	Sawant et al. (2015)
	Fruit's pulp, seed, seed coat, and kernel extracted with petroleum ether, ethyl acetate, methanol, and water at conc. 0.1–300 µg and acarbose standard	ICMEs	porcine pancreatic α-amylase	α-amylase inhibition; kernel had better inhibition than other parts [IC ₅₀ 8.3 µg/mL]; acarbose [IC ₅₀ 24.7 µg/mL]	Gajera et al. (2017)
	Polyphenolic-rich leaf extract; conc. 100 µg/mL	Insulin secretagogues	INS-1E β cell culture	↑insulin secretion, ↑glucose-stimulated insulin secretion	Chagas et al. (2018)
	Ursolic acid and oleanolic acid from ethyl acetate leaf extract; conc. 20–1000 µg/mL	ICMEs	Porcine pancreatic α-amylase and α-glucosidase	α-amylase inhibition [IC ₅₀ : 39.9 µg/mL] α-glucosidase inhibition [IC ₅₀ : 28.2 µg/mL] standard IC ₅₀ not reported	Poongunran et al. (2017)
<i>Syzygium guineense</i> (Willd.) DC	80% methanol leaf extract; 0.625–10 mg/mL	ICMEs	α-glucosidase	α-glucosidase inhibition [IC ₅₀ 6.15 mg/mL]	Ezenyi et al. (2016)
<i>Terminalia sericea</i> Burch. ex DC	β-sitosterol and lupeol from acetone stem bark extract at 0.2 mg/mL. Acarbose standard	ICMEs	α-glucosidase, α-amylase	α-glucosidase inhibition [IC ₅₀ 54.5 and 66.5 µM] respectively. α-amylase inhibition [IC ₅₀ : 216.02 and 140.7 µM] respectively; acarbose [IC ₅₀ 65.2 µM]	Nkobile et al. (2011)
<i>Withania somnifera</i> (L.) Dunal ^a	Leaf and root extracts and withanolides (withaferin A, withanone, withanolide A, withanolide B, and withanoside IV); conc 0.1–100 µM and insulin standard	Insulin secretion and glucose uptake	Pancreatic RIN-5F (CRL-2058) cells, L6 myotubes, and 3T3 adipocytes	↑insulin secretion; ↑glucose uptake in a dose-dependent manner (Withanolide A)	Jonathan et al. (2015)
	Three compounds; 20β hydroxy-1-oxo (22R)- witha-2,5,24 trienolide (1), (20R, 22R-14a,20a)-dihydroxy-1-oxowitha-2,5,16,24 tetraenolide (2), and (20R,22R)-1- oxo-5a,8b-	ICMEs	α-glucosidase from <i>saccharomyces</i> sp	α-glucosidase inhibition; [IC ₅₀ 98.60, 38.20, and 40.65 µg/mL] respectively While standard had [IC ₅₀ 422.33 µM]	Khan et al. (2014)

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Table 2 (continued)

Plant species	Extract/fraction(s) or compounds	Mechanism of action	System/model	Outcomes	References
	dihydroxywitha-6a,7b-epoxide-2,24-dienolide (withasomilide) (3) from whole plant and deoxy nojirimycin standard. Conc 100 µg/mL				

^a Antidiabetic activity reported in both *in vivo* and clinical trials.

^b Antidiabetic activity reported in *in vivo* studies.

identification including the voucher number. Similarly, about 26 plant species had a detailed description of the traditional method of preparations and use. According to the available information, the liquid was the most preferred traditional dosage form. The dosage form was prepared mainly by hot water maceration or decoction. Generally, a quantity of medicine sufficient for a daily dose is prepared each day for the duration of treatment. Other methods of preparation reported included grinding plant parts to powder form as well as boiling and eating the whole plant part (Table 1).

Interestingly, plants reported for traditional management of DM were also found useful for the management of other health conditions such as infertility, ulcers, erectile dysfunction, hypertension, stroke, eye problem, etc. Many of these conditions are also well-established complications of DM.

3.3. Validation

3.3.1. Phytochemicals

Researchers have isolated and tested about 55 pure compounds with diverse chemical structures from thirteen plant species. These compounds are majorly polyphenolics, phytosterols, and triterpenoids. Among the plant species with pure compounds, *A. esculentus*, *A. vera*, and *M. charantia* had promising drug lead molecules. Quercetin from *A. esculentus*, charantin from *M. charantia*, and several phytosterols from *A. vera* have been extensively applied for DM management. However, the phytochemistry of several other plant species used traditionally in Tanzania remains largely unknown (Supplementary material S2).

3.3.2. In vitro activities

Forty-one studies investigated *in vitro* antidiabetic activities of extracts, fractions, or pure compounds from eighteen plant species; *Abelmoschus esculentus* (L.) Moench, *Acacia tortilis* (Forsk) Hayne, *Aloe vera* (L.) Burm.f., *Annona muricata* L., *Caesalpinia bonduc* (L.) Roxb, *Cassia abbreviata* Oliv., *Centella asiatica* (L.) Urb., *Clausena anisata* (Willd) Hook. f. ex Benth., *Cymbopogon citratus* (DC.) Stapf, *Euphorbia hirta* L., *Momordica charantia* L., *Moringa oleifera* Lam, *Persea americana* Mill., *Solanum americanum* Mill., *Syzygium cumini* (L.) Skeels, *Syzygium guineense* (Willd.) DC., *Terminalia sericea* Burch. ex DC., and *Withania somnifera* (L.) Dunal. The most frequently tested plant parts were fruits (12 studies), whole plants (6 studies), and leaves (6 studies). Water was also the most preferred solvent for the preparation of plant extracts. The pure compounds investigated for *in vitro* antidiabetic activities were from *A. esculentus*, *A. tortilis*, *A. vera*, *M. charantia*, *M. oleifera*, *S. cumini*, *T. sericea*, and *W. somnifera* (Table 2.). All pure compounds tested have shown a certain degree of antidiabetic activity, and more often than not, their activity is stronger than that exerted by standards. On the other hand, the antidiabetic activities of the crude extract were generally weak compared to that of standards.

