South African Journal of Botany 146 (2022) 585–602

Contents lists available at ScienceDirect

South African Journal of Botany

journal homepage: www.elsevier.com/locate/sajb

Antidiabetic compounds from medicinal plants traditionally used for the treatment of diabetes in Africa: A review update (2015–2020)

Aminu Mohammed[a,*], Nasir Tajuddeen[b]

[a] Department of Biochemistry, Ahmadu Bello University, Zaria, Nigeria
[b] Department of Chemistry, Ahmadu Bello University, Zaria, Nigeria

ARTICLE INFO

Article History:
Received 7 April 2021
Revised 23 September 2021
Accepted 16 November 2021
Available online xxx

Edited by Dr R. Maharaj

Keywords:
African medicinal plants
Antidiabetic
Antihyperglycemic
Diabetes mellitus
Phytochemicals

ABSTRACT

Africa has a rich biodiversity of plants and an active traditional medicine system that takes advantage of the rich biodiversity to treat various diseases, including diabetes mellitus (DM). The folkloric use of some of these plants in treating diabetes has been documented in various databases and publications, and validated with *in vitro* and *in vivo* models. In this regard ethnopharmacology remains the major tool in the search for bioactive compounds from African medicinal plants. Our previous review, covering 1977–2014, revealed that fifty-three (53) compounds isolated from African medicinal plants showed varying levels of antidiabetic activity. Since then, several further antidiabetic agents have been isolated from African plants, mostly based on ethnomedicinal information, but they have not been critically reviewed in any previous publication. Therefore, this article provides an insightful commentary on the antidiabetic compounds from African medicinal plants, along with an attempt to highlight the structure-activity relationships. Relevant literature, from 2015 to 2020, was collected by searching the major electronic scientific databases including PubMed, ScienceDirect, Web of Science, and Google Scholar, using appropriate keyword combinations. A total of eighty-four (84) compounds, isolated from different parts of twenty-four (24) African medicinal plants, including, leaves, stem barks, roots, tubers, and aerial parts, were investigated as possible antidiabetic agents. The flavonoids quercetin, kaempferol and apigenin, and the triterpenoids convallatoxin and combretin B are the most promising antidiabetic compounds. In spite of the interesting *in vitro* and *in vivo* evidence for antidiabetic activity, not a single compound was investigated in a clinical study. Several compounds from African ethnomedicinal plants have shown promising *in vitro* or *in vivo* antidiabetic activity. Some of these compounds are ubiquitous plants metabolites with known non-specific biological activities, but some others are rare phytochemicals that show structure specific bioactivities and should be further investigated. It is hoped that this review would motivate the further studies of these compounds along the drug discovery pipeline. In addition, this review shows that selection of plants based on ethnopharmacological information from African plants is a promising drug discovery strategy.

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder with multiple etiologies, characterized by hyperglycemia due to defective insulin secretion and/or insulin action, both leading to impaired metabolism of carbohydrates, lipids and proteins (American Diabetes Association, 2018a). Generally, DM is classified into type 1 DM, type 2 DM, gestational DM and the specific types of DM (monogenic diabetes syndromes, diseases of the exocrine pancreas and drug- or chemical-associated diabetes) (Amrican Diabetes Association, 2018b). The global prevalence of DM is increasing at an alarming rate. Recent data indicates that the disease affects over 463 million people globally and the number is likely to rise to 578 million by 2030, and 700 million by 2045 (Saeedi et al., 2019). In Africa, more than 19.4 million people suffer from diabetes, accounting for about 4.7% of the adult (20–79 years) population (Saeedi et al., 2019).

Treatment options to control DM remain life style modification, insulin injection and the use of conventional antidiabetic drugs. The fear of insulin injection coupled with the lack of consistency in dietary modification are major obstacles in DM treatment (Davies et al., 2013). On the other hand, conventional drugs such as sulphonylureas, glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-IV) inhibitors and

Abbreviations: AMPK, AMP-activated protein kinase; bw, Body Weight; DM, Diabetes Mellitus; DPP-4, Dipeptidyl Peptidase-4; FBG, Fasting Blood Glucose; GLUT4, glucose transporter 4; IC50, Inhibitory Concentration (half maximum); IR, Insulin receptor; PPAR-γ and α, Peroxisome Proliferator-Activated Receptors Gamma and Alpha; PTP 1B, Protein Tyrosine Phosphatase; ROS, Reactive Oxygen Species; STZ, Streptozotocin; SAR, Structure-Activity Relationship; TNF-α, Tumor Necrosis Factor Alpha

* Corresponding author.
E-mail addresses: alamindagash27@gmail.com, aminumohammed@abu.edu.ng (A. Mohammed).

https://doi.org/10.1016/j.sajb.2021.11.018
0254-6299/

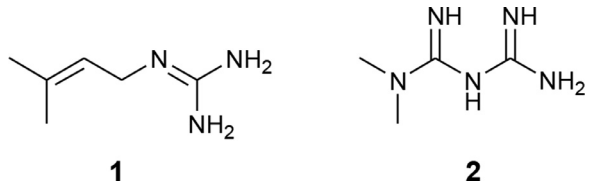


Fig. 1. Naturally occurring galegine (**1**) and its synthetic analogue metformin (**2**).

biguanides have characteristic profiles of serious side effects, including excessive hypoglycemia, weight gain, gastrointestinal discomfort and nausea, liver and heart failure, and diarrhea (Hossain and Pervin, 2018). These limitations coupled with an exponential increase in the prevalence of DM motivated researchers to look for alternative therapies for DM.

In the past, medicinal plants and ethnopharmacological knowledge contributed to the development of some antidiabetic agents. For example, galegine (**1**) (Fig. 1), isolated from *Galega officinalis* L. (Fabaceae) a plant used traditionally to treat diabetes in North Africa, Europe and Middle East, was the lead structure in the development of the most widely used oral antidiabetic drug metformin (**2**) (Cornara et al., 2016; Funke and Melzig, 2006). The ethnopharmacological approach is a major tool in the search for drug candidates from medicinal plants in Africa (Howes et al., 2020; Karou et al., 2007), a result of an active traditional medicine system. For instance, Lifongo et al. (2014) reported that more than 80% of compounds isolated from thirty-three (33) Nigerian plants matched the ethnopharmacological uses of the plants. Incidentally in Africa, the search for antidiabetic agents has focused on vegetal-derived natural products, especially from plants used in traditional medicine to treat DM. The ultimate goal of these investigations being the development of compounds, with improved potency and safety profiles, for the management of DM and its associated complications. This is due to the fact that medicinal plants are an integral component of the health care delivery system in Africa (Stark et al., 2013).

Previous reviews on the antidiabetic activity of African medicinal plants have been published (Mohammed et al., 2014; Ezuruike and Prieto, 2014; Osadebe et al., 2014; Ndip et al., 2013; Afolayan and Sunmonu, 2010). However, these studies were all conducted before 2015 and mainly focused on the antidiabetic activity of the plant extracts and fractions. A major review of the antidiabetic compounds from African medicinal plants covering the literature from 1977 to 2014 has been conducted (Mohammed et al., 2017a). However, several further antidiabetic compounds from African medicinal plants have been reported since 2015. Hence, this article reviews the literature on antidiabetic compounds from African medicinal plants from January, 2015 to December, 2020. The discussion is organized according to the various *in vitro* and *in vivo* antidiabetic assay methods used, with emphasis on structure-activity relationships and the mechanisms of action.

2. Methods

One hundred and twenty-three (123) articles were obtained by searching the major scientific databases ScienceDirect, Scopus, PubMed, Web of Science and Google Scholar, using various combinations of appropriate keywords, including, African medicinal plants, ethnopharmacology, folk and traditional medicine, phytochemicals, phytochemistry, antidiabetic, hypoglycemic, antihyperglycemic and insulin sensitivity. Additional articles were tracked through citations from other publications or by directly searching the journals' website.

The articles that met the following inclusion criteria were selected for the review:

(i) studies that investigated the antidiabetic, antihyperglycemic and/or insulin sensitizing potential of compounds from African medicinal plants using *in vitro* and *in vivo* models.
(ii) papers published from January, 2015 to December, 2020.

Studies reporting only the antidiabetic activity of crude extracts, fractions or herbal formulations without characterizing the bioactive compound were generally not included. Thirty (30) articles met the inclusion criteria and, hence, were included in the present study.

The chemical structures were drawn using the ChemDraw Ultra 8.0 software, and the scientific names of the plants were verified by checking The Royal Botanical Gardens, Kew Science website (https://mpns.science.kew.org/mpns-portal/plantDetail?plantId=441226&).

3. Results and discussion

Within the period under review (2015-2020), a total of eighty-two (82) compounds, mostly belonging to the terpenoid and flavonoid classes, were isolated from twenty-four (24) plants in various parts of Africa, and investigated for antidiabetic activity using various *in vitro* and *in vivo* models. Interestingly, with the exception of *Arthrocnemum glaucum* (Moq.) Ung.-Sternb. (Amaranthaceae), *Combretum fragrans* F.Hoffm. (Combretaceae), *Icacina oliviformis* (Poir.) J. Raynal (Icacinaceae), *Plectranthus madagascariensis* (Pers.) Benth. (Lamiaceae) and *Trigonella stellata* Forssk. (Fabaceae), all the plants are used traditionally to treat diabetes in various parts of Africa. (Table 1). The number of isolated compounds, in the five years between 2015 and 2020, represents a 56% increase compared to the previous 37 years, from 1977 to 2014 (53 compounds), reported in our previous review on antidiabetic compounds from African medicinal plants (Mohammed et al., 2017a). These numbers show the increased interest and intensity of research on the topic by the scientific community. Among the reported compounds, sixty-six (66) were assayed by various *in vitro* methods, nine (9) were studied *in vivo* and seven (7) compounds were investigated both *in vitro* and *in vivo*. Moreover, seven compounds (Fig. 2), quercetin (**3**), epicatechin (**4**), protocatechuic acid (**5**), kolaviron (**6**), oleanolic acid (**7**), ursolic acid (**8**) and lupeol (**9**), were among the antidiabetic compounds from African medicinal plants that were reported in our previous review (Mohammed et al., 2017a). It is commendable that there were no overlapping or repeated investigations with compounds (**3-9**), rather, all the studies involving these compounds in the period under review have attempted to deepen our knowledge of their antidiabetic activity. However, despite some promising preclinical results, none of the 83 compounds in this review has advanced beyond the preliminary stages of drug discovery. The lack of clinical trials was highlighted in our previous review as a major drawback against the development of plant-derived antidiabetic agents from African medicinal plants (Mohammed et al. 2017a). This limitation, which remains relevant, could be due to lack of the necessary financial support from Government and relevant industries.

3.1. In vitro *studies*

3.1.1. *α-Glucosidase and α-amylase inhibitors*

Inhibition of the activity of enzymes involved in carbohydrate metabolism such as α-glucosidase and α-amylase is one of the approaches developed for the treatment of DM. These enzymes are crucial to the breakdown of dietary carbohydrates into absorbable monosaccharides. Inhibitors of α-glucosidase and α-amylase activities delay the overall digestion of carbohydrates by increasing the digestion period, thereby reducing the rate of intestinal glucose absorption, which in turn diminishes postprandial hyperglycemia (Bischoff, 1995). Several compounds, isolated from African medicinal plants showed remarkable inhibition of the activity of α-glucosidase

Table 1
African medicinal plants used in traditional medicine to treat diabetes.

Plant species	Part(s) used	Place used	Preparation	Refs.
Aframomum melegueta K. Schum. (Zingiberaceae)	Fruit, Seed	Nigeria	Dried fruit or seed is ground into powder and taken with hot pap.	Gbolade et al. (2009)
Agave americana L. (Asparagaceae)	Leaf	Morocco	The young leaf, decocted in a liter of water, is used against diabetes, at a rate of taking a glass per day after breakfast	Benkhnigue et al. (2014)
Antidesma madagascariense Lam. (Phyllanthaceae)	Leaf, Stem bark	Madagascar	Leaf is boiled in form of tea and take it orally	Gurib-Fakim and Brendler (2004)
Bridelia duvigneaudii J.Léonard (Phyllanthaceae)	Root	Tanzanian	One teaspoon of boiled fresh or dried roots taken three times daily for one to two weeks	Moshi et al. (2006)
Bryophyllum pinnatum (Lam.) Oken. (Crassulaceae)	Leaf	Mauritius	Prepare a decoction with the leaves and use it as a footbath.	Mootoosamy and Mahomoodally (2014)
Cassia singueana Delile syn. *Senna singueana* (Caesalpiniaceae)	Stem bark, Leaf	Nigeria, Kenya	Boiling plant part and consumed orally	Keter and Mutiso (2012), Etuk et al. (2010)
Corchorus olitorius L. (Malvaceae)	Leaf	Nigeria	Soaking the leaf in form of tea and consume orally	Abo et al. (2008)
Garcinia kola Heckel (Clusiaceae syn. Guttiferae)	Seed	Nigeria	Dried powder seed is mixed with palm, water and onion and taken in the morning	Soladoye et al. (2012)
Khaya senegalensis A. Juss (Meliaceae)	Stem bark	Nigeria, Togo	Decoction made of *K. senegalensis* stem bark and garlic is taken orally	Karou et al. (2011), Makinde et al. (2015)
Leonotis ocymifolia (Burm.f.) Iwarsson (Lamiaceae)	Aerial parts	Namibia	Fresh and dry decoction to be taken twice orally	Kaitjizemine and Mumbengegwi, 2019
Moringa stenopetala (Baker f.) Cufod. (Moringaceae)	Leaf	Kenya and Ethiopia	Boiling the leaf in water and taken it daily	Jahn (1991)
Myrianthus arboreus P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	Ghana	Decoction prepared from the stem is consumed orally	Adinortey et al. (2019)
Newbouldia laevis (P.Beauv.) Seem. ex Bureau (Bignoniaceae)	Leaf	Nigeria	An Infusion of the leaf is taken orally twice daily	Marles and Farnsworth (1994)
Parkia biglobosa (Jacq.) G.Don (Fabaceae)	Leaf	Nigeria, Togo	Decoction made of *P. biglobosa* leaf and garlic is taken orally	Karou et al. (2011), Etuk et al. (2010)
Parquetina nigrescens (Afzel.) Bullock (Asclepiadaceae)	Root bark	Nigeria	Juice extract or infusion is taken one time daily	Gbolade, 2009
Salvia africana-lutea L. (Lamiaceae)	Aerial parts	South Africa	Boiling the aerial part and administered orally	Philander (2011)
Vernonia amygdalina Delile (Compositae)	Leaf	Nigeria	Juice extract from leaf is mixed with salt and taken orally	Gbolade (2009)
Xylopia aethiopica (Dunal) A. Rich. (Annonaceae)	Fruit	Nigeria, Guinea, Togo, Senegal	Half a glass cup containing boiled *X. aethiopica* fruit and *C. papaya* is taken in the morning	Soladoye et al. (2012)
Ziziphus mucronata Wild. (Rhamnaceae)	Stem bark, Leaf	South Africa	Tea prepared from the *Z. mucronate* leaf combined with powdered material from *Viscum* species for the treatment of diabetes	Deutschländer et al. 2009

and α-amylase, these compounds and their inhibitory activities are summarized in Table 2.