Of the 18 plant species studied, 14 (42.4%) had either α -glucosidase and/or α -amylase inhibition effects. The researchers used Baker's yeast α -glucosidase, α -glucosidase and α -amylase enzymes, Porcine/Hog pancreatic α -amylase, and rat's small intestine's α -glucosidase model. These plant species exhibited a varied degree of inhibition of carbohydrate metabolizing enzymes. Quercetin from *A. esculentus*; Hirtacoumaroflavonoid and Hirtaflavonoid-B from the whole plant of

E. hirta, Polypeptide-K, momordicin and Charantin from fruits of *M. charantia* and extracts of *A. esculentus*, *A. tortilis*, *C. bonduc*, *C. citratus*, and *E. hirta* had the superior inhibitory effect to that of standard acarbose. On the other hand, *C. anisata* had no inhibitory effect on both the enzymes.

M. charantia L. was the most extensively investigated with at least 13 *in vitro* studies reported on several mechanisms of glucose-lowering action (Table 2). Researchers reported that water and ethanol extract of fruit and seed at a concentration of 0.2, 0.3, and 0.4 mg/mL increased glucose uptake and adiponectin release in 3T3-L1 adipocytes (Roffey et al., 2007). Polypeptide-K and protein extract from fruits increased insulin secretion and glucose uptake. Furthermore, cucurbitane-type triterpenoids from fruits inhibited protein tyrosine phosphatase 1 B (PTP1B), increased insulin receptor substrate-1 (IRS-1), increased basal and insulin-stimulated glucose uptake, increased GLUT-4 translocation, and increased GLP-1 secretion. (Table 2).

3.3.3. In vivo studies

Of the 62 plant species, 30 (42%) were investigated in animal models of DM (Table 3) of which 16 had reports on *in vitro* studies (Table 1). Cumulative analysis indicated that streptozotocin (STZ) was the most preferred substance for the chemical induction of DM in animals (29 studies). The STZ was used at varying doses and routes of administration. The review has also found other less commonly used models to include; STZ-nicotinamide, Alloxan monohydrate, high-fat diet combined with a low dose of STZ, and genetically modified mice.

We identified comprehensive reviews of *in vivo* studies for three plant species reported; *M. oleifera*, *A. muricata*, *M. charantia*. The data for these plant species were thus excluded in Table 3. Such detailed evidence of *in vivo* activities of these plant species is referred to in previous reviews (Alwan et al., 2020; Nova et al., 2020; Peter et al., 2020). Overall, evidence from previous reviews supports the antidiabetic effect of the *M. oleifera*, *A. muricata*, *M. charantia* with varied degree of certainty.

All the plants investigated had a glucose-lowering effect at different doses of extracts, fractions, or pure compounds. These plant species have diverse molecular and metabolic targets in the liver, skeletal muscles, adipose tissues, pancreases, and stomach (Fig. 2).

More than half 15 (53%) of the plants studied in animals have multiple cellular targets, with *Centella asiatica* having antidiabetic activity on all of the key target sites. On the contrary, *Acacia tortilis* (Forsk) Hayne, *Syzygium guineense* Willd.) DC and *Artemisia afra* Jacq. ex Willd. acted only on one target (Fig. 2).

Our findings indicated that about 33 plant species traditionally used for DM in Tanzania had not been scientifically validated for such use. The plants included; *A. kirkii*, *A. quanzenis*, *A. anthelmintica*, *C. umbraticola*, *C. africana*, *C. lanceolatum*, *C. crassifolia*, *C. junceum*, *C. burchanaii*, *D. borbonica*, *D. cinerea*, *D. praeheensis*, *D. loureiroana*, *E. amoena*, *E. natalensis*, *F. fischeri*, *H. abyssinica*, *L. schimperii*, *M. obtusifolia*, *M. scandens*, *M. calantha*, *O. confusa*, *P. tortuosum*, *P. maprouneifolia*, *S. americanum*, *S. madagascariensis*, *T. mollis*, *U. bisexualis*, *V. apiculata*, *V. infausta*, *V. mombassae*, *W. stuhlmannii*, and *Z. acanthopodium*. Their use in the management of DM is reported for the first time in Tanzania (Table 1).

Table 3*In vivo* antidiabetic activities of plants traditionally used in Tanzania.