The leaf infusion of *Newbouldia laevis* (P.Beauv.) Seem. ex Bureau (Bignoniaceae), native to west Africa, is used traditionally to treat DM in the southern part of Nigeria (Marles and Farnsworth, 1994). As a validation of this folkloric use of the plant, the leaf ethanol extract was reported to inhibit α-amylase activity (IC_{50}: 102.9 μg/ml) and reduce fasting blood glucose (FBG) in diabetes animal model (Mbagwu et al., 2020a). Subsequently, two new caffeic acid glycosides, newboulasides A (**10**) and B (**11**) (Fig. 3) were isolated from leaf

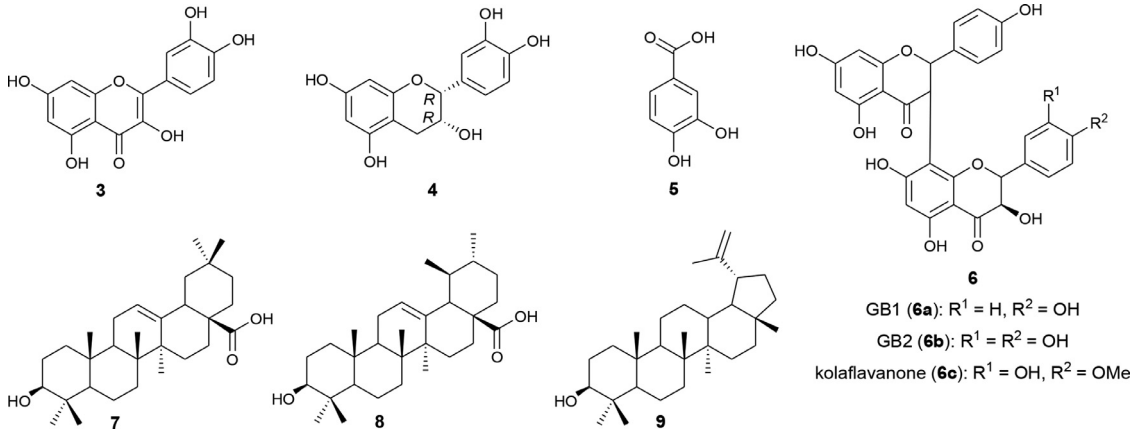


Fig. 2. Compounds from African medicinal plants with antidiabetic activity in our previous review (Mohammed et al., 2017a) and also reported in the present article.

Table 2
In vitro studies on the antidiabetic potential of compounds isolated from African medicinal plants.

Assay model	Compound	Plant (family)	Plant part	Bioactivity	Refs.
Inhibition of DPP-IV	Amentoflavone (35)	*Antidesma madagascariense* Lam. (Phyllanthaceae)	Leaf	DPP-IV (IC_{50}: 3.9 μM)	Beidokhti et al. (2018)
Inhibition of α-Glucosidase and α-Amylase	Apigenin (16)	*Agave americana* L. (Asparagaceae)	Leaf	α-Amylase (IC_{50}: 75.1 μM)	Sahnoun et al. (2018)
	Epicatechin (4)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	α-Amylase (IC_{50}: 111.7 μM)	Harley et al. (2020)
	Epigallocatechin (21)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	α-Amylase (IC_{50}: 85.3 μM)	Harley et al. (2020)
	Dulcisflavan (22)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	α-Amylase (IC_{50}: 89.9 μM)	Harley et al. (2020)
	Euscaphic acid (24)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	α-Amylase (IC_{50}: 215.2 μM)	Harley et al. (2020)
	Tormentic acid (25)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	α-Amylase (IC_{50}: 121.5 μM)	Harley et al. (2020)
	Sitosterol-3-*O*-β-D-glucopyranoside (31)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	α-Amylase (IC_{50}: 217.2 μM)	Harley et al., 2020
	Arjunolic acid (26)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	α-Amylase (IC_{50}: 151.9 μM)	Harley et al. (2020)
	Newboulaside A (10)	*Newbouldia laevis* (P.Beauv.) Seem. (Bignoniaceae)	Leaf	α-Amylase (IC_{50}: 8 μM)	Mbagwu et al. (2020b)
	Newboulaside B (11)	*Newbouldia laevis* (P.Beauv.) Seem. (Bignoniaceae)	Leaf	α-Amylase (IC_{50}: 5.8 μM)	Mbagwu et al. (2020b)
	Cirsimaritin (20)	*Combretum fragrans* F.Hoffm. (Combretaceae)	Leaf	α-Glucosidase (IC_{50}: >500 μM)	Dawé et al. (2018)
	Belamcanidin (18)	*Combretum fragrans* F.Hoffm. (Combretaceae)	Leaf	α-Glucosidase (IC_{50}: >500 μM)	Dawé et al. (2018)
	Velutin (17)	*Combretum fragrans* F.Hoffm. (Combretaceae)	Leaf	α-Glucosidase (IC_{50}: >500 μM)	Dawé et al. (2018)
	Cirsilineol (19)	*Combretum fragrans* F.Hoffm. (Combretaceae)	Leaf	α-Glucosidase (IC_{50}: >500 μM)	Dawé et al. (2018)
	Combretin A (29)	*Combretum fragrans* F.Hoffm. (Combretaceae)	Leaf	α-Glucosidase (IC_{50}: 32.9 μM)	Dawé et al. (2018)
	Combretin B (30)	*Combretum fragrans* F.Hoffm. (Combretaceae)	Leaf	α-Glucosidase (IC_{50}: 47.2 μM)	Dawé et al. (2018)
	19-Acetoxy-12-methoxycarnosic acid (72)	*Salvia africana-lutea* L. (Lamiaceae)	Aerial parts	Inactive	Etsassala et al. (2019)
	3β -Acetoxy-7α-methoxyrosmanol (32)	*Salvia africana-lutea* L. (Lamiaceae)	Aerial parts	Inactive	Etsassala et al., 2019
	19-Acetoxy-7α-methoxyrosmanol (33)	*Salvia africana-lutea* L. (Lamiaceae)	Aerial parts	Inactive	Etsassala et al. (2019)
	19-Acetoxy-12-methoxycarnosol (34)	*Salvia africana-lutea* L. (Lamiaceae)	Aerial parts	Inactive	Etsassala et al. (2019)
	Clinopodiolide A (35)	*Salvia africana-lutea* L. (Lamiaceae)	Aerial parts	Inactive	Etsassala et al. (2019)
	Clinopodiolide B (34)	*Salvia africana-lutea* L. (Lamiaceae)	Aerial parts	α-Glucosidase (IC_{50}: 81.7 μM) α-Amylase (Inactive)	Etsassala et al. (2019)
	Oleanolic acid (7)	*Salvia africana-lutea* L. (Lamiaceae)	Aerial parts	α-Glucosidase (IC_{50}: 22.9 μM) α-Amylase (IC_{50}: 12.5 μM)	Etsassala et al. (2019)
	Oleanolic acid (7)	*Aframomum Melegueta* K. Schum. (Zingiberaceae)	Fruit	α-Glucosidase (IC_{50}: 17.4 μM) α-Amylase (IC_{50}: 91.7 μM)	Mohammed et. al. (2017b)
	Oleanolic acid (7)	*Xylopia aethiopica* (Dunal) A. Rich. (Annonaceae)	Fruit	α-Glucosidase (IC_{50}: 46.1 μM) α-Amylase (IC_{50}: 89 μM)	Mohammed et. al. (2019)
	Ursolic acid (8)	*Salvia africana-lutea* L. (Lamiaceae)	Aerial parts	α-Glucosidase (IC_{50}: 11.3 μM) α-Amylase (IC_{50}: 66.1 μM)	Etsassala et al. (2019)
	11,12-Dehydroursolic acid lactone (23)	*Salvia africana-lutea* L. (Lamiaceae)	Aerial parts	α-Glucosidase (IC_{50}: 85.8 μM) α-Amylase (Inactive)	Etsassala et al. (2019)

(*continued on next page*)

Table 2 (*Continued*)

Assay model	Compound	Plant (family)	Plant part	Bioactivity	Refs.
	β-Amyrin (27)	*Salvia africana-lutea* L. (Lamiaceae)	Aerial parts	α-Glucosidase (IC_{50}: 17.1 μM) α-Amylase (IC_{50}: 76.6 μM)	Etsassala et al. (2019)
	Quercetin (3)	*Bryophyllum pinnatum* (Lam.) Oken. (Crassulaceae)	Leaf	α-Glucosidase (IC_{50}: 11.1 μM) α-Amylase (IC_{50}: 57.4 μM)	Ibitoye et al. (2018)
	Kaempferol (15)	*Bryophyllum pinnatum* (Lam.) Oken. (Crassulaceae)	Leaf	α-Glucosidase (IC_{50}: 25.8 μM) α-Amylase (IC_{50}: 43.8 μM)	Ibitoye et al. (2018)
	Lupeol (9)	*Parkia Biglobosa* (Jacq.) G.Don (Fabaceae)	Leaf	α-Glucosidase (IC_{50}: 45.1 μM) α-Amylase (IC_{50}: 256.5 μM)	Ibrahim et al. (2016)
	Bicyclo[2.2.0]hexane-2,3,5-triol (37)	*Khaya Senegalensis* A. Juss (Meliaceae)	Stem bark	α-Glucosidase (IC_{50}: 45.9 μM) α-Amylase (IC_{50}: 63.3 μM)	Ibrahim et al. (2017)
	3β-O-Acetylbetulinic acid (26)	*Cassia singueana* Delile syn. *Senna singueana* (Caesalpiniaceae)	Stem bark	α-Glucosidase (IC_{50}: 45.1 μM) α-Amylase (IC_{50}: 98.5 μM)	Ibrahim et al. (2017)
	2,7-Dihydroxy-4*H*-1-benzopyran-4-one (38)	*Ziziphus mucronata* Wild. (Rhamnaceae)	Stem bark	α-Glucosidase (IC_{50}: 39 μM) α-Amylase (IC_{50}: 93.7 μM)	Ibrahim et al. (2017
	6-Paradol (12)	*Aframomum melegueta* K. Schum. (Zingiberaceae)	Fruit	α-Glucosidase (IC_{50}: 243.3 μM) α-Amylase (IC_{50}: 664.6 μM)	Mohammed et al. (2017)
	6-Shogaol (13)	*Aframomum melegueta* K. Schum. (Zingiberaceae)	Fruit	α-Glucosidase (IC_{50}: 326.1 μM) α-Amylase (IC_{50}: 443.2 μM)	Mohammed et al. (2017)
	6-Gingerol (14)	*Aframomum melegueta* K. Schum. (Zingiberaceae)	Fruit	α-Glucosidase (IC_{50}: 21.6 μM) α-Amylase (IC_{50}: 81.8 μM)	Mohammed et al. (2017)
	Kolaviron (6)	*Garcinia kola* Heckel (Clusiaceae syn. Guttiferae)	Seed	α-Glucosidase (IC_{50}: 31.1 μM) α-Amylase (IC_{50}: 24.6 μM)	Salau et al. (2020)
Inhibition of intestinal glucose uptake	Kolaviron (6)	*Garcinia kola* Heckel (Clusiaceae syn. Guttiferae)	Seed	Inhibits intestinal glucose absorption	Salau et al. (2020)
	Kolaviron (6)	*Garcinia kola* Heckel (Clusiaceae syn. Guttiferae)	Seed	Inhibits intestinal glucose absorption	Salau et al. (2020)
Stimulation of muscle glucose uptake	β-Amyrin (27)	*Salvia africana-lutea* L. (Lamiaceae)	Aerial parts	Stimulates glucose uptake	Etsassala et al. (2020)
	Ursolic acid (8)	*Salvia africana-lutea* L. (Lamiaceae)	Aerial parts	Stimulates glucose uptake	Etsassala et al. (2020)
	Oleanolic acid (7)	*Salvia africana-lutea* L. (Lamiaceae)	Aerial parts	Stimulates glucose uptake	Etsassala et al., 2020
	Clinopodiolide B (34)	*Salvia africana-lutea* L. (Lamiaceae)	Aerial parts	Stimulates glucose uptake	Etsassala et al. (2020)
	Clinopodiolide A (73)	*Salvia africana-lutea* L. (Lamiaceae)	Aerial parts	Stimulates glucose uptake	Etsassala et al. (2020)
	19-Acetoxy-12-methoxycarnosol (74)	*Salvia africana-lutea* L. (Lamiaceae)	Aerial parts	Stimulates glucose uptake	Etsassala et al. (2020)
	19-Acetoxy-7α-methoxyrosmanol (75)	*Salvia africana-lutea* L. (Lamiaceae)	Aerial parts	Stimulates glucose uptake	Etsassala et al. (2020)
	3β -Acetoxy-7α-methoxyrosmanol (76)	*Salvia africana-lutea* L. (Lamiaceae)	Aerial parts	Stimulates glucose uptake	Etsassala et al. (2020)
	19-Acetoxy-12-methoxycarnosic acid (72)	*Salvia africana-lutea* L. (Lamiaceae)	Aerial parts	Stimulates glucose uptake	Etsassala et al., 2020
	Carnosolon (65)	*Plectranthus madagascariensis* (Pers.) Benth. (Lamiaceae)	Aerial parts	Stimulates glucose uptake	Etsassala et al. (2020)
	6β ,7α-Dihydroxyroyleanone (66)	*Plectranthus madagascariensis* (Pers.) Benth. (Lamiaceae)	Aerial parts	Stimulates glucose uptake	Etsassala et al., 2020
	7β-Acetoxy-6 -hydroxyroyleanone (67)	*Plectranthus madagascariensis* (Pers.) Benth. (Lamiaceae)	Aerial parts	Stimulates glucose uptake	Etsassala et al. (2020)
	Horminone (68)	*Plectranthus madagascariensis* (Pers.) Benth. (Lamiaceae)	Aerial parts	Stimulates glucose uptake	Etsassala et al. (2020)
	Coleon U quinone (69)		Aerial parts	Stimulates glucose uptake	Etsassala et al., 2020

(*continued on next page*)

Table 2 (*Continued*)