Scientific name	Extract/fraction(s) or compounds, dose with the route of administration	Model/sample size	Mechanism of actions	References
<i>Abelmoschus esculentus</i> (L.) Moench	Peel and seed powder; doses 100 and 200 mg/kg and standard-glibenclamide 5 mg/kg (p.o) for 28days	STZ (60 mg/kg, i.p.); male Wistar albino rats/n = 5	↓: PG, HbA1c%; ↓: TGs, LDL-c, TC, VLDL-c, TP; ↑HDL-c; ↑liver, kidney and pancreas SOD, CAT, GPx, GSH; ↓TBARS	(Sabitha et al, 2011, 2012)
	Polysaccharide from pods; dose 200 mg/kg and standards- glimepiride 5 mg/kg and metformin 200 mg/kg p.o for 10days	STZ (45 mg/kg, i.p.); male C57BL/6 mice/n = not reported	↓PG closer to standard; ↓PPG in 120min	Liu et al. (2018)
	Pectic polysaccharide WOP-2 from fruit; doses 50 and 150 mg/kg (p.o) for 10days. No active control used	STZ (100 mg/kg, i.p); male ICR mice/n = 10	↓serum MDA, ↑serum insulin and ↑serum SOD activity	Zhang et al. (2018)
	Okra powder; dose 200 mg/kg and metformin 200 mg/kg (p.o) for 30days;	HFD-STZ (35 mg/kg, i.p); adult female Wistar rats/n = 5	↓: HOMA-IR, FPG; ↑serum insulin; ↓: TGs, TC, LDL-c, VLDL-c; ↑HDL-c; ↓PPAR-γ and PPAR-α expression in the pancreas; ↑β-cells; ↓Serum MDA ↑: SOD, GPx, and CAT	(Majd et al, 2018, 2019)
<i>Acacia tortilis</i> (Forsk) Hayne	Fractions F1 and F2 from fruit; doses 0.23 and 0.45 mg/kg (p.o) for 84days. No active control used	HFD-STZ (35 mg/kg, i.p); male Sprague Dawley rats/n = 8	↓Creatine phosphate kinase and ketone bodies; ↓DPP-4 expression; ↑GLP-1R	Peng et al. (2019)
	Gum polysaccharide (AEATP); doses 250, 500, and 1000 mg/kg and glimepiride 10 mg/kg (p.o) for 28 days	STZ-nicotinamide (230-65 mg/kg, i.p); male Wistar albino rats/n = 6	↓: FPG, HbA1c%; ↑serum insulin and pancreatic insulin content. ↓: TC, TG, LDL-c, VLDL-c and ↑HDL-c	Kumar Bhateja and Singh (2014)
	Aqueous leaves extract; doses 50 and 100 mg/kg (p.o) for 14 days. No active control	STZ (60 mg/kg, i.p); male Wistar albino rats/n = 6	↓PG; ↑: serum insulin, pancreases/body ratio	Afolayan and Sunmonu (2011)
	Aqueous leaves and stems extract; doses 50, 100, 200 and 300 mg/kg, glibenclamide 3 mg/kg (p.o) once	Alloxan (186.9 mg/kg, i.p); male Swiss albino mice/n = 5	↑: pancreases SOD, GR, GPx activity	Zg et al. (2019)
<i>Aspilia mossambicensis</i> (Oliv.) Willd			↓PG comparable to standard in 24hr	
<i>Bridelia duvigneaudii</i> J.Léonard	Stigmasterol from roots at dose of 50, 100 and 200 mg/kg and chlorpropamide 100 mg/kg standard (p.o) once. Glucose measured at 0.5, 1, 2, 3, and 4 h of glucose load	Male and female albino mice/n = 6	↓PPG at 30min	Credo et al. (2018)
<i>Bridelia micrantha</i> Bertol	Ethyl acetate leaves extract; doses 300 and 600 mg/kg and glibenclamide 2 mg/kg (p.o) for 21 days	STZ (50 mg/kg, i.p); Wistar albino rats of either sex (n = 5)	↓FPG but, inferior to standard, ↑: serum CAT, GSH; ↓serum MDA; ↓: TGs, TC	Nwaehujor Chinaka et al. (2013)
	Methanol leaves extract; doses 125, 250, and 500 mg/kg and glibenclamide 2 mg/kg (p.o) for 14 days	Alloxan (160 mg/kg, i.p); male albino Wistar rats/n = 6	↓PPG at dose 125 mg/kg	Omeh et al. (2014)
	Aqueous and ethanol seed extracts; doses 100 mg/kg and glibenclamide 10 mg/kg (p.o) for 10 days	STZ (50 mg/kg, i.p); Wistar albino rats of either sex/n = 6	↓PG; ↓: TC, TGs	Sharma et al. (1997)
	Aqueous and ethanol seeds extract; dose 250 mg/kg, and metformin (250 mg/kg) & glibenclamide (1.25 mg/kg) (p.o) bid for 28 days	STZ (90 mg/kg, i.p); Long-Evans rats of either sex (n = 8)	Insulin secretagogue; ↑liver glycogen; ↑serum fructosamine	Chakrabarti et al. (2005)
<i>Caesalpinia bonduc</i> (L.) Roxb	Ethanol, Pet. ether, kernel extract and ethanol seed coat extract; dose 300 mg/kg & rosiglitazone 0.01 mg/kg (p.o) for 14 days	Alloxan (150 mg/kg, i.p); Wistar rats of either sex (n = 6)	↓: PPG	Kannur et al. (2006)
	Hydro-methanol seed extracts; doses 250 mg/kg and glibenclamide 0.6 mg/kg (p.o) for 21 days	STZ (40 mg/kg, IM); male Wistar albino rats (n = 6)	↓: TC, LDL-c, TGs; ↑HDL-c	
	Polyphenolics leaves extract; doses 250 and 500 mg/kg (p.o) and saline (1.5 mL/kg, ip) for 8 weeks. No active control	Alloxan (120 mg/kg, i.p.); male adult Wistar albino rats (n = 15).	↑: hexokinase, glucose-6-phosphate dehydrogenase, glycogen (muscle and liver)	Jana et al. (2012)
			↓: HbA1c%, leptin, amylin, PYY in a dose-dependent manner.	Ifitikhar et al. (2020)
<i>Cajanus cajan</i> (L.) Millsp.	Methanol leaves extract; dose 400 and 600 mg/kg and glibenclamide 0.5 mg/kg (p.o) once;	Alloxan (100 mg/kg; i.p.); adult Swiss albino rats of either sex (n = 6).	↓: Mapk-8,Traf-4, Traf-6; ↑: Pdx-1, Ins-1, ngn-3, GLUT-4, and IRS-1in pancreatic cells	Ezike et al. (2010)
<i>Cassia abbreviata</i> Oliv.	Ethanol bark extract; doses 150 and 300 mg/kg and metformin 180 mg/kg (p.o) daily for 21 days;	HFD + STZ (35 mg/kg, i.p); male Sprague-Dawley albino rats (n = 5).	↓PPG in 60 min	
<i>Centella asiatica</i> (L.) Urb.	Plant powder; doses 50, 100, 200 mg/kg and metformin 150 mg/kg (p.o) for 22 days	Alloxan (120 mg/kg, i.p); male long Evan rat (n = 4).	↓FPG, ↓glucose-6-phosphatase, ↑hexokinase	Bati et al. (2017)
	Asiatic acid; dose 5, 10 and 20 mg/kg and glibenclamide 600 µg/kg (p.o) for 45 days	STZ (40 mg/kg, i.p); adult male Wistar albino rats (n = 8)	↓PPG in 30 min and normalize glucose in 180 min	
	Methanol leaves extract; doses 500 mg/kg and metformin 300 mg/kg (p.o) for 14 days	Fructose (10%)-STZ (40 mg/kg, i.p) in male Sprague-Dawley rats (n = 6)	↓: PG, TC, TGs, LDL-c; ↑ HDL-c	Rahman et al. (2011)
	Ethanol leaves extract; doses 125, 250 and 500 mg/kg; saponin rich fraction and non-saponin fraction dose 75, 150 and 300 mg/kg; asiaticoside dose 1.4, 2.8 and 5.6 mg/kg and glibenclamide 6.5 mg/kg (p.o) for 21 days	Alloxan (65 mg/kg, i.v); male Swiss albino mice (n = 5).	↓: PG, HbA1c%, glucose-6-phosphatase, fructose-1,6-bis phosphatase	Ramachandran and Saravanan (2013)
			↑: plasma insulin, glucagon	
			↓FPG; ↑skeletal muscle: glycogen, PFK, FBpase, GST, and GPx; ↓ hepatic MDA; ↑FRAP;	(Oyenihni et al, 2017, 2019)
			↓hepatic: IL-1b, MCP-1, and TNF-α;	
			All interventions ↓: PPG; ↑serum insulin;	Fitrianda et al. (2017)
			↓HbA1c%	
		Alloxan (120 mg/kg, i.p); Wistar rats (n = not reported)	↓: TC, TGs; Glucose-6-phosphate, fructose-1,6-bisphosphatase inhibition	Arsia et al. (2018)

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Table 3 (continued)

Scientific name	Extract/fraction(s) or compounds, dose with the route of administration	Model/sample size	Mechanism of actions	References
<i>Clausena anisata</i> (Willd) Hook.f. ex Benth.	Ethanol leaf and root extract; doses 100 mg/kg and 200 mg/kg; Glibenclamide (1 mg/kg) p.o for 30 days	STZ (90 mg/kg, i.p); male wistar rats (n = not reported)	↓FPG	Ojewole (2002)
<i>Crossopteryx febrifuga</i> (Afzel. ex G.Don) Benth.	Methanol root extract; 100–800 mg/kg and glibenclamide 0.5 mg/kg p.o. once.	Alloxan (150 mg/kg, i.p); wistar albino rats both sex (n = 6)	↑ HDL-c; ↓LDL-c; ↓FPG	Idris and Nenge (2019)
	Ethanol stem bark extract; doses 500 mg/kg, 1000 mg/kg and 1500 mg/kg and glibenclamide p.o for 7 days			
	Ethanol root extract; doses 375 and 500 mg/kg and glibenclamide 10 mg/kg, p.o. OGTT was also assessed	Alloxan (150 mg/kg, i.p); male albino rats (n = 5)	↓PPG in 60 min; ↓FPG, ↑ HDL-c, ↓LDL-c	Ojewale (2014)
<i>Croton macrostachyus</i> Hochst. ex Delile	Aqueous leaf extract; doses 48.4 mg/kg, 93.5 mg/kg, 180.9 mg/kg, 350 mg/kg (p.o), and 3 mg/kg of glibenclamide	Alloxan (186.9 mg/kg, i.p); male Swiss White Albino mice	↓FPG	Arika et al. (2015)
<i>Cymbopogon citratus</i> (DC.) Stapf	Organic and non-organic leaf extracts; doses 100 and 200 mg/kg and glibenclamide 10 mg/kg (p.o) for 21 days	Nicotinamide 210 mg/kg and STZ 180 mg/kg, (i.p); Swiss albino mice of either sex (n = 6).	↓PPG but inferior to standard ↓: TC, TGs, LDL-c; ↑ HDL-c; enlarged pancreas and ↑new islets	Itankar et al. (2019)
<i>Entada abyssinica</i> A. Rich	Leaves extract; dose 5% of the diet for 5 weeks. No active control	Alloxan (180 mg/kg, i.p); mice (n = 4)	↓: FPG, Serum MDA level	Gwarzo and Muhammad (2014)
<i>Erythrina abyssinica</i> DC.	Herbal extract; dose 500 mg/kg and glibenclamide 6 mg/kg p.o; once. OGTT was assessed	Guinea pigs; male (n = 6)	↓PPG at 90 min; standard had a superior effect	Amuri et al. (2017)
<i>Euphorbia hirta</i> L.	Ethanol whole plant extract; doses 100–400 mg/kg (p.o), and 5% povidone iodine ointment 50 mg/kg/day for 16 days	Alloxan (120 mg/kg, i.p); female Swiss albino rats with excision wounds sized 4.90 cm ² and of 2 mm depth (n = 3)	Closed open wound in a dose-dependent manner; ↓FPG; ↓: serum MDA, NO	Tuhin et al. (2017)
	Ethanol leaf extract; dose 300 mg/kg and Gliclazide 5 mg/kg (p.o) for 30 days	STZ (50 mg/kg, i.p) male albino Wistar rats (n = 6)	↓: FPG, HbA1c%; ↑Serum insulin ↓: TGs, TC; ↑TP ↑serum: SOD, CAT, GPx, and GST	Subramanian et al. (2011)
<i>Kigelia africana</i> (Lamarck) Benth.	Aqueous and ethyl acetate leaves extract; doses 50, 100, 200, and 300 mg/kg (i.p/p.o) and insulin 1 IU/kg i.p or glibenclamide 3 mg/kg p.o once	Alloxan (186.9 mg/kg i.p); male Swiss albino mice (n = 5)	↓PG in a dose-independent manner	Njogu et al. (2018)
<i>Maprounea africana</i> Müll. Arg.	Maprouneacin from roots; dose 0.5 mg/kg and metformin 250 mg/kg (p.o) qd.	Genetically diabetic db/db mice (n = not mention)	↓PG, PKC-mediated response	Carney et al. (1999)
	ethanolic leaf extract; doses 37–111 mg/kg and glibenclamide 10 mg/kg p.o. for 14 days	Aloxan (130 mg/kg, i.p); Swiss albino rats box sex (n = 6)	↓FPG; ↓: TGs, TC, LDL-c, and VLDL-c; ↑HDL-c levels	Akpan et al. (2012)
<i>Persea americana</i> Mill.	Hydroalcohol leaf extract; doses 0.15 and 0.3 g/kg and metformin 0.5 g/kg (p.o) for 30days	STZ (50 mg/kg, i.p); male Wistar albino rats (n = 7)	↓: FPG, PPG, hepatic glycogen; ↑: TC, TG in a dose-dependent manner	Lima et al. (2012)