Assay model	Compound	Plant (family)	Plant part	Bioactivity	Refs.
		Plectranthus madagascariensis (Pers.) Benth. (Lamiaceae)			
	Leonurun (70)	*Leonotis ocymifolia* (Burm.f.) Iwarsson (Lamiaceae)	Aerial parts	Stimulates glucose uptake	Etsassala et al. (2020)
	20-Acetoxy-marrubiin (71)	*Leonotis ocymifolia* (Burm.f.) Iwarsson (Lamiaceae)	Aerial parts	Stimulates glucose uptake	Etsassala et al. (2020)
Improvement of pancreatic β-cell integrity	Rutin (78)	*Moringa stenopetala* (Baker f.) Cufod. (Moringaceae)	Leaf	Protects human pancreatic β-cells	Habtemariam (2015)
Interaction with PPARα and PPARγ	(3*S*,4*R*)-4,2′,4′-Trihydroxy-7-methoxyisoflavan (48)	*Trigonella stellata* Forssk. (Fabaceae)	Leaf	PPARα and PPARγ agonists	Eldin et al. (2018)
	(3*R*,4*S*)-4,2′,4′-Trihydroxy-7-methoxy-4′-*O*-β-D-glucopyranosylisoflavan (49)	*Trigonella stellata* Forssk. (Fabaceae)	Leaf	PPARα and PPARγ agonists	Eldin et al. (2018)
	(2*S*,3*R*,4*R*)-4,2′,4′-Trihydroxy-2,7-dimethoxyisoflavan (50)	*Trigonella stellata* Forssk. (Fabaceae)	Leaf	PPARα and PPARγ agonists	Eldin et al. (2018)
	p-Hydroxybenzoic acid (51)	*Trigonella stellata* Forssk. (Fabaceae)	Leaf	PPARα and PPARγ agonists	Eldin et al., 2018
	7,4′-Dihydroxyflavone (52)	*Trigonella stellata* Forssk. (Fabaceae)	Leaf	Unable to activate PPARα and PPARγ	Eldin et al. (2018)
	Dihydromelilotoside (53)	*Trigonella stellata* Forssk. (Fabaceae)	Leaf	Unable to activate PPARα and PPARγ	Eldin et al. (2018)
	Quercetin-3,7-*O*-α-L-dirhamnoside (54)	*Trigonella stellata* Forssk. (Fabaceae)	Leaf	Unable to activate PPARα and PPARγ	Eldin et al. (2018)
	Soyasaponin I (55)	*Trigonella stellata* Forssk. (Fabaceae)	Leaf	Unable to activate PPARα and PPARγ	Eldin et al. (2018)
Interaction with glucose metabolizing enzymes	3β-*O*-Trans-feruloyl-2α,19α-dihydroxyurs-12-en-28-oic acid (59)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	Decreases glucose-6-phosphatase activity and activates glycogen synthase activity	Kasangana et al. (2018)
	Ursolic acid (8)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	Decreases glucose-6-phosphatase activity and activates glycogen synthase activity	Kasangana et al. (2018)
	2α-Acetoxy-3β-*O*-trans-feruloyl-19α-hydroxyurs-12-en-28-oic acid (60)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	Decreases glucose-6-phosphatase activity and activates glycogen synthase activity	Kasangana et al. (2018)
	3β-*O*-Trans-feruloyl-2α-hydroxy-19α-methoxyurs-12-en-28-oic acid (61)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	Inactive	Kasangana et al. (2018)
	2α-Acetoxy-3β-*O*-trans-(3′-methoxy-4′-formyl) cinnamoyl-19α-methoxyurs-12-en-28-oic acid (62)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	Inactive	Kasangana et al. (2018)
	Isoorientin (57)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	Decreases glucose-6-phosphatase activity and activates glycogen synthase activity	Kasangana et al. (2018)
	Orientin (56)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	Decreases glucose-6-phosphatase activity and activates glycogen synthase activity	Kasangana et al. (2018)
	Protocatechuic acid (5)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	Inactive	Kasangana et al. (2018)
	3,4-Dihydroxybenzaldehyde (58)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	Decreases glucose-6-phosphatase activity and activates glycogen synthase activity	Kasangana et al. (2018)
	Chlorogenic acid (58)		Stem bark	Inactive	Kasangana et al. (2018)

(*continued on next page*)

Table 2 (*Continued*)

Assay model	Compound	Plant (family)	Plant part	Bioactivity	Refs.
		Myrianthus arboreus P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)			
Inhibition of adipogenesis	Isorhamnetin-3-*O*-[apiosyl-(1→6)-glucosyl] 7-*O*-rhamnoside (63)	*Arthrocnemum glaucum* (Moq.) Ung.-Sternb. (Amaranthaceae)	Leaf	Inhibits adipogenesis	Sekii et al. (2015)
	Isorhamnetin-3-*O*-rutinoside (64)	*Arthrocnemum glaucum* (Moq.) Ung.-Sternb. (Amaranthaceae)	Leaf	Inhibits adipogenesis	Sekii et al. (2015)
Inhibition of PTP 1B	Oliviformislactone A (36)	*Icacina oliviformis* (Poir.) J. Raynal (Icacinaceae)	Tuber	IC_{50}: 6.78 μM	Zhou et al. (2019)
	Oliviformislactone B (37)	*Icacina oliviformis* (Poir.) J. Raynal (Icacinaceae)	Tuber	IC_{50}: 32.2 μM	Zhou et al. (2019)
	Secopimaranlactone A (38)	*Icacina oliviformis* (Poir.) J. Raynal (Icacinaceae)	Tuber	IC_{50}: 3.24 μM	Zhou et al. (2019)
	Secocleistanthone A (39)	*Icacina oliviformis* (Poir.) J. Raynal (Icacinaceae)	Tuber	IC_{50}: 12.72 μM	Zhou et al. (2019)
	3-O-Methylhumirianthol (40)	*Icacina oliviformis* (Poir.) J. Raynal (Icacinaceae)	Tuber	IC_{50}: > 80 μM	Zhou et al. (2019)
	3-O-Methyl-14-hydroxy-humirianthol (41)	*Icacina oliviformis* (Poir.) J. Raynal (Icacinaceae)	Tuber	IC_{50}: > 80 μM	Zhou et al. (2019)
	3-O-Methyl-14-methoxyhumirianthol (42)	*Icacina oliviformis* (Poir.) J. Raynal (Icacinaceae)	Tuber	IC_{50}: > 80 μM	Zhou et al. (2019)
	Humirianthol (43)	*Icacina oliviformis* (Poir.) J. Raynal (Icacinaceae)	Tuber	IC_{50}: > 80 μM	Zhou et al. (2019)
	Icacinol (44)	*Icacina oliviformis* (Poir.) J. Raynal (Icacinaceae)	Tuber	IC_{50}: > 80 μM	Zhou et al. (2019)
	14α-methoxyhumirianthol (45)	*Icacina oliviformis* (Poir.) J. Raynal (Icacinaceae)	Tuber	IC_{50}: > 80 μM	Zhou et al. (2019)
	Icacinlactone I (46)	*Icacina oliviformis* (Poir.) J. Raynal (Icacinaceae)	Tuber	IC_{50}: > 80 μM	Zhou et al. (2019)
	12-hydroxylcacinlactone A (47)	*Icacina oliviformis* (Poir.) J. Raynal (Icacinaceae)	Tuber	IC_{50}: 58.05 μM	Zhou et al. (2019)

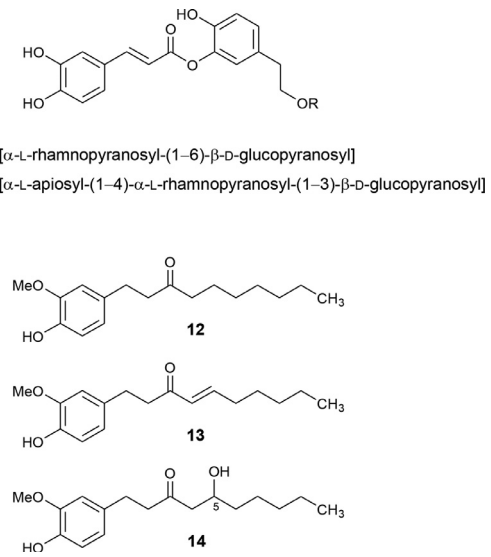


Fig. 3. Structures of caffeic acid glycosides **10** and **11**, and phenolic compounds **12**-**14**.

ethanol extract and found to have potent α-amylase inhibitory activities (IC_{50}: 8 μM and 5.8 μM for **10** and **11**, respectively) comparable to acarbose standard (IC_{50}: 2.61 μM) (Mbagwu et al., 2020b). The two phenolic acid glycosides differ only by the presence of an additional pentose sugar (α-L-apios) moiety in newboulaside B (**11**) which could account for its higher α-amylase inhibitory activity compared to newboulaside A (**10**).

Aframomum melegueta K. Schum. (Zingiberaceae) fruit, commonly known as alligator pepper, is widely used as a spice in food preparation. In Nigeria and other West African countries, dried fruits of *A. melegueta* is ground into powder and taken with hot pap to treat DM (Gbolade, 2009). The fruit ethyl acetate extract of the plant inhibited the activities of α-amylase (IC_{50}: 68.7 μg/ml) and α-glucosidase (IC_{50}: 40.4 μg/ml) and reduced hyperglycemia in type 2 diabetes rat model (Mohammed et al., 2015). Three phenolic compounds 6-paradol (**12**), 6-shogaol (**13**) and 6-gingerol (**14**) (Fig. 3) were subsequently isolated from this extract (Mohammed et al., 2017b). The three compounds, **12-14**, have in common a 4-hydroxy-3-methoxyphenyl moiety and differ only in the oxidation level of the side chain, due to the biosynthetic conversion of 6-paradol (**12**) to 6-gingerol (**14**) by hydroxylation, while dehydration of **14** gives 6-shogoal (**13**). Compounds **12-14** inhibited the activities of α-glucosidase and α-amylase (Table 2) and 6-gingerol (**14**) with a β-hydroxy group relative to the side chain carbonyl showed the best inhibitory activity (IC_{50}: 21.6 μM and 81.8 μM for α-glucosidase and α-amylase respectively), better than acarbose used as standard (IC_{50}: 82.2 μM and 85.2 μM, respectively, for α-glucosidase and α-amylase). Compound **14** further showed a non-competitive mode of inhibition against the activities of the two enzymes (Mohammed et al., 2017b). The better activity of **14** against α-glucosidase and α-amylase compared to **12** and **13** suggested that the aliphatic side chain hydroxy group at C-5 of 6-gingerol (**14**) contributed to the potency and indicated an SAR role for the side chain that could be further explored.

Bryophyllum pinnatum (Lam.) Oken. (Crassulaceae) is an edible vegetable, widely cultivated across the world, with a long history of use for the treatment of diabetes in Mauritius (Mootoosamy, and Mahomoodally, 2014). The ethyl acetate fraction of the methanol leaf extract of *B. pinnatum* was found to inhibit α-glucosidase (IC_{50}: 110.2 μg/ml) and α-amylase (IC_{50}: 137.9 μg/ml) activities *in vitro* and significantly lower blood glucose in alloxan–induced diabetic rats (Ibitoye et al., 2018). Phytochemical investigation of the active extract led to the isolation of two flavonoids, quercetin (**3**) and kaempferol (**15**) (Fig. 4), with inhibitory activities against α-glucosidase and

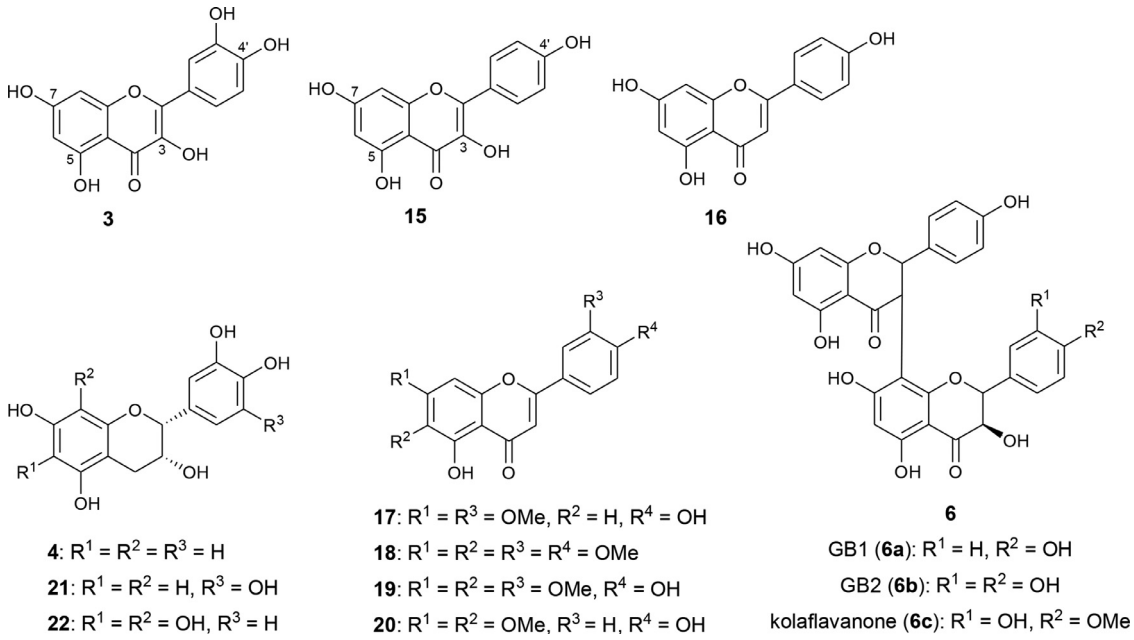


Fig. 4. Flavonoids showing activity against α-glucosidase and α-amylase.

α-amylase. Quercetin (**3**) showed higher α-glucosidase inhibition (IC_{50}: 11.1 μM) than kaempferol (**15**) (IC_{50}: 25.8 μM) which could be attributed to the presence of an additional hydroxy group at C-5′ in ring B of quercetin (**3**) (Ibitoye et al., 2018). However, kaempferol (**15**) showed relatively higher α-amylase inhibition (IC_{50}: 43.8 μM) compared to quercetin (**3**) (IC_{50}: 57.4 μM), suggesting that the two compounds interacted differently with the active sites of the enzymes. Molecular docking studies revealed that quercetin (**3**) and kaempferol (**15**) interacted with amino acid residues within the active site cleft of α−amylase and α−glucosidase that normally bind/hydrolyze amylose and amylopectin with binding affinities comparable to the co-crystallized ligand casuarine and the standard drug acarbose (Ibitoye et al., 2018).

Another flavonoid apigenin (**16**) (Fig. 4) isolated from the leaves of *Agave americana* L. (Asparagaceae), a plant native to North Africa and taken daily as a leaf infusion after breakfast to manage DM (Benkhnigue et al., 2014), displayed a lower activity against α-amylase (IC_{50}: 75.1 μM) compared to quercetin (**3**) and kaempferol (**15**) (Sahnoun et al. 2018). The lower α-amylase inhibition of the flavone **16** compared to the flavonols **3** and **15** suggested that the pattern and degree of hydroxylation of the flavonoid scaffold influenced the interaction of the compounds with the enzymes. Previous SAR studies have also shown that presence of the C-3 and C-5 hydroxy groups, and increased hydroxylation of ring B in flavonoids, enhanced the activity against α-glucosidase. But among flavonoids with similar hydroxylation of rings A and B, a hydroxy group at C-3 was reported to be detrimental for α-amylase inhibition (Tadera et al., 2006). In agreement with these structure-activity relationship (SAR) observations, four flavones **17-20** (Fig. 4) isolated from the leaf extract of *C. fragrans*, a popular plant in Cameroon traditional medicine with multiple folkloric usage (Dawé et al. 2018), showed weak inhibition against α-glucosidase activity with IC_{50} values of $>$ 500 μM (Dawé et al., 2018).

Myrianthus arboreus P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg) is a tropical medicinal plant indigenous to West and Central Africa. The stem bark decoction is used for the management of DM in several communities in Ghana (Adinortey et al., 2019). The plant root bark extract has previously exhibited antidiabetic potential by modulating hepatic glucose homeostasis (Kasangana et al., 2017). Similarly, a hydro-ethanolic extract of *M. arboreus* stem bark was reported to exert considerable hypoglycaemic and anti-hyperlipidaemic activities in streptozotocin (STZ)-induced diabetic rats (Dickson et al., 2016). Further fractionation of the active stem bark extract showed that the ethyl acetate fraction retained the antidiabetic activity (Harley et al., 2017), significantly stimulated the uptake of deoxy glucose in C2C12 and 3T3-L1 cell lines, and inhibited the activities of α-glucosidase and α-amylase. Chromatographic purification of the fraction afforded epicatechin (**4**), epigallocatechin (**21**) and dulcisflavan (**22**) (Fig. 4). Compounds **4, 21** and **22** inhibited α-amylase activity with an IC_{50} values of 111.7, 85.3 and 89.9 μM, respectively, comparable to acarbose (IC_{50}: 97.3 μM) (Harley et al. 2020). These flavan-3-ol derivatives differ in the degree of hydroxylation of rings A and B, with an attendant effect on their activity against α-amylase. Analogue **21** having three hydroxy groups on ring B was the most active, in agreement with earlier SAR reports (Tundis et al., 2010; Tadera et al., 2006).