	Aqueous seeds extract; doses; 20, 30, 40 g/L and glibenclamide 0.5 mg/kg, (p.o) for 21 days	Alloxan (150 mg/kg, i.p); male Wistar albino rats (n = 5)	↑PKB Reversed the histopathological damage of the pancreas, kidneys, and liver	Ezejiofor et al. (2013)
<i>Phyllanthus amarus</i> Schumach. & Thonn.	Aqueous leaf and seed extract; dose 150–600 mg/kg and glibenclamide 1 mg/kg (p.o) for 30 days	10% sucrose; male Wistar rats (n = 5)	↓FPG; ↑: insulin, FIGH and FIRI levels ↑: TC, TG, LDL-c (dose dependent)	Adeneye (2012)
	Ethanol leaf extract; doses 200 and 500 mg/kg, p.o. and glibenclamide 5 mg/kg for 21 days. OGTT assessed	STZ (40 mg/kg, i.p); male Wistar rats (n = 6)	↓: PPG in 90 min, FPG; ↑: Serum insulin, expression of insulin receptor A mRNA; ↑: Hepatic glycogen, hexokinase; ↓hepatic glucose-6-phosphatase	Sèlidji Eugène et al. (2018)
<i>Syzygium cumini</i> (L.) Skeels	Alcohol seeds extract; doses 25, 50, 100 mg/kg (p.o) and protamine zinc insulin (6U/kg) for 42 days	Alloxan (150 mg/kg, i.p); male Wistar albino rats (n = 6)	↓: FPG in dose-dependent; ↑: TC, FFAs in serum	Prince et al. (2004)
	Aqueous seeds extract; doses 100, 200 and 400 mg/kg and metformin 100 mg/kg (p.o) for 21 days;	HFD-STZ (40 mg/kg, i.p); male Wistar albino rats (n = 10)	↓: FPG, serum insulin, HOMA-IR; ↑HOMA-B; ↓: TC, TGs, LDL-c, HDL-c; ↓TNF-α; ↑PPARδ and PPARα expression. ↓pancreatic: TBARS, SOD, CAT, and GSH-Px activity; restored β-cell damage	Sharma et al. (2017)
	Polyphenolic-rich leaf extract; dose 400 mg/kg and metformin 5 mg/kg (p.o.) daily for 14 days	Alloxan (150 mg/kg, i.p); female Wistar rats (n = ?)	↓: FPG, HbA1c%, HOMA-IR; ↓glucose-6-phosphatase, ↑hexokinase activity, ↑HOMA-β; ↓liver MDA ↑liver: SOD, CAT, GPx; ↑GLUT 2, ↓NF-kB	Ajiboye et al. (2018)
<i>Syzygium guineense</i> (Willd.) DC	80%v/v methanol leaf extract, doses; 250, 500, and 1000 mg/kg; and metformin (100 mg/kg) p.o. OGTT assessed.	STZ (60 mg/kg, ip); Wistar albino rats of both sex (n = 5)	↓PPG in 30 min; ↓TC, TGs	Ezenyi et al. (2016)
<i>Withania somnifera</i> (L.) Dunal	Withaferin A dose of 2 & 10 mg/Kg, p.o. for 28 days	STZ (40 mg/kg, i.p); male Swiss albino mice (n = 8)	↓ FPG; ↓IL-6 and TNF-α; modulation of Nrf2/NFκB signaling; ↑ serum insulin; ↓tissue MDA; ↑serum GSH; protect pancreatic β-cells	Tekula et al. (2018)
	Root extract, dose of 35 mg/kg (p.o) given for 30days	STZ (60 mg/kg, i.p); male Wistar rats (n = 10)	↓ oxidative stress in the hypothalamus; stabilized mitochondrial functions	Parihar et al. (2016).
	Aqueous leaf extract; 200 and 400 mg/kg for 5 weeks. No active control	STZ (100 mg/kg, i.p); Wistar rats, sex not reported (n = 6) Alloxan (150 mg/kg, i.p); male Wistar albino rats (n = 6)	↓: HbA1c, serum insulin, PPG in 1 and 2 h; ↑ insulin sensitivity index	Anwer et al. (2008)
				(Udayakumar et al, 2009, 2010)

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Table 3 (continued)

Scientific name	Extract/fraction(s) or compounds, dose with the route of administration	Model/sample size	Mechanism of actions	References
	Phenolic compounds of ethanol roots & leaf extract; doses 100 & 200 mg/kg (p.o) for 8 weeks Powder 6.25% premixed with chow-fed for 8 weeks	Fructose (10 %w/v); male Wistar albino rats (n = 12)	↑liver glycogen; ↑ liver, kidney, heart; CAT, SOD, GST, GPx and ↓LPO; ↓LDL-c, TC, TGs; ↑HDL-c; ↓liver glucose-6-phosphatase ↓: serum insulin, HOMA-IR, IL-6, and TNF-α	Samadi Noshahr et al. (2015)

Superoxide dismutase (SOD); glutathione peroxidase (GPx); catalase (CAT); glutathione Reductase (GR); Reduced glutathione (GSH); malondialdehyde (MDA); postprandial plasma glucose (PPG); Homeostasis model assessment of insulin resistance (HOMA-IR); Homeostasis model assessment of β -cell function (HOMA-B); Peroxisome proliferator activated receptor gamma (PPAR- δ); Peroxisome proliferator activated receptor alpha (PPAR- α); aldose reductase (AR); protein-tyrosine phosphatase 1B (PTP1B); ferric reducing power (FRAP); 1,1-diphenyl-2-picryl-hydrazil (DPPH); alkaline phosphatase (ALP); gamma glutamyl transferase (GGT); aspartate transaminases (AST); GGtne transaminases (ALT); very low density lipoprotein cholesterol (VLDL-c); Trolox equivalent antioxidant capacity (TEAC); oxygen radical absorbance capacity (ORAC); hexokinase (HK); phosphofructokinase (PFK); fructose 1,6- bisphosphatase (FBPase); glycogen synthase (GS); glycogen phosphorylase (GP); adenosine deaminase (ADA), advanced oxidation protein products (AOPP); Protein Kinase C β isoform (PKC- β).

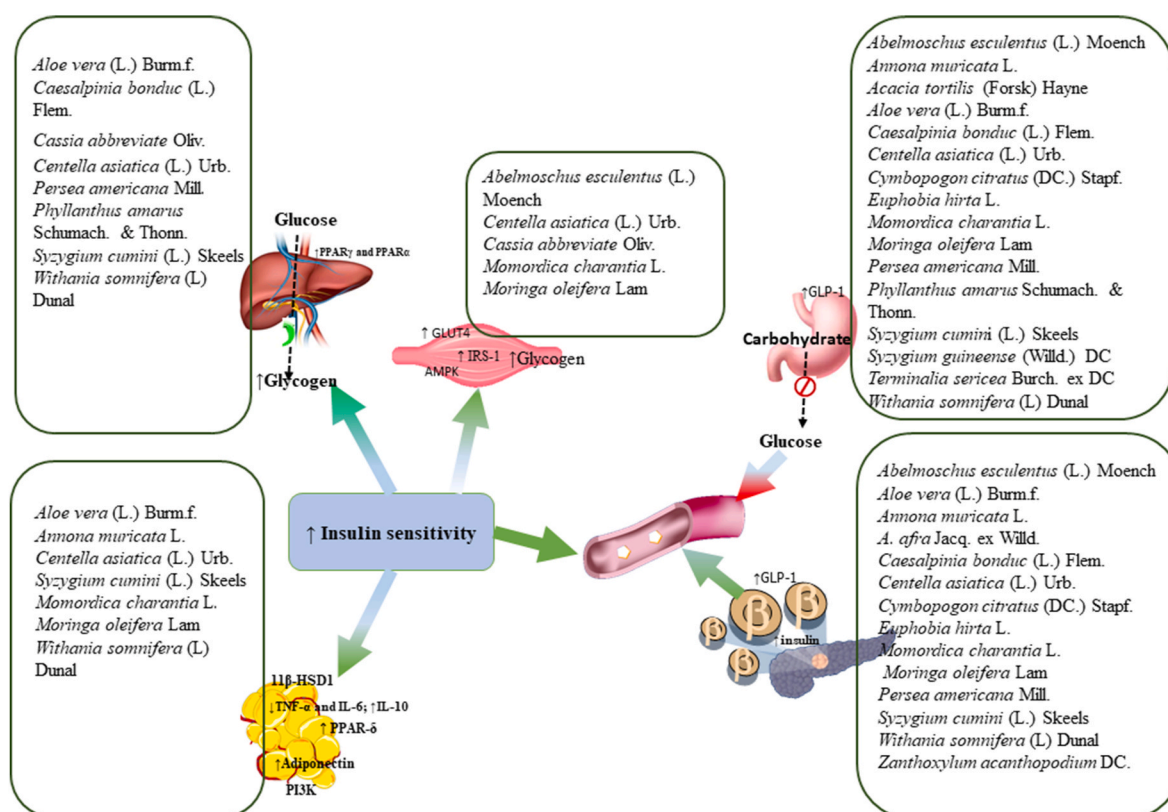


Fig. 2. Molecular and metabolic targets of plant species.

3.3.4. Clinical trials

About six plant species had clinical use-reports for the management of diabetes mellitus. These plant species were also studied *in vitro* and *in vivo* studies (Table 1). Synthesis of clinical evidence indicated that, *Abelmoschus esculentus* (L.) Moench had a significant antidiabetic and antihyperlipidemic effect when 10 g of its powder blended with yogurt and taken for 8 weeks (Moradi et al., 2020). Similarly, a series of meta-analysis of efficacy of *Aloe vera* revealed its ability to reduce the levels of fasting plasma glucose, glycosylated haemoglobin A1c, triglyceride, total cholesterol, and low density lipoprotein cholesterol, also, increased the levels of high density lipoprotein cholesterol in prediabetes and early non-treated diabetic patients (Suksomboon et al., 2016; Zhang et al., 2016). In another meta-analysis of randomized controlled clinical trials, *Momordica charantia* L. fruit extract was shown to significantly alleviate diabetes mellitus among individuals with type 2 diabetes mellitus (Peter et al., 2019). Also, *Withania somnifera* significantly restored the elevated levels of blood glucose, glycosylated

haemoglobin (HbA1c), insulin, and lipid profile (Durg et al., 2020). On the other hand, *Syzygium cumini* tea prepared from leaves of *S. cumini* had no antidiabetic effect (Teixeira et al., 2006).