Garcinia kola Heckel (Clusiaceae syn. Guttiferae), commonly known as bitter cola and native to West and Central Africa is widely used in folk medicine across Africa for the treatment of various diseases. The seed is used in the management of DM in southern Nigeria (; Soladoye et al., 2012; Abo et al., 2008) and has been shown to contain a complex mixture of bioactive compounds including biflavonoids, polyphenols, prenylated benzophenones and xanthones (Hussain et al., 1982; Iwu and Igboko, 1982; Waterman and Hussain, 1983). Studies have shown that a mixture of biflavonoids, kolaviron (**6**), composed of GB1 (**6a**), GB2 (**6b**) and kolaflavanone (**6c**) (Fig. 4), is responsible for the *in vitro* and *in vivo* antidiabetic properties of *G. cola* seed (Adaramoye, 2013; Iwu et al., 1990). To further understand the mechanism of antidiabetic action of kolaviron, the α-glucosidase (IC_{50}: 31.1 μM) and α-amylase (IC_{50}: 24.6) inhibitory activities were investigated, showing that the mixture was active against the enzymes with IC_{50} values of 31.1 μM and 24.6 μM respectively (Salau et al., 2020).

In addition to flavonoids and other phenolic compounds, some terpenoids with inhibitory activities against α-glucosidase and α-amylase were also isolated from African medicinal plants that are used in traditional medicine for the management of diabetes. Among triterpenoids bearing an ursane structure, ursolic acid (**8**) (Fig. 5) from the methanol extract of *Salvia africana-lutea* L. (Lamiaceae) was the most active terpenoids against α-glucosidase (IC_{50}: 11.3 μg/ml)

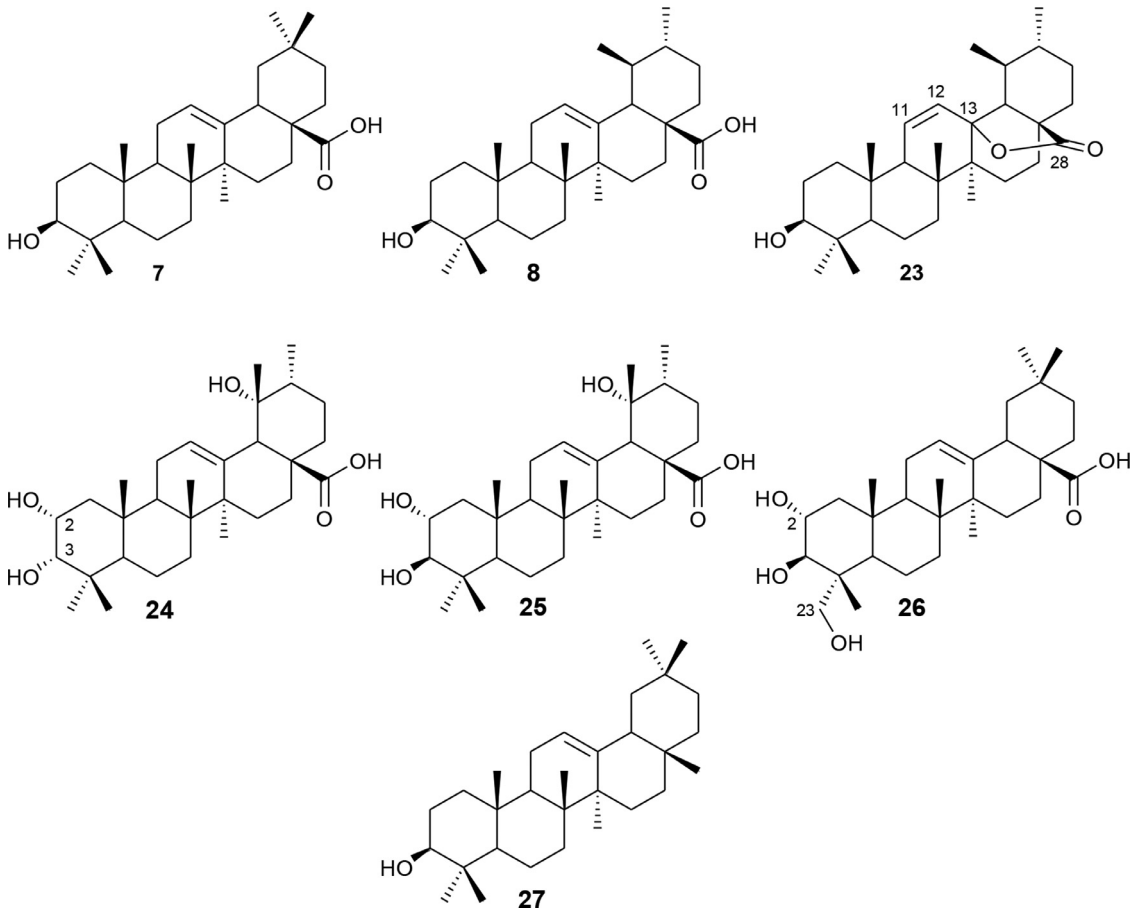


Fig. 5. Oleanane- and ursane-type triterpenoids with α-glucosidase and α-amylase inhibitory activities.

and α-amylase (IC_{50}: 66.1 μg/ml) activities (Etsassala et al., 2019). Lactonization of the C-28 carboxylic acid moiety with C-13 and the resultant migration of the C-12/C-13 double bond to C-11/C-12 as in 11,12-dehydroursolic acid lactone (**23**) (Fig. 5) significantly reduced the potency against α-glucosidase (IC_{50}: 85.5 μM) and cancelled the activity against α-amylase (Etsassala et al., 2019). *S. africana-lutea* is distributed from Namaqualand to the Eastern Cape Province of South Africa and ingestion of fresh aerial parts is used traditionally to treat DM in South Africa (Philander, 2011).

Two further ursane-type triterpenes, euscaphic acid (**24**) and tormentic acid (**25**) (Fig. 5) isolated from *M. arboreus* inhibited the activity of α-amylase with IC_{50} values of 215.2 μM for 22 and 121.5 μM for 23 (Harley et al. 2020). The additional hydroxy groups at C-2 and C-19 resulted in a decrease in the activities of these triterpenoids compared to ursolic acid (**8**), suggesting that too much hydrophilicity is detrimental to potency. Euscaphic acid (**24**) and tormentic acid (**25**) are isomers with different orientations of the hydroxy groups at C-2 and C-3. In **25**, the two OH groups occupy equatorial positions while orientation of the C-2 hydroxy is equatorial and C-3 OH is axially oriented in **24**. The weaker activity of **24** against α-amylase compared to 23 maybe due to this stereochemical difference by affecting the interaction of the compounds with the enzymes (Harley et al. 2020).

The fruit decoction of *Xylopia aethiopica* (Dunal) A. Rich. (Annonaceae) is widely used in folkloric medicine of some West African countries, including Nigeria, Guinea, Togo and Senegal for the management of DM (Soladoye et al., 2012; Diallo et al., 2012; Karou et al., 2011; Diéye et al., 2008). Previous study by the authors' group revealed promising inhibitory activity of the acetone extract of the fruit against α-glucosidase (IC_{50}: 86.2 μM) and α-amylase (IC_{50}: 155.4 μM) (Mohammed et al., 2016). In subsequent chemical investigations, oleanolic acid (**7**) (Fig. 5) was isolated from the acetone extract. The oleanane pentacyclic triterpene showed remarkable α-glucosidase (IC_{50}: 46.1 μM) and α-amylase (IC_{50}: 89 μM) inhibitions, better than the extract and acarbose standard (α-glucosidase $IC_{50:}$ 157 μM, α-amylase $IC_{50:}$ 82.2 μM) (Mohammed et al., 2019). Similar inhibition of α-glucosidase and α-amylase activities by oleanolic acid (**7**) isolated from *Aframomum melegueta* and *S. africana-lutea* have been reported (Etsassala et al., 2019; Mohammed et al., 2017). Arjunolic acid (**26**) (Fig. 5), a 2,23-dihydroxy derivative of oleanolic acid (**7**), isolated from *M. arboreus* also inhibited α-amylase (IC_{50}: 151.9 μM), but the activity was lower compared to 5 (Harley et al., 2020). Another oleanane analogue β-amyrin (**27**) (Fig. 5) which lacks the carboxylic acids group at C-28 of oleanolic acid (**7**) displayed a better activity than **7** against α-glucosidase (IC_{50}: 17.1 μM) and α-amylase (IC_{50}: 76.6 μM) (Etsassala et al., 2019). These results show that similar to the ursanes, too much hydrophilicity reduced the potency of oleanane-type triterpenoids against the enzymes. Interestingly, molecular docking studies revealed that **7** does not interact with binding sites of the enzymes by hydrogen bonding, suggesting that other non-covalent forces such as hydrophobic interactions might be responsible for stabilizing the ligand-enzymes complexes (Mohammed et al., 2019).

Parkia biglobosa (Jacq.) G.Don (Fabaceae) and *Cassia singueana* Delile (syn. *Senna singueana*) (Caesalpiniaceae) are indigenous to Africa and used for the treatment of various disorders including DM (Keter and Mutiso, 2012; Karou et al., 2011; Etuk et al., 2010; Moshi and Mbwambo, 2002). The *in vivo* antidiabetic activity of the butanol fraction of *P. biglobosa* leaf extract has been reported (Ibrahim et al., 2016). Additionally, the acetone extract of *C. singueana* stem bark

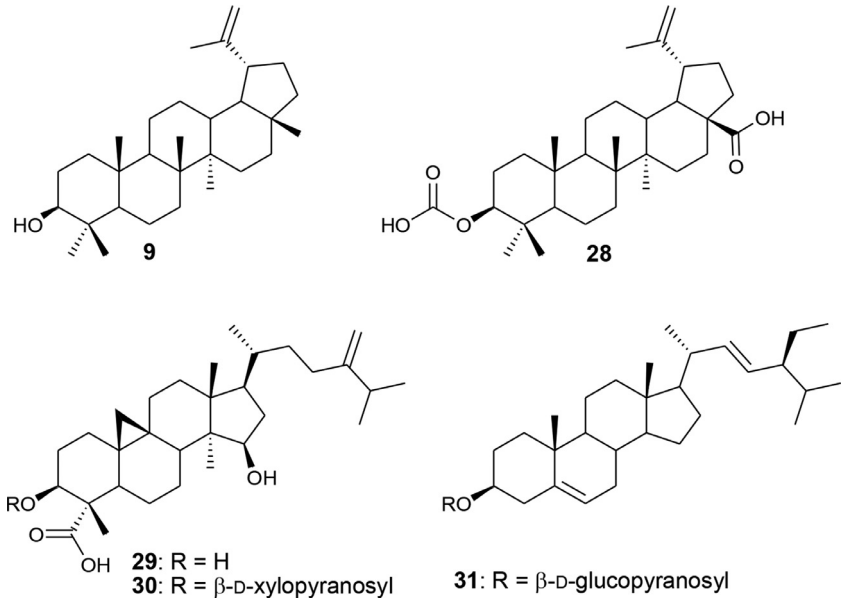


Fig. 6. Other triterpenoids and steroid with α-glucosidase and α-amylase inhibitory activities.

extract exhibited potent activity against α-glucosidase and α-amylase (Ibrahim and Islam, 2014a). Phytochemical investigations of the two plants resulted in the isolation of lupeol (**9**) (Fig. 6) from *P. biglobosa* leaf butanol extract (Ibrahim et al., 2016) and 3β-*O*-acetyl betulinic acid (**28**) (Fig. 6) from the acetone extract of *C. singueana* stem bark (Ibrahim et al., 2016; 2017). The two lupane-type triterpenes showed similar inhibition against the activity of α-glucosidase (IC_{50}: 45.1 μM). However, 3β-*O*-acetyl betulinic acid (**28**) exhibited higher α-amylase inhibition than lupeol (**9**) (IC_{50}: **28**: 98.5 μM versus **9:** 256.5 μM), possibly due to the acetylation of the C-3 hydroxy group and replacement of the methyl group at C-28 by carboxylic acid function.

Two cycloartane-type triterpenes combretins A (**29**) and B (**30**) (Fig. 6) from the methanol leaf extract of *C. fragrans* have also inhibited α-glucosidase (Dawé et al., 2018). The glycosylated analogue combretin B (**30**) was less active against α-glucosidase (IC_{50}: 47.2 μM) than combretin A (**29**) with a free hydroxy group at C-3 (IC_{50}: 32.9 μM), indicating an SAR role for the C-3 hydroxy that could be further investigated. The steroidal glycoside sitosterol-3-*O*-β-D-glucopyranoside (**31**) (Fig. 6) has been isolated together with other inhibitors of α-amylase from the ethyl acetate stem bark extract of *M. arboreus* (IC_{50}: 217.2 μM), but **31** showed a weaker activity than the standard drug acarbose (IC_{50}: 97.3 μM) (Harley et al., 2020).

The decoction of two further popular African medicinal plants *Khaya senegalensis* A. Juss (Meliaceae) and *Ziziphus mucronata* Wild. (Rhamnaceae) have been used in traditional medicine to treat diabetes in Togo (Karou et al., 2011) and Nigeria (Makinde et al., 2015). The butanol fraction of the extracts obtained from the two plants showed potent antidiabetic activity in rat model (Ibrahim and Islam, 2017; Ibrahim and Islam, 2014a). Bioassay guided purification of the active fractions afforded bicyclo[2.2.0]hexane-2,3,5-triol (**32**) from *K. senegalensis* and 2,7-dihydroxy-4*H*-1-benzopyran-4-one (**33**) (Fig. 7) from *Z. mucronata*. Compound **32** showed a non-competitive inhibition of α-glucosidase (IC_{50}: 45.9 μM) and α-amylase (IC_{50}: 63.3 μM). The benzopyran **33** was also a non-competitive inhibitor α-amylase with IC_{50} of 93.7 μM, but its inhibitory activity against α-glucosidase (IC_{50}: 39 μM) was uncompetitive (Ibrahim et al., 2017). The antidiabetic activity of the extract of *Z. mucronata* could be attributed, in part, to the presence of chromone **33**, which is a known remarkable inhibitor of α-glucosidase and α-amylase (Wang et al., 2017).

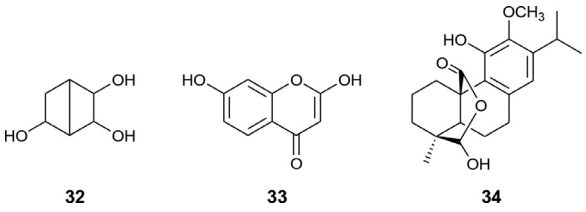


Fig. 7. Structures of other compounds showing α-glucosidase and α-amylase inhibition.

Among a series of six abietane diterpenes isolated from the methanol extract of the aerial parts of *S. africana-lutea*, only clinopodiolide B (**34**) (Fig. 7) showed inhibitory activity against α-glucosidase with an IC_{50} value of 81.7 μM, but was inactive against α-amylase activities (Etsassala et al., 2019).