3.3.5. Toxicological evidence

Researchers have investigated on toxicity aspects of 21 plant species out of 62 used locally (Table 4). These studies revealed that 18 plant species had no toxicity effect on animals. However, *Aspilia mossambicensis* (Oliv.) Willd, *Caesalpinia bonducella* (L.) Flem., and *Phyllanthus amarus* Schumach. & Thonn has shown mild toxicity in animals. These plant species increased liver enzymes and cause liver necrosis at high dose and long duration of oral administration. It is worth noting that, only 21 (33.9%) of the total plant species (62) had toxicity profile, this means the majority 41 (66%) of plant species had unknown toxicity profile.

Table 4

Toxicological aspects of plants traditionally used for diabetes mellitus in Tanzania.

Plant names	Toxicological/interaction
<i>Abelmoschus esculentus</i> (L.) Moench	Oral acute toxicity of fruit extracts, AEPP, and AESP was safe up to a dose of 2000 mg/kg (Sabitha et al., 2011). In another study, the water-soluble fraction reduced the absorption of metformin (Khatun et al., 2011).
<i>Acacia tortilis</i> (Forsk) Hayne	The oral dose of 5000 mg/kg in rats did not exhibit any sign of toxicity, behavioral changes, and mortality (Bisht et al., 2013).
<i>Aloe vera</i> (L.) Burm.f.	Oral toxicity of aloe vera gel extract (AVGE) at a dose of 150 mg/kg didn't cause deaths or notable abnormalities. Also, a 90-d toxicity test at a dose of 30 or 150 mg/kg showed no abnormalities. It was non-mutagenic in the Ames test and a chromosomal aberration test at concentrations of 5000 µg/plate and 1600 µg/plate, respectively (Tanaka et al., 2012).
<i>Annona muricata</i> L.	A single dose of 2000 mg/kg or 5000 mg/kg did not cause behavior change or mortality. No toxicity or death was recorded after a daily oral dose of 200, 400, and 800 mg/kg for 4 weeks. (Florence et al., 2014).
<i>Artemisia afra</i> Jacq. ex Willd.	The aqueous extract was regarded as nontoxic because it has LD ₅₀ above 5000 mg/Kg (Issa and Bule, 2015). Similar results were reported in a study that investigated the effect of acute and chronic effects of the extract. Besides, it had a hepatoprotective effect at high dose (Mukinda and Syce, 2007).
<i>Aspilota mossambicensis</i> (Oliv.) Willd	Sub-chronic toxicity indicated mild toxicity due to a significant elevation of liver enzymes at a daily dose 1000 mg/kg orally (Zg et al., 2019).
<i>Bridelia micrantha</i> Bertol	Brine shrimp toxicity evaluation reported very low toxicity with LC ₅₀ 32.0 µg/ml (Moshi et al., 2010). In another study, leaf extracts were safe at a dose of 2000 mg/kg (Nwaehujor et al., 2015).
<i>Caesalpinia bonducella</i> (L.) Flem.	Leaves and young twigs extract did not cause mortality up to a dose of 5000 mg/kg. however, at high dose liver enzymes were significantly elevated and hepatic necrosis indicating toxic to animals tested (Ogunlana et al., 2013).
<i>Cajanus cajan</i> (L.) Millsp.	A study of acute oral toxicity of leaf extract reported LD ₅₀ above 5000 mg/kg (Ezike et al., 2010). Neither mortality nor changes in behavioral abnormality were observed in an acute toxicity evaluation of aqueous and ethanol leaf extract. But increased kidney weight, reduced testes, and epididymis weight were observed in a sub-chronic study (Tang et al., 2017).
<i>Centella asiatica</i> (L.) Urb.	No mortality at an oral dose of 2000 mg/kg; ethanol extract was safe at a dose of 2000 mg/kg daily for 28 days (Yadav et al., 2019).
<i>Crossopteryx febrifuga</i> (Afzel. ex G.Don) Benth.	In acute oral toxicity, the lethal dose was 2.145 g/kg (Ojewale, 2014).
<i>Cymbopogon citratus</i> (DC.) Stapf.	Acute oral toxicity reported no mortality at a dose of 2000 mg/kg (Itankar et al., 2019); similarly, acute oral toxicity of aqueous leaf extract showed no sign of toxicity at a dose of 5000 mg/kg, p.o. (Adeneye and Agbaje, 2007).
<i>Dichrostachys cinerea</i> (L.) Wight & Arn.	Acute toxicity study of methanol leaf extract reported no mortality up to a dose of 3000 mg/kg. however, maximum mortality was observed at a dose of 4000 mg/kg. researchers have also provided evidence of the hepatoprotective effect of the extract (Babu et al., 2011).
<i>Euphorbia hirta</i> L.	A single dose of 5000 mg/kg of methanol extract did not cause mortality or any sign of toxicity in Sprague Dawley rats while sub-chronic toxicity indicated the extract was safe up to 1000 mg/kg for 90 days (Yuet Ping et al., 2013). Whereas, the acute toxicity study of leaf and stem extract showed that the toxic dose may be above 3000 mg/kg (Fofie et al., 2015).

Table 4 (continued)

Plant names	Toxicological/interaction
<i>Kigelia africana</i> (Lamarck) Benth.	Brine shrimp toxicity reported an LC ₅₀ of 7.2 µg/ml (Moshi et al., 2007).
<i>Momordica charantia</i> L.	Batran and colleagues investigated the acute toxicity of ethanol fruit extract in mice and reported the LD ₅₀ of 3623.4 mg/kg while that of aqueous extract was 919 mg/kg. Two hours after injecting the extracts, animals showed general depression, shallow deep respiration, and weak heartbeats. Other toxicity symptoms included abdominal convulsions, nervous disturbance, jumping, and hurried respiration (Batran et al., 2006).
<i>Moringa oleifera</i> Lam.	Oral toxicological evaluation of aqueous leaf extract in male Wistar albino mice up to a dose of 6400 mg/kg reported LD ₅₀ of 1585 mg/kg. Indicated a relatively safe to experimental animals tested (Awodele et al., 2012). In another study, the methanol extract had the median lethal dose in the rat of 3873 mg/kg (Ajibade et al., 2013).
<i>Persea americana</i> Mill.	Using the OECD 423 protocol, Kamagate and colleagues assessed acute oral toxicity of aqueous, ethanol, and methanol leaf extracts; These extracts were well tolerated at a dose of 2000 mg/kg. However, animals showed sight hepatitis (Mamadou et al., 2016).
<i>Phyllanthus amarus</i> Schumach. & Thonn.	Genotoxicity and sperm morphology assays of aqueous extract at concentrations; 100, 200, 400, 800, and 1600 mg/kg body were investigated. Compared with the vehicle, the extract that was given orally for ten days induced an increased frequency of micronucleated polychromatic erythrocytes and sperm abnormalities in mice. Total white blood cell and lymphocyte counts were also significantly increased; and significant pathological changes in the liver, kidney, and testis (AA et al., 2015). In another study, acute toxicity of 70% ethanol leaf extract produced 100% mortality at a dose of 2000 mg/kg, p.o. (Mbagwu et al., 2011).
<i>Syzygium guineense</i> (Willd.) DC	Researchers used Lorke's method to investigate oral acute toxicity of methanol leaf extract, no mortality at a dose of 5000 mg/kg (Ezenyi et al., 2016). A similar observation was reported in another study that used 80% ethanol extract (Loha et al., 2019).
<i>Withania somnifera</i> (L.)Dunal	An oral acute toxicity study at a dose of 2000 mg/kg had a no-observed effect (Patel et al., 2016). Similar findings were reported in another study of hydro-alcohol root extract. Also, no sign of toxicity or mortality observed when a dose of up to 2000 mg/kg, p.o. were given to rats for 28 days (Prabu et al., 2013). No evidence of maternal or foetal toxicity was observed when root extract was given to pregnant rats at a dose of up to 2000 mg/kg (Prabu and Panchapakesan, 2015).

4. Discussion

Our findings revealed that local communities in Tanzania use at least 62 different plant species to manage DM. Some of these species such as *M. charantia*, *A. esculentus*, and *W. somnifera* had phytochemicals extensively investigated for the management of DM with promising findings. However, 33 species have not been scientifically investigated. It could mean an uncovered potential opportunity to discover useful drug lead compounds through focusing research effort on traditionally used plant species.

The species investigated in preclinical and *in vitro* studies are shown to exert their effect at multiple cellular and molecular targets in the liver, skeletal muscles, gastrointestinal tract, pancreases, and adipocytes. These plants inhibit α-amylase and α-glucosidase, sucrase and maltase enzymes; regenerate pancreatic β-cells, and reduce fat accumulation in adipocyte through activation of signaling pathways (PPAR-α, and PPAR-δ). Other molecular actions include inhibition of nuclear

inflammatory signaling pathway by modulation of nuclear factor- κ B signaling (Tekula et al., 2018) and suppressing pro-inflammatory cytokines IL-1 α , IL-1 β (Oyenih et al., 2017, 2019), as well as tumor necrosis factor (TNF)- α (Bao et al., 2020; Ma et al., 2017; Oyenih et al., 2017, 2019; Sharma et al., 2017).

In recent years, it has been recognized that the pathophysiology of DM involved multiple cellular and molecular abnormalities (Olokoba et al., 2012; Rehman and Akash, 2017). Thus drug which could have multiple targets has become the focus for effective management of DM.

In vitro studies of plant preparations were reported with a dose range up to 1000 μ g/mL and much higher doses of up to 1500 mg/kg were also common in preclinical studies. While there is no standard cut-off dose of either extract or pure compounds to be tested in either *in vitro* or *in vivo*, it is well recognized that the tested dose should be adequate to produce a meaningful pharmacological response and could be realistically converted to clinical dose. Such large doses tested could pose potential challenges in converting it to a human equivalent dose. Heinrich and colleagues recommended a dose of plant extract ranged 100–200 mg/kg and that of its pure compound being much lower as adequate for pharmacological evaluation of herbal products (Heinrich et al., 2020).

Several methodological drawbacks have been noted in the review of scientific evidence. Some studies reported a significantly large difference in effect size between the standard drug and test substance. To take a case in point (Sheliya et al., 2016), reported a significant α -amylase activity of water extract of *Euphorbia hirta* L., however, compared to standard acarbose (IC₅₀ 8.07 μ g/mL) the IC₅₀ of the extract was far larger (213.63 μ g/mL). Lack of dose optimization, method of preparation, and incomplete ethnomedical information such as no adequate description of the method of identification and voucher specimen is another form of methodological challenges observed. The huge differences in IC₅₀ and mismatch of doses in preclinical studies could indicate potential challenges in translating such results to clinical practice.

5. Conclusion

Local communities in Tanzania use at least 62 plant species for the management of DM. However, only a fraction of such plant species has scientific evidence. *A. mossambicensis*, *C. bonduc.*, and *P. amarus* had shown signs of mild toxicity in animals. Together, our findings call for future researches to focus on *in vitro*, *in vivo*, and phytochemical investigation of identified plant species of which their use in DM had not been scientifically investigated.

Conflicts of interest

The authors declare that they have no competing interests.

Funding

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

Ethical consideration

The study does not require ethical approval.

Author's contribution

ELP conceived and drafted an earlier version of the manuscript. SH, EA, AK collected data and revised the drafts of the manuscript. CDS, PBN provided mentorship; CDS, PBN, NT revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Acknowledgement

This work is part of a Ph.D. thesis of ELP. World Bank supports the Ph.D. training through the PHARMBIOTRAC-ACE II fellowship administered at Mbarara University of science and technology. The authors wish to thank the fellowship program leadership for training support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jep.2020.113715>.

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