3.1.2. Dipeptidyl peptidase-IV (DPP-IV) inhibitors

Inhibitors of dipeptidyl peptidase-IV (DPP-IV) stimulate the breakdown of endogenous incretin hormones and thus promote pancreatic glucose-dependent insulin secretion (Deacon, 2011). Extracts from African ethnomedicinal plants with a history of use for the management of diabetes have shown potent activity against DPP-IV.

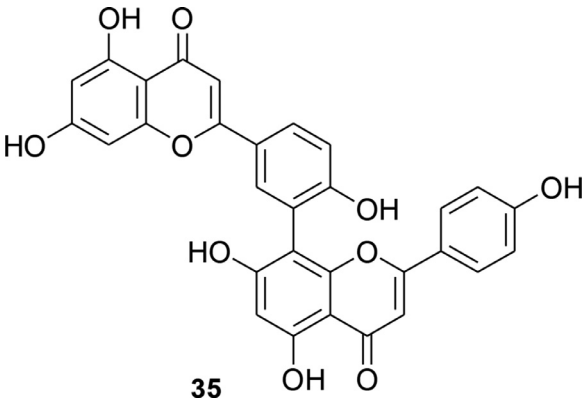


Fig. 8. Amentoflavone, a biflavonoid with activity against DPP-IV.

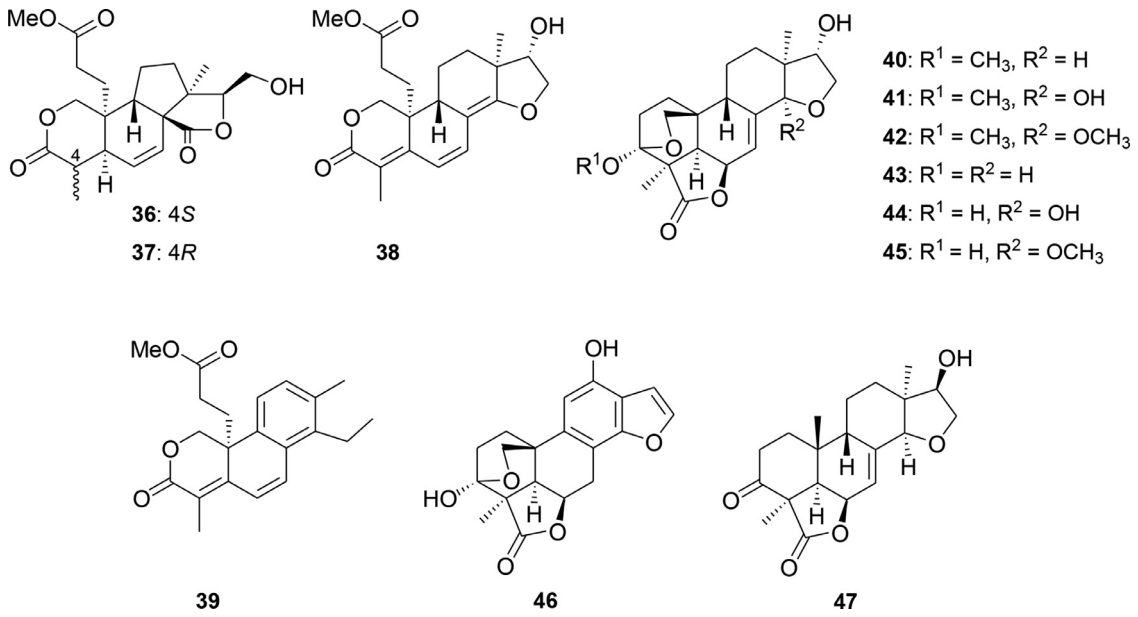


Fig. 9. Structures of diterpenoids from *Icacina oliviformis* with activity against PTP 1B.

The leaf and stem bark decoctions of *Antidesma madagascariense* Lam. (Phyllanthaceae) are used in folk medicine in Madagascar for the management of DM (Mahomoodally et al., 2015; Gurib-Fakim and Brendler, 2004). In a phytochemical investigation, amentoflavone (**35**) (Fig. 8), a biflavonoid obtained by the phenol oxidative coupling of two apigenin (**16**) (Fig. 4) units through C-3′ and C-8″, was isolated from *A. madagascariense* leaf ethyl acetate extract (Beidokhti et al., 2018). The extract and amentoflavone (**35**) inhibited the DPP-IV activity with an IC_{50} values of 79.2 μg/ml and 3.9 μM, respectively (Beidokhti et al., 2018). This inhibition indicated the ability of the extract and amentoflavone (**35**) in improving insulin sensitivity to the target tissues, and suggests that **35** is the major DPP-IV inhibitor in the extract. Interestingly, several studies have also reported the antidiabetic activity of amentoflavone (**35**) in various models (Su et al., 2019; Zhang et al., 2019; Zheng et al., 2013).

3.1.3. Protein tyrosine phosphatase 1B (PTP 1B) inhibitors

Protein tyrosine phosphatase 1B (PTP 1B) is a negative regulator of insulin receptor (IR) signaling pathway (Verma et al., 2017). Inhibitors of PTP 1B activate the phosphorylation of cellular substrates of the IR kinase which stimulate phosphoinositide-3-kinase (PI3K) and the downstream expression of protein kinase B. Stimulation of PI3K and the downstream expression of protein kinase B further activate the translocation of glucose transporter 4 (GLUT4) from intracellular vesicles to the plasma membrane and hence, promote the uptake of glucose into the cells for generation of energy (Wang et al., 2010; Wade et al., 2018). Several compounds from African medicinal plants have been screened for activity against PTP 1B with some promising results.

Icacina oliviformis (Poir.) J. Raynal (Icacinaceae) is native to West and Central Africa and the root has been used in food preparation (Catarino et al., 2016). Phytochemical investigation of the ethyl acetate fraction of the plant tuber afforded seven new (**36-42**) and five known (**43-47**) (Fig. 9) pimarane diterpenes (Zhou et al., 2019). Oliviformislactones A (**36**) and B (**37**), *seco*pimaranlactone A (**38**) and *seco*-cleistanthone A (**39**) all of which had a δ-lactone moiety as ring A, inhibited PTP 1B activity with IC_{50} values between 3.24 and 32.2 μM (Table 2). The other isolated pimaranes with a cyclohexane ring A showed lower (IC_{50} >80 μM) inhibitory potential (Table 2), suggesting that the δ-lactone unit is essential for the PTP 1B activity of 3,4-*seco* pimarane diterpenes. Compounds **36** and **37** are epimers, differing only in the relative configuration of the methyl group at C-4, which apparently affected their interaction with the enzyme, leading to marked difference in potency. Interestingly, derivatization of compound **36** by replacing the hydrogen atom of the hydroxymethyl group with a liphophilic *p*-bromobenzoyl moiety dramatically increased the activity (IC_{50}: 87.51 nM), suggesting that, for 3,4-*seco*-pimaranes having a δ-lactone moiety as ring A, a hydrophobic substituent at C-16 is beneficial for PTP 1B inhibition (Zhou et al., 2020).

3.1.4. Interactions with peroxisome proliferator-activated receptors (PPARs)

The peroxisome proliferator activated receptors (PPARs) are a group of ligand-activated transcription factors that are involved in energy metabolism, cell proliferation, and inflammation (Tyagi et al., 2011). The PPARs (especially PPARγ) agonists promote insulin sensitivity, glucose and lipid uptake and storage in peripheral tissues via increasing GLUTs expression, stimulation of hepatic glycogenesis and muscle lipogenesis (Ahmadian et al., 2013). In search of PPARs agonists from African plants, *Trigonella stellata* Forssk. (Fabaceae) was investigated. The ethyl acetate fraction showed activation of both PPARα (1.5-fold at 50 μg/mL) and PPARγ (1.8-fold at 50 μg/mL) receptors (Eldin et al., 2018). After chromatographic purification of the aerial parts and roots ethyl acetate and butanol fractions of *T. stellata*, five flavonoids **48-52** including three new isoflavans **48-50**, two phenolic compounds **53** and **54**, and a saponin **55** (Fig. 10) were isolated (Eldin et al. 2018). The new flavans **48-50** increased the activity of PPARα, while only compound **49** activated PPARγ, comparable to ciprofibrate and rosiglitazone. *p*-Hydroxybenzoic acid (**53**) and soyasaponin I (**55**) showed only moderate activation of PPARγ without activating PPARα (Eldin et al., 2018).

3.1.5. Interaction with glucose and glycogen metabolizing enzymes

The synthesis and breakdown of glucose and glycogen are crucial in the management of hyperglycemia in DM. Impaired activation of glycogen synthase and inhibition of glucose-6-phosphatase increase the risk of developing type 2 diabetes (Ashcroft et al., 2017). These enzymes play key roles in gluconeogenesis and hepatic storage of glucose, and targeting their activity is a valid strategy in the control of DM.

The ethyl acetate and hexane fractions of the root bark ethanol extract of *M. arboreus* were shown to significantly reduce hepatic

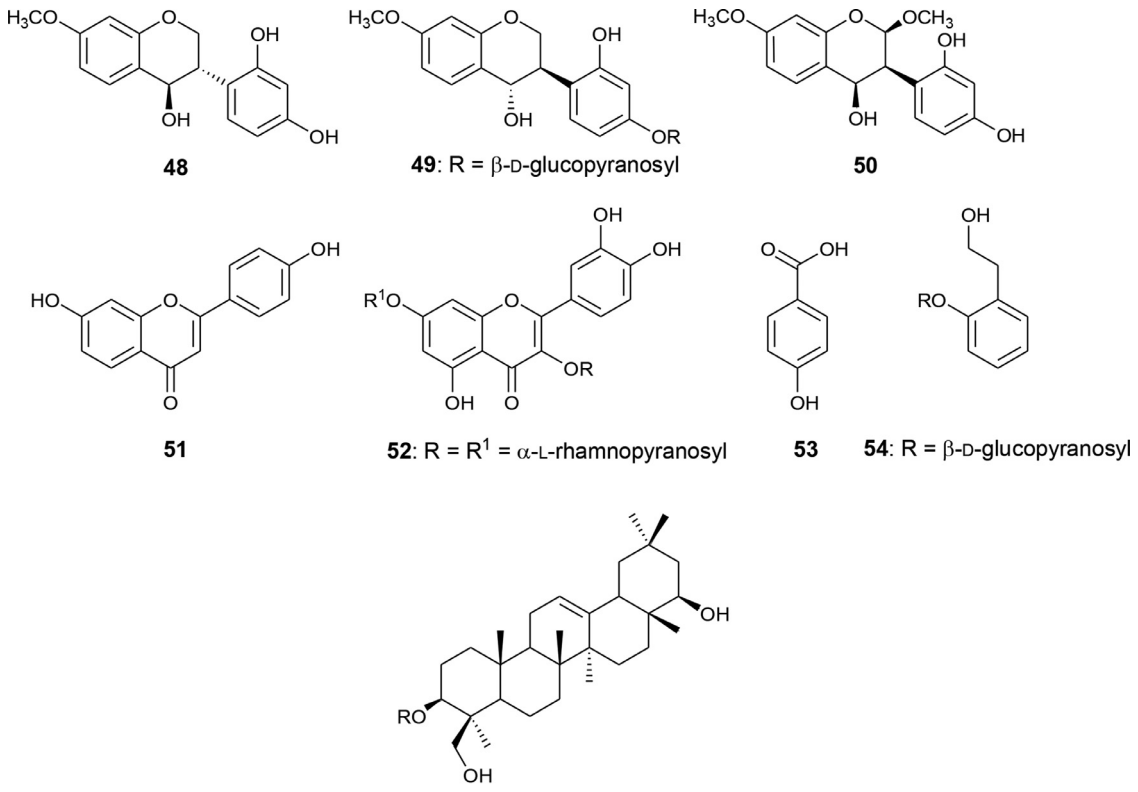


Fig. 10. Compounds from *Trigonella stellata* showing interaction with PPARs.

glucose production by decreasing the activity of glucose-6-phosphatase and by increasing glucose storage through an increase in glycogen synthase activity (Kasangana et al., 2018). Among other bioactive compounds isolated from the active ethyl acetate fraction (Kasangana et al., 2019), two C-glycosylated flavone regioisomers orientin (**56**) and isoorientin (**57**), and 3,4-dihydroxybenzaldehyde (**58**) (Fig. 11) decreased the activity of glucose-6-phosphatase in H4IIE cells and activated glycogen synthase activity in HepG2 cells (Table 2) (Kasangana et al., 2019). Bioassay-guided purification of the hexane fraction afforded four new Δ^{12} ursene-type triterpene esters (**59-62**) (Fig. 11) and ursolic acid (**8**) (Kasangana et al., 2018). Compounds **59** and **60**, and ursolic acid (**8**) (Fig. 11), also reduced the activity of glucose-6-phosphatase in H4IIE cells and stimulated glycogen synthase activity in HepG2 cells (Table 2) (Kasangana et al., 2018). The two tritepene esters exhibited better activity against the enzymes compared to ursolic acid, suggesting that the feruloyl group is beneficial for

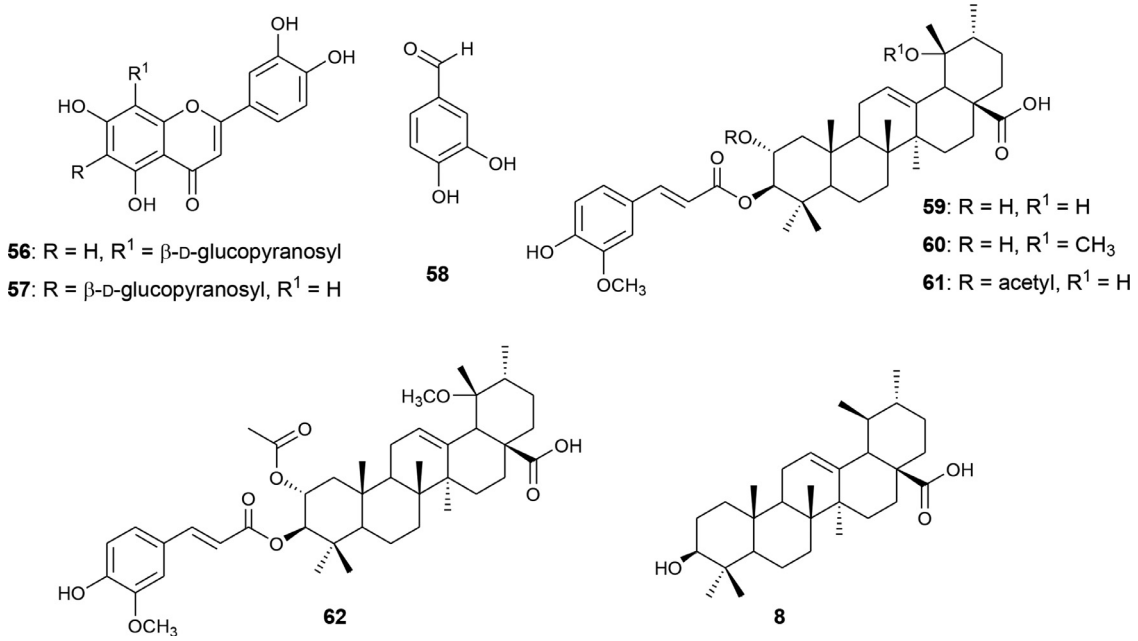
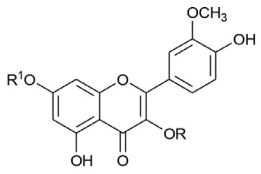


Fig. 11. Isolated metabolites from *Myrianthus arboreus*: compounds **8** and **56**-**60** showed interaction with glucose and glycogen metabolizing enzymes.



63: R = 3-*O*-[apiosyl-(1–6)-β-D-glucopyranosyl], R^1 = α-L-rhamnopyranosyl

64: R = 3-*O*-[α-L-rhamnopyranosyl-(1–6)-β-D-glucopyranosyl], R^1 = H

Fig. 12. Isorhamnetin glycosides **63** and **64** showing ability to inhibit adipogenesis.

activity (Kasangana et al., 2018). The fractions and active compounds **59-62** further increased the *p*-AMPK/AMPK ratio in H4IIE hepatocyte cells, and increased the phosphorylation of glycogen synthase kinase, suggesting that the molecular mechanism of action was through increased phosphorylation of AMPK and GSK-3 (Kasangana et al. 2019). The presence of these metabolites in the ethyl acetate and hexane fractions of *M. arboreus* could be partly responsible for the glucose regulating ability of the plant extract. Therefore, these compounds could serve as markers for the quality assurance of antidiabetic herbal preparation containing *M. arboreus*.

3.1.6. Inhibition of adipogenesis

The dysfunction of adipose tissues, such as excessive differentiation of adipocytes, may increase the risk of DM and related metabolic disorders (Sohn and Kim, 2010). Accumulation of lipids in peripheral tissues cause insulin insensitivity and the failure of insulin secretion from pancreatic *β*-cells to overcome the insulin insensitivity may lead to impaired glucose tolerance and eventually DM (Lee et al., 2013). Thus, compounds that are able to inhibit adipogenesis have a crucial role to play in the management of DM. Preliminary investigation showed that the leaf methanol extract of *A. glaucum* collected at the Sahara Desert in Tunisia inhibited adipogenesis in 3T3-L1 cells. Bioassay-guided purification of the extract afforded two isorhamnetin glycosides **63** and **64** (Fig. 12), which also showed ability to inhibit adipogenesis in 3T3-L1-adipocytes (Table 2) (Sekii et al., 2015). These compounds could be responsible for the antidiabetic activity of the plant and their ability to inhibit adipogenesis gives credence to the folkloric use of the desert plant in the management of diabetes.

3.1.7. Stimulation of muscles glucose uptake

Leonotis ocymifolia (Burm.f.) Iwarsson, *S. africana-lutea* and *P. madagascariensis*, all belonging to the family Lamiaceae, are indigenous to Africa and used in traditional medicine for the treatment of several diseases (Etsassala et al., 2020). *S. africana-lutea* and *L. ocymifolia* are used to treat DM locally (Kaitjizemine and Mumbengegwi, 2019; Philander, 2011). In search of compounds with ability to improve glucose uptake, extracts from these plants were phytochemically investigated, resulting in the isolation of five abietane diterpenes **65-69** (Fig. 12) from *P. madagascariensis*, two labdanes **70** and **71** (Fig. 12) from *L. ocymifolia*, and six further abietanes **72-77**

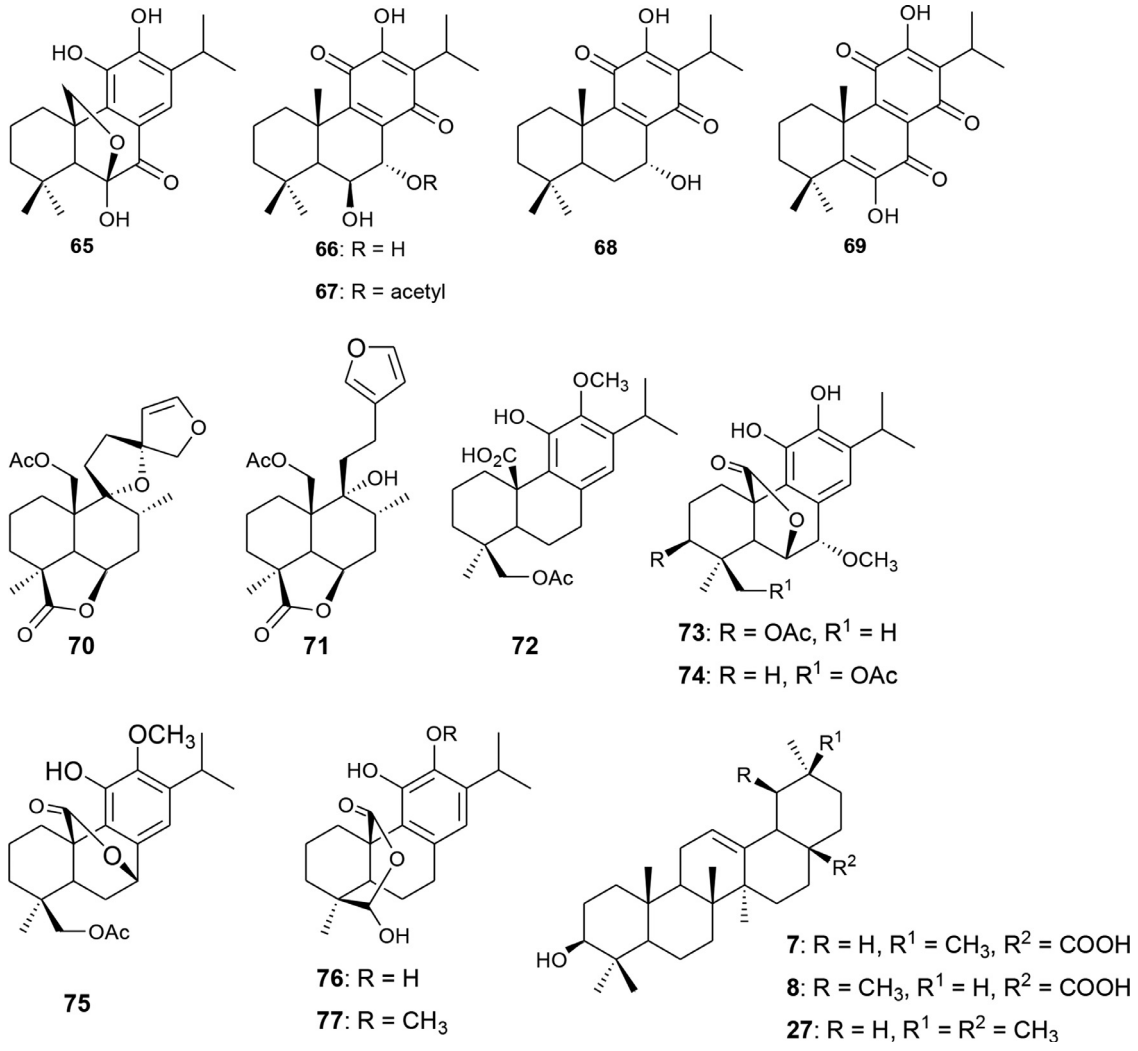
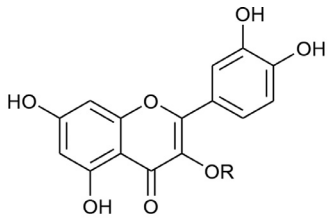


Fig. 13. Structures of di- and tri-terpenoids showing an effect on muscle glucose uptake.



78: 3-*O*-[α-L-rhamnopyranosyl-(1–6)-β-D-glucopyranosyl]

Fig. 14. Rutin, a flavonoid glycoside with ability to improve the integrity of pancreatic β-cell.

(Fig. 12) and three pentacyclic triterpenes **7, 8** and **27,** from *S. africana-lutea* (Fig. 12). Among the isolated compounds ursolic acid (**8**), 19-acetoxy-12-methoxycarnosic acid (**72**), and clinopodiolide B (**77**) demonstrated marked increase in glucose uptake in HEK293 kidney cells. All the other isolated compounds showed only a marginal increase in glucose uptake (Etsassala et al., 2020). However, the exact mechanism is not yet clear and should be a subject of future studies.

3.1.8. Improving pancreatic β-cell integrity

Moringa stenopetala (Baker f.) Cufod. (Moringaceae) is used in Kenya and Ethiopia for managing a variety of illnesses including diabetes (Jahn, 1991). The plant fresh and dried powdered leaves are sold widely in Ethiopian cities and other parts of the world as a nutritional supplement (Jahn, 1991). The antidiabetic activity and cholesterol lowering effect of the plant leaf extract have been demonstrated in various *in vivo* models (Toma et al., 2012; 2015). Chemical purification of the methanol leaves and seeds extract afforded rutin (**78**) as the major bioactive metabolite (Fig. 14). The isolated compound **78** and the ethanol extract inhibited H_2O_2-induced human pancreatic β-cell death (Habtemariam, 2015). This finding suggests that the antidiabetic properties of the plant leaves might be mediated in part by protection of pancreatic β-cells. To support our suggestion, rutin (**78**) was shown to suppress glucotoxicity via the activation of insulin receptor substrate 2 (IRS 2) and AMPK signaling pathways (Cai and Lin, 2009).

3.2. In vivo *studies*

Compared to the number of studies reporting on the *in vitro* antidiabetic potential of compounds derived from African medicinal plants with a history of use in traditional medicine for the management of diabetes, relatively few *in vivo* investigations were reported in the period under review (2015-2020). The structures of these compounds are presented in Fig. 15 and their activities are summarized in Table 3. Interestingly, some of the compounds that demonstrated promising activities *in vitro* have also shown potent *in vivo* results. The discussion of the *in vivo* antidiabetic activity of these compounds has been organized according to the model used.

3.2.1. Alloxan-induced hyperglycemic animal model

In alloxan–induced diabetic rats, quercetin (**3**) and kaempferol (**15**) reduced hyperglycemia by 77.3% and 75.4%, respectively, after 2 weeks administration/treatment period (Ibitoye et al., 2018). The two compounds additionally reversed altered lipid profiles and oxidative stress biomarkers induced by diabetes in the treated animals (Ibitoye et al., 2018), supporting the *in vitro* activities of the compounds against α–amylase and α–glucosidase. Therefore, inhibition of these enzymes could be part of the mode of antidiabetic activity of quercetin (**3**) and kaempferol (**15**). In the same animal model, apigenin (**16**) reduced blood glucose (68.5%) and stimulated hepatic and muscle glucose uptake comparable to glibenclamide (Osigwe et al., 2017). In another study, stearic acid ethyl ester (**79**) (Fig. 15) isolated from *Corchorus olitorius* L. (Malvaceae) reduced blood glucose level by 17% comparable to glibenclamide (18.8%) (Egua et al., 2015). Interestingly, an infusion of the leaf or seed of *C. olitorius* is consumed locally in Nigeria as a remedy for DM (Abo et al., 2008) and extracts from the plant have shown antidiabetic activity in various animal models (Airaodion, et al., 2019; Egua et al., 2013).

3.2.2. Streptozotocin (STZ)-induced hyperglycemic animal model

Epigallocatechin (**21**), dulcisflavan (**22**), tormentic acid (**25**), sitosterol-3-*O*-β-D-glucopyranoside (**31**) and arjunolic acid (**26**) administered for 3 weeks, reduced hyperglycemia in STZ-induced diabetic rat model (Harley et al., 2020). Dulcisflavan (**22**) at 30 mg/kg bw was the

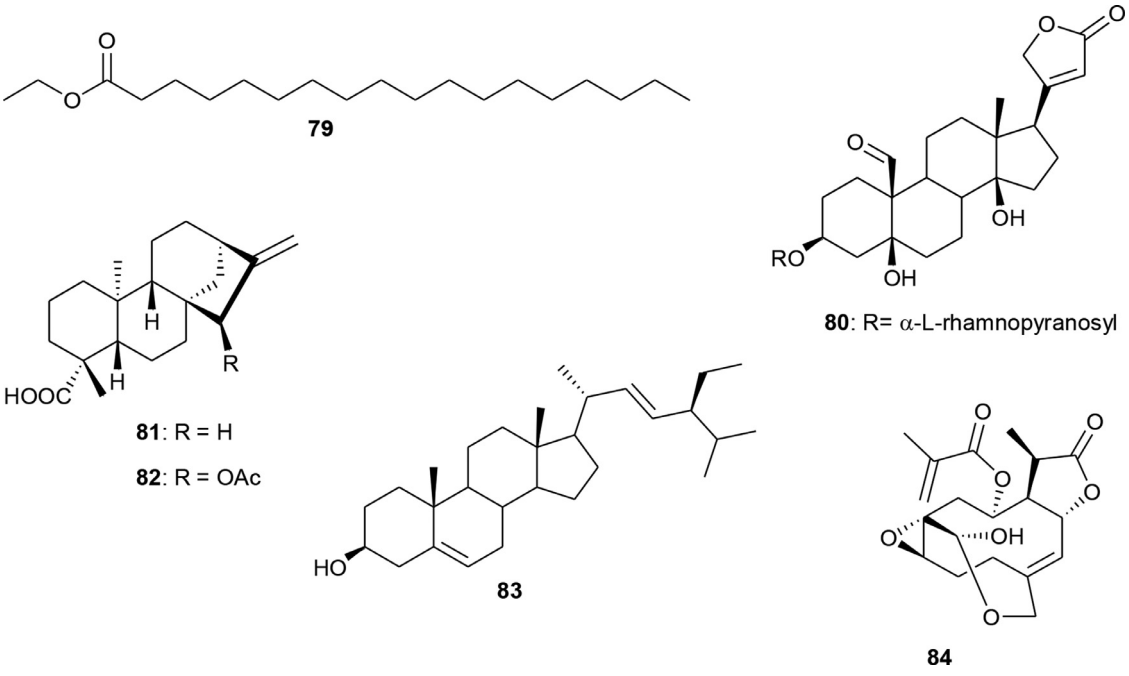


Fig. 15. Compounds from African medicinal plants with *in vivo* antidiabetic activity, compounds **3, 6, 15, 16, 21, 22, 25, 26, 29-31** and **79-84.**

Table 3
In vivo studies on the antidiabetic potential of compounds isolated from African medicinal plants.

Assay model (dosage)	Compound	Plant (family)	Plant part	Bioactivity	Refs.
STZ-induced diabetic rats (20 mg/kg bw)	Convallatoxin (80)	*Parquentina nigrescens* (Afzel.) Bullock (Asclepiadaceae)	Root bark	Antihyperglycemic	Faloye et al. (2018)
STZ-induced diabetic mice (25, 50 mg/kg bw)	Combretin A (29)	*Combretum fragrans* F.Hoffm. (Combretaceae)	Leaf	Antihyperglycemic, antioxidant	Mbiantcha et al. (2019)
STZ-induced diabetic mice (25, 50 mg/kg bw)	Combretin B (30)	*Combretum fragrans* F.Hoffm. (Combretaceae)	Leaf	Antihyperglycemic, antioxidant	Mbiantcha et al. (2019)
STZ-induced diabetic rats (15, 30 mg/kg bw)	Epigallocatechin (21)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	Antihyperglycemic	Harley et al. (2020)
STZ-induced diabetic rats (15, 30 mg/kg bw)	Dulcisflavan (22)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	Antihyperglycemic	Harley et al. (2020)
STZ-induced diabetic rats (15, 30 mg/kg bw)	Tormentic acid (25)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	Antihyperglycemic	Harley et al. (2020)
STZ-induced diabetic rats (15, 30 mg/kg bw)	Sitosterol-3-O-β-D-glucopyranoside (31)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	Antihyperglycemic	Harley et al., 2020
OSTZ-induced diabetic rats (15, 30 mg/kg bw)	Arjunolic acid (26)	*Myrianthus arboreus* P.Beauv. (Urticaceae syn. Cecropiaceae C. C. Berg)	Stem bark	Antihyperglycemic	Harley et al. (2020)
Alloxan induced diabetic rats (72.3 mg/kg bw)	Quercetin (3)	*Bryophyllum pinnatum* (Lam.) Oken. (Crassulaceae)	Leaf	Antihyperglycemic, antihyperlipidemic, antioxidant	Ibitoye et al. (2018)
Alloxan induced diabetic rats (54.6 mg/kg bw)	Kaempferol (15)	*Bryophyllum pinnatum* (Lam.) Oken. (Crassulaceae)	Leaf	Antihyperglycemic, antihyperlipidemic, antioxidant	Ibitoye et al. (2018)
Alloxan induced diabetic rats (230 mg/kg bw)	Stearic acid ethyl ester (79)	*Corchorus olitorius* L. (Malvaceae)	Leaf	Antihyperglycemic	Egua et al. (2015)
Alloxan induced diabetic rats (25, 50 mg/kg bw)	Apigenin (16)	*Newbouldia laevis* P.Beauv.) Seem.	Leaf	Antihyperglycemic, stimulates hepatic and muscle glucose uptake	Osigwe et al. (2017)
STZ-induced diabetic rats (100 mg/kg bw)	Kolaviron (6)	*Garcinia kola* Heckel (Clusiaceae syn. Guttiferae)	Seed	Antioxidant	Oyenihi et al. (2015)
High glucose-loaded mice (10, 20 mg/kg bw)	Kaurenoic acid (81)	*Xylopia aethiopica* (Dunal) A. Rich. (Annonaceae)	Fruit	Hypoglycemic	Famuyiwa et al. (2018)
High glucose-loaded mice (10, 20 mg/kg bw)	Xylopic acid (82)	*Xylopia aethiopica* (Dunal) A. Rich. (Annonaceae)	Fruit	Hypoglycemic	Famuyiwa et al. (2018)
High glucose-loaded mice (10-200 mg/kg bw)	Stigmasterol (83)	*Bridelia duvigneaudii* J.Léonard (Phyllanthaceae)	Root	Hypoglycemic	Credo et al. (2018)
High-fats fed STZ-treated-induced diabetic rats (10 mg/kg bw)	11β,13-Dihydrovernolide (84)	*Vernonia amygdalina* Delile (Compositae)	Leaf	Antihyperglycemic	Okoduwa et al. (2020)

most potent in reducing hyperglycemia (43.8%) and alterations in lipid profiles induced by diabetes, although lower than glibenclamide (74.5%) (Harley et al., 2020). The results further corroborated the remarkable α-amylase inhibition by the compounds (Harley et al., 2020). Oral administration of the cardenolide convallatoxin (**80**) (Fig. 15) isolated from the root methanol extract of *Parquetina nigrescens* (Afzel.) Bullock (Asclepiadaceae) decreased blood glucose level (82.6%), better than glibenclamide (39.1%), in STZ-induced diabetic rats (Faloye et al., 2018). Although, the detail antidiabetic activity of *P. nigrescens* has not been reported, the juice extract or infusion is taken one time daily in Nigeria to treat DM (Gbolade, 2009).

Oral administration of combretins A (**29**) and B (**30**), isolated from *C. fragrans* leaf methanol extract, reduced FBG by 45% and 57%, respectively, in STZ-induced diabetic mice (Mbiantcha et al., 2019). Furthermore, combretins A (**29**) and B (**30**) reduced the levels of tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β) and improved antioxidant status in the serum, sciatic nerves, and brain of the treated diabetic animals (Mbiantcha et al., 2019). Oyenihi et al. (2015) reported the ability of kolaviron (**6**) to ameliorate diabetes-induced oxidative stress in streptozotocin (STZ)-induced diabetic rat model. This is not surprising as kolaviron (**6**) has been reported to possess antioxidant potential in addition to the antidiabetic ability (Onasanwo et al., 2016; Farombi et al., 2013).

3.2.3. High glucose-induced hyperglycemic animal model

Kaurenoic acid (**81**) and xylopic acid (**82**) (Fig. 15) obtained from *X. aethiopica* decreased blood glucose level by 48.5% and 37%, respectively, in high glucose-induced hyperglycemic rats (Famuyiwa et al., 2018). The authors further showed that, compounds **81** and **82** improved glucose utilization in the treated animals comparable to glibenclamide (Famuyiwa et al., 2018). Previous investigations have reported similar antihyperglycemic effect of kaurenoic acid (**81**) (Raga et al., 2010; Bresciania et al., 2004). Stigmasterol (**83**) (Fig. 15), isolated from *Bridelia duvigneaudii* J.Léonard (Phyllanthaceae) decreased blood glucose level (63.7%) in high glucose-loaded mice (Credo et al., 2019). In Tanzanian, fresh or dried roots of *B. duvigneaudii* is boiled and one teaspoonful is used three times a day for one to two weeks for DM treatment (Moshi et al., 2006).

3.2.4. High fats fed STZ-induced hyperglycemic animal model

Vernonia amygdalina Delile (Compositae) is widely available in all parts of Africa with tremendous biological potential against several diseases including diabetes. The juice extracted from the leaf mixed with salt is taken in the traditional treatment of DM in Nigeria (Gbolade, 2009). 11β,13-Dihydrovernolide (**84**) (Fig. 15) isolated from *V. amygdalina* reduced blood glucose level (12.6%) though lower than metformin (18.1%) after 4 h treatment in high fats fed STZ-induced diabetic rats (Okoduwa et al. 2020). 11β,13-Dihydrovernolide (**84**) is a sesquiterpene lactone common to the genus vernonia (Kraft et al. 2003; Rabe et al. 2002) and could be partly responsible for the antidiabetic properties of *V. amygdalina*.

4. Conclusion

This review has shown that African medicinal plants are endowed with novel chemical compounds that could be lead structures for the development of improved antidiabetic agents. Because of their potent activities in various *in vitro* and *in vivo* antidiabetic models, quercetin (**3**), kaempferol (**15**), apigenin (**16**), convallatoxin (**80**), and combretin B (**30**) could be regarded as the most promising antidiabetic compounds from African medicinal plants. These compounds are recommended for further investigations beyond *in vitro* and *in vivo* studies, such as conducting lead optimization, pharmacokinetic, and toxicity studies, and ultimately clinical trials. Other compounds such as ursolic acid (**8**), amentoflavone (**35**), oliviformislactone A (**36**), *seco*pimaranlactone A (**38**), *seco*cleistanthone A (**39**), newboulasides A (**10**) and B (**11**), with extremely low IC_{50} values deserve further *in vivo* studies. This is crucial as compounds with such promising activity at *in vitro* stage excel beyond the proof of concept and may as well be drug candidates. It is hoped that the present study will serve as a template for the development of antidiabetic drug from African flora.

Declaration of Competing Interest

The author wishes to confirm that there is no known conflict of interests associated with this publication and there has been no financial support for this work that could have influenced its outcome.

CRediT authorship contribution statement

Aminu Mohammed: Writing – original draft, Writing – review & editing. **Nasir Tajuddeen:** Funding acquisition, Writing – original draft, Writing – review & editing.

References

Abo, K.A., Fred-Jaiyesimi, A.A., Jaiyesimi, A.E.A., 2008. Ethnobotanical studies of medicinal plants used in the management of diabetes mellitus in South Western Nigeria. J. Ethnopharmacol. 115, 67–71.

Adaramoye, O., 2013. Antidiabetic effect of kolaviron, a biflavonoid complex isolated from *Garcinia kola* seeds, in Wistar rats. Afri. Health Sci. 12 (4), 498–506.

Adinortey, M.B., Agbeko, R., Boison, D., Ekloh, W., Kuatsienu, L.E., Biney, E.E., Affum, O.O., Kwarteng, J., Nyarko, A.K., 2019. Phytomedicines used for diabetes mellitus in Ghana: a systematic search and review of preclinical and clinical evidence. Evid. Based Complement. Alternat. Med. https://doi.org/10.1155/2019/6021209 2019.

Afolayan, A.J., Sunmonu, T.O., 2010. *In vivo* studies on antidiabetic plants used in South African herbal medicine. J. Clin. Biochem. Nutr. 47 (2), 98–106.

Ahmadian, M., Suh, J.M., Hah, N., Liddle, C., Atkins, A.R., Downes, M., Evans, R.M., 2013. PPAR-γ signaling and metabolism: the good, the bad and the future. Nat. Med. 19 (5), 557.

Airaodion, A.I., Akinmolayan, J.D., Ogbuagu, E.O., Airaodion, E.O., Ogbuagu, U., Awosanya, O.O., 2019. Effect of methanolic extract of *Corchorus olitorius* leaves on hypoglycemic and hypolipidaemic activities in albino rats. Asian Plant Res. J. 2 (4), 1–13.

American Diabetes Association (ADA)., 2018b. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2018. Diabetes Care 41, S13–S27.

American Diabetes Association (ADA)., 2018a. 15. Diabetes advocacy: standards of medical care in diabetes-2018. Diabetes Care 41, S152–S153.

Ashcroft, F.M., Rohm, M., Clark, A., Brereton, M.F., 2017. Is type 2 diabetes a glycogen storage disease of pancreatic β cells? Cell Metabol. 26 (1), 17–23.

Beidokhti, M.N., Lobbens, E.S., Rasoavaivo, P., Staerk, D., Jäger, A.K., 2018. Investigation of medicinal plants from Madagascar against DPP-IV linked to type 2 diabetes. S. Afr. J. Bot. 115, 113–119.

Benkhnigue, O., Ben Akka, F., Salhi, S., Fadli, M., Douira, A., Zidane, L., 2014. Catalogue des plantes médicinales utilisées dans le traitement du diabète dans la région d'Al Haouz-Rhamna (Maroc). J. Anim. Plant Sci. 23, 3539–3568.

Bischoff, H., 1995. The mechanism of alpha-glucosidase inhibition in the management of diabetes. Clin. Invest. Med. 18 (4), 303–311.

Bresciania, L.F.V., Yunes, R.A., Bürger, C., De Oliveira, L.E., Bóf, K.L., Cechinel-Filho, V., 2004. Seasonal variation of kaurenoic acid, a hypoglycemic diterpene present in *Wedelia paludosa* (*Acmela brasiliensis*) (Asteraceae). Z. Naturforsch. C 59 (3-4), 229–232.

Cai, E.P., Lin, J.K., 2009. Epigallocatechin gallate (EGCG) and rutin suppress the glucotoxicity through activating IRS2 and AMPK signaling in rat pancreatic β cells. J. Agric. Food Chem. 57 (20), 9817–9827.

Catarino, L., Havik, P.J., Romeiras, M.M., 2016. Medicinal plants of Guinea-Bissau: Therapeutic applications, ethnic diversity and knowledge transfer. J. Ethnopharmacol. 183, 71–94.

Cornara, L., Xiao, J., Burlando, B., 2016. Therapeutic potential of temperate forage legumes: a review. Crit. Rev. Food Sci. Nutr. 56, S149–S161.

Credo, D., Masimba, P.J., Machumi, F., Heydenreich, M., 2018. Isolation of Stigmasterol from 80% aqueous ethanol root extract of *Bridelia duvigneaudii* J. Leon and its hypoglycaemic activity on oral glucose loaded white albino mice. Int. J. Res. Pharm. Chem. 8 (4), 492–501.

Davies, M.J., Gagliardino, J.J., Gray, L.J., Khunti, K., Mohan, V., Hughes, R., 2013. Real-world factors affecting adherence to insulin therapy in patients with Type 1 or Type 2 diabetes mellitus: a systematic review. Diabet. Med. 30 (5), 512–524.

Dawé, A., Mbiantcha, M., Yakai, F., Jabeen, A., Ali, M.S., Lateef, M., Ngadjui, B.T., 2018. Flavonoids and triterpenes from *Combretum fragrans* with anti-inflammatory, antioxidant and antidiabetic potential. Z. Naturforsch. C 73 (5-6), 211–219.

Deacon, C.F., 2011. Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review. Diabetes Obes. Metabol. 13 (1), 7–18.

Deutschländer, M.S., Lall, N., Van De Venter, M., 2009. Plant species used in the treatment of diabetes by South African traditional healers: an inventory. Pharm. Biol. 47 (4), 348–365.

Diallo, A., Traore, M.S., Keita, S.M., Balde, M.A., Keita, A., Camara, M., Miert, S.V., Pieters, L., Balde, A.M., 2012. Management of diabetes in Guinean traditional medicine: an ethnobotanical investigation in the coastal low lands. J. Ethnopharmacol. 144, 353–361.

Dickson, R.A., Harley, B.K., Berkoh, D., Ngala, R.A., Titiloye, N.A., Fleischer, T.C., 2016. Antidiabetic and haematological effect of *Myrianthus arboreus* P. Beauv. Stem bark extract in streptozotocin-induced diabetic rats. Int. J. Pharm. Sci. Rev. Res. 7, 4812–4826.

Diéye, M.A., Sarr, A., Diop, S.N., Ndiaye, M., Sy, G.Y., Diarra, M., Gaffary, I.R., Sy, A.N., Faye, B., 2008. Medicinal plants and the treatment of diabetes in Senegal: survey with patients. Fundam. Clin. Pharmacol. 22, 211–216.

Egua, M.O., Etuk, E.U., Bello, S.O., Hassan, S.W., 2013. Anti-diabetic activity of ethanolic seed extract of *Corchorus olitorius*. Int. J. Sci. Basic Appl. Res. 12 (1), 8–21.

Egua, M.O., Etuk, E.U., Bello, S.O., Hassan, S.W., 2015. Isolation and structural characterization of the most active antidiabetic fraction of *Corchorus olitorius* seed extract. J Adv. Med. Pharm. Sci. 2 (3), 75–88.

Eldin, S.M., Radwan, M.M., Wanas, A.S., Habib, A.A.M., Kassem, F.F., Hammoda, H.M., Khan, S.I., Klein, M., Elokely, K.M., ElSohly, M.A., 2018. Bioactivity-guided isolation of potential antidiabetic and antihyperlipidemic compounds from *Trigonella stellata*. J. Nat. Prod. 81 (5), 1154–1161.

Etsassala, N.G., Badmus, J.A., Waryo, T.T., Marnewick, J.L., Cupido, C.N., Hussein, A.A., Iwuoha, E.I., 2019. Alpha-glucosidase and alpha-amylase inhibitory activities of novel abietane diterpenes from *Salvia africana-lutea*. Antioxidants 8 (10), 421. https://doi.org/10.3390/antiox8100421.

Etsassala, N.G., Ndjoubi, K.O., Mbira, T.J., Pearce, B., Pearce, K., Iwuoha, E.I., Hussein, A.A., Benjeddou, M., 2020. Glucose-uptake activity and cytotoxicity of diterpenes and triterpenes isolated from Lamiaceae plant species. Molecules 25 (18), 4129. https://doi.org/10.3390/molecules25184129.

Etuk, E.U, Bello, S.O, Isezuo, S.A, Mohammed, B.J, 2010. Ethnobotanical survey of medicinal plants used for the treatment of diabetes mellitus in the north western region of Nigeria. Asian J. Exp. Biol. Sci 1 (1), 55–59.

Ezuruike, U.F., Prieto, J.M., 2014. The use of plants in the traditional management of diabetes in Nigeria: pharmacological and toxicological considerations. J. Ethnopharmacol. 155 (2), 857–924.

Faloye, K.O., Ayoola, M.D., Amos-Tautua, B.M., Famuyiwa, S.O., 2018. Anti-diabetic activity of convallatoxin isolated from the root bark of *Parquetina nigrescens* (Afzel.) bullock (Asclepiadaceae). Eur. J. Med. Plants 25 (4), 1–9.

Famuyiwa, F.G, Ayoola, M.D, Famuyiwa, S.O, Aladesanmi, A.J, 2018. Hyperglycaemia lowering effect of kaurane diterpenoids from the Fruits of *Xylopia aethiopica* (A. Dunal) Rich. Int. J. Med. Plants Nat. Prod 4 (3), 11–18.

Farombi, E.O., Adedara, I.A., Ajayi, B.O., Ayepola, O.R., Egbeme, E.E., 2013. Kolaviron, a natural antioxidant and anti-inflammatory phytochemical prevents dextran sulphate sodium-induced colitis in rats. Basic Clin. Pharmacol. Toxicol. 113 (1), 49–55.

Funke, I., Melzig, M.F., 2006. Traditionally used plants in diabetes therapy: phytotherapeutics as inhibitors of alpha-amylase activity. Braz. J. Pharmacog. 16 (1), 1–5.

Gbolade, A.A., 2009. Inventory of antidiabetic plants in selected districts of Lagos State, Nigeria. J. Ethnopharmacol. 121 (1), 135–139.

Gurib-Fakim, A., Brendler, T., 2004. Medicinal and Aromatic Plants of Indian Ocean Islands. Medpharm GmbH Scientific Publishers, Stuttgart, Germany.

Habtemariam, S., 2015. Investigation into the antioxidant and antidiabetic potential of *Moringa stenopetala*: identification of the active principles. Nat. Prod. Comm. 10 (3), 475–478.

Harley, B.K., Dickson, R.A., Amponsah, I.K., Ben, I.O., Adongo, D.W., Fleischer, T.C., Habtemariam, S., 2020. Flavanols and triterpenoids from *Myrianthus arboreus* ameliorate hyperglycaemia in streptozotocin-induced diabetic rats possibly via glucose uptake enhancement and α-amylase inhibition. Biomed. Pharmacother. 132, 110847.

Harley, B.K., Dickson, R.A., Fleischer, T.C., 2017. Antioxidant, glucose uptake stimulatory, α-glucosidase and α-amylase inhibitory effects of *Myrianthus arboreus* stem bark. Nat. Prod. Chem. Res. 5, 273–279.

Hossain, M.A., Pervin, R., 2018. Current antidiabetic drugs: Review of their efficacy and safety. Nutritional and Therapeutic Interventions for Diabetes and Metabolic Syndrome, 34. Academic Press, pp. 455–473. 2nd Ed.

Howes, M.J.R., Quave, C.L., Collemare, J., Tatsis, E.C., Twilley, D., Lulekal, E., Farlow, A., Li, L., Cazar, M.E., Leaman, D.J., Prescott, T.A.K., Milliken, W., Martin, C.,

De Canha, M.N., Prescott, T.A., 2020. Molecules from nature: Reconciling biodiversity conservation and global healthcare imperatives for sustainable use of medicinal plants and fungi. Plants People Planet 2 (5), 463–481.
Hussain, R.A., Owegby, A.G., Parimoo, P., Waterman, P.G., 1982. Kolavonone, a novel polyisoprenylated benzophenone with antimicrobial properties from fruit of *Garcinia kola*. Planta Med. 44, 78–81.
Ibitoye, O.B., Olofinsan, K.A., Teralı, K., Ghali, U.M., Ajiboye, T.O., 2018. Bioactivity-guided isolation of antidiabetic principles from the methanolic leaf extract of *Bryophyllum pinnatum*. J. Food Biochem. 42 (5), e12627.
Ibrahim, M.A., Habila, J.D., Koorbanally, N.A., Islam, M.S., 2016. Butanol fraction of *Parkia biglobosa* (Jacq.) G. Don leaves enhance pancreatic β-cell functions, stimulates insulin secretion and ameliorates other type 2 diabetes-associated complications in rats. J. Ethnopharmacol. 183, 103–111.
Ibrahim, M.A., Habila, J.D., Koorbanally, N.A., Islam, M.S., 2017. α-Glucosidase and α-amylase inhibitory compounds from three African medicinal plants: an enzyme inhibition kinetics approach. Nat. Prod. Commun. 12 (7), 1125–1128.
Ibrahim, M.A., Islam, M.S., 2014. Anti-diabetic effects of the acetone fraction of *Senna singueana* stem bark in a type 2 diabetes rat model. J. Ethnopharmacol. 153 (2), 392–399.
Ibrahim, M.A., Islam, M.S., 2014a. Butanol fraction of *Khaya senegalensis* root modulates β-cell function and ameliorates diabetes-related biochemical paramaters in a type 2 diabetes rat model. J. Ethnopharmacol. 154, 832–838.
Ibrahim, M.A., Islam, M.S., 2017. Effects of butanol fraction of *Ziziphus mucronata* root ethanol extract on glucose homeostasis, serum insulin and other diabetes-related parameters in a murine model for type 2 diabetes. Pharm. Biol. 55 (1), 416–422.
Iwu, M., Igboko, O., 1982. Flavonoids of *Garcinia kola* seeds. J. Nat. Prod. 45 (5), 650–651 .
Iwu, M.M., Igboko, O.A., Okunji, C.O., Tempesta, M.S., 1990. Antidiabetic and aldose reductase activities of biflavanones of *Garcinia kola*. J. Pharm. Pharmacol. 42 (4), 290–292.
Jahn, S.A.A., 1991. The traditional domestication of a multipurpose tree *Moringa stenopetala* (Bak. f.) Cuf. in the Ethiopian Rift Valley. Ambio 244–247.
Kaitjizemine, K., Mumbengegwi, I.D.P.D., 2019. Anti-diabetic properties of medicinal plants in Hardap region. In: Proceedings of the 3rd Multi/Interdisciplinary Research Conference, pp. 18–22.
Karou, D., Nadembega, W.M., Ouattara, L., Ilboudo, D.P., Canini, A., Nikiéma, J.B., Simpore, J., Colizzi, V., Traore, A.S., 2007. African ethnopharmacology and new drug discovery. Med. Aromat. Plant Sci. Biotechnol. 1 (1), 61–69.
Karou, S.D., Tchacondo, T., Djikpo Tchibozo, M.A., Abdoul-Rahaman, S., Anani, K., Koudouvo, K., Batawila, K., Agbonon, A., Simpore, J., de Souza, C., 2011. Ethnobotanical study of medicinal plants used in the management of diabetes mellitus and hypertension in the Central Region of Togo. Pharm. Biol. 49 (12), 1286–1297.
Kasangana, P.B., Haddad, P.S., Eid, H.M., Nachar, A., Stevanovic, T., 2018. Bioactive Pentacyclic triterpenes from the root bark extract of *Myrianthus arboreus*, a species used traditionally to treat type-2 diabetes. J. Nat. Prod. 81 (10), 2169–2176.
Kasangana, P.B., Eid, H.M., Nachar, A., Stevanovic, T., Haddad, P.S., 2019. Further isolation and identification of anti-diabetic principles from root bark of *Myrianthus arboreus* P. Beauv.: The ethyl acetate fraction contains bioactive phenolic compounds that improve liver cell glucose homeostasis. J. Ethnopharmacol. 245, 112167.
Kasangana, P.B., Nachar, A., Eid, H.M., Stevanovic, T., Haddad, P.S., 2017. Root bark extracts of *Myrianthus arboreus* P. Beauv. (Cecropiaceae) exhibit anti-diabetic potential by modulating hepatocyte glucose homeostasis. J. Ethnopharmacol. 211, 117–125.
Keter, L.K., Mutiso, P.C., 2012. Ethnobotanical studies of medicinal plants used by Traditional Health Practitioners in the management of diabetes in Lower Eastern Province. Kenya. J. Ethnopharmacol. 139 (1), 74–80.
Kraft, C., Jenett-Siems, K., Siems, K., Jakupovic, J., Mavi, S., Bienzle, U., Eich, E., 2003. *In vitro* antiplasmodial evaluation of medicinal plants from Zimbabwe. Phytother. Res. 17 (2), 123–128.
Lee, S.M., Shin, M.J., Seong, S.I., Hwang, K.Y., Lee, J.Y., Kwon, O., Jin, T., Chung, J.H., 2013. 1-Deoxynojirimycin isolated from a *Bacillus subtillis* stimulates adiponectin and GLUT4 expressions in 3T3-L1 adipocytes. J. Microbiol. Biotechnol. 23, 637–643.
Lifongo, L.L., Simoben, C.V., Ntie-Kang, F., Babiaka, S.B., Judson, P.N., 2014. A bioactivity versus ethnobotanical survey of medicinal plants from Nigeria, West Africa. Nat. Prod. Bioprospect. 4 (1), 1–19.
Mahomoodally, M.F., Korumtollee, H.N., Chady, Z.Z.B.K., 2015. Ethnopharmacological uses of *Antidesma madagascariense* Lam. (Euphorbiaceae). J. Intercult. Ethnopharmacol. 4 (1), 86–89.
Makinde, S.C.O., Ojekale, A.B., Oshinaike, T.S., Awusinu, T.S., 2015. An ethnomedical and ethnobotanical survey of plants herbal therapy used for obesity, asthma, diabetes and fertility by the Badagry people of Lagos state, Nigeria. J. Med. Plants Stud. 3 (5), 01–06.
Marles, R.J., Farnsworth, N.R., 1994. Plants as sources of anti-diabetic agents. In: Wagner, H., Farnsworth, N.R. (Eds.), Economic and Medical Plant Research. Academic Press Ltd., pp. 149–187.
Mbagwu, I.S., Akah, P.A., Ajaghaku, D.L., 2020a. *Newbouldia laevis* improved glucose and fat homeostasis in a Type-2 diabesity mice model. J. Ethnopharmacol. 251, 112555.
Mbagwu, I.S., Akah, P.A., Ajaghaku, D.L., Ike, J.C., Okoye, F.B.C., 2020b. Newboulasides A and B, two new caffeic acid glycosides from *Newbouldia laevis* with α-amylase inhibitory activity. Nat. Prod. Res. https://doi.org/10.1080/14786419.2020.1799362.
Mbiantcha, M., Khalid, R., Dawe, A., Mehreen, A., Atsamo, D.A., Ateufack, G., Hamza, D., Nana, W.Y., Bomba, F.T.D., Naeem, R.U., Izhar, A., 2019. Antihypernociceptive and neuroprotective effects of Combretin A and Combretin B on streptozotocin-induced diabetic neuropathy in mice. N. S. Arch. Pharmacol. 392 (6), 697–713.
Mohammed, A., Gbonjubola, V.A., Ibrahim, M.A., Koorbanally, N.A., Islam, M.S., 2019. Oleanolic acid as a potential antidiabetic component of *Xylopia aethiopica* (Dunal) A. Rich. (Annonaceae) fruit: bioassay guided isolation and molecular docking studies. Nat. Prod. Res. https://doi.org/10.1080/14786419.2019.1596094.
Mohammed, A., Gbonjubola, V.A., Koorbanally, N.A., Islam, M.S., 2017b. Inhibition of key enzymes linked to type 2 diabetes by compounds isolated from *Aframomum melegueta* fruit. Pharm. Biol. 55 (1), 1010–1016.
Mohammed, A., Ibrahim, H., Islam, M.S., 2017a. Plant-derived antidiabetic compounds obtained from African medicinal plants: a short review. Studies in Natural Products Chemistry, 54. Elsevier, pp. 291–314.
Mohammed, A., Ibrahim, M.A., Islam, M.S., 2014. African medicinal plants with antidiabetic potentials: A review. Planta Med. 80 (05), 354–377.
Mohammed, A., Koorbanally, N.A., Islam, M.S., 2015. Ethyl acetate fraction of *Aframomum melegueta* fruit ameliorates pancreatic β-cell dysfunction and major diabetes-related parameters in a type 2 diabetes model of rats. J. Ethnopharmacol. 175, 518–527.
Mohammed, A., Koorbanally, N.A., Islam, M.S., 2016. Anti-diabetic effect of *Xylopia aethiopica* (Dunal) A. Rich. (Annonaceae) fruit acetone fraction in a type 2 diabetes model of rats. J. Ethnopharmacol. 180, 131–139.
Mootoosamy, A., Mahomoodally, M.F., 2014. Ethnomedicinal application of native remedies used against diabetes and related complications in Mauritius. J. Ethnopharmacol. 151 (1), 413–444.
Moshi, M.J., Mbwambo, Z.H., 2002. Experience of Tanzanian traditional healers in the management of non-insulin dependent diabetes mellitus. Pharm. Biol. 40 (7), 552–560.
Moshi, M.J., Mbwambo, Z.H., Nondo, R.S., Masimba, P.J., Kamuhabwa, A., Kapingu, M.C., Thomas, P., Richard, M., 2006. Evaluation of ethnomedical claims and brine shrimp toxicity of some plants used in Tanzania as traditional medicines. Afr. J. Tradit. Complement. Alternat. Med. 3 (3), 48–58.
Ndip, R.N, Tanif, N.F, Kuete, V, 2013. Antidiabetes activity of African medicinal plants. Medicinal Plant Research in Africa. Elsevier, pp. 753–786.
Okoduwa, S.I., Umar, I.I.A., James, D.B., Inuwa, H.M., Habila, J.D., Venditti, A., 2020. Bioguided fractionation of hypoglycaemic component in methanol extract of *Vernonia amygdalina*: an *in vivo* study. Nat. Prod. Res. https://doi.org/10.1080/14786419.2020.1805605.
Onasanwo, S.A., Velagapudi, R., El-Bakoush, A., Olajide, O.A., 2016. Inhibition of neuroinflammation in BV2 microglia by the biflavonoid kolaviron is dependent on the Nrf2/ARE antioxidant protective mechanism. Mol. Cell Biochem. 414 (1-2), 23–36.
Osadebe, P.O., Odoh, E.U., Uzor, P.F., 2014. The search for new hypoglycemic agents from plants. Afr. J. Pharm. Pharmacol. 8 (11), 292–303.
Osigwe, C.C., Akah, P.A., Nworu, C.S., Okoye, F.B., 2017. Apigenin: A methanol fraction component of *Newbouldia laevis* leaf, as a potential antidiabetic agent. J. Phytopharmacol. 6, 38–44.
Oyenihi, O.R., Brooks, N.L., Oguntibeju, O.O., 2015. Effects of kolaviron on hepatic oxidative stress in streptozotocin induced diabetes. BMC Complement. Alternat. Med. 15 (1), 236.
Philander, L.A., 2011. An ethnobotany of Western Cape Rasta bush medicine. J. Ethnopharmacol. 138 (2), 578–594.
Rabe, T., Mullholland, D., Van Staden, J., 2002. Isolation and identification of antibacterial compounds from *Vernonia colorata* leaves. J. Ethnopharmacol. 80 (1), 91–94.
Raga, D.D., Alimboyoguen, A.B., del Fierro, R.S., Ragasa, C.Y., 2010. Hypoglycaemic effects of tea extracts and *ent*-kaurenoic acid from *Smallanthus sonchifolius*. Nat. Prod. Res. 24 (18), 1771–1782.
Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., Colagiuri, S., Guariguata, L., Motala, A.A., Ogurtsova, K., Shaw, J.E., Bright, D., Williams, R., On behalf of the IDF Diabetes Atlas Committee, 2019. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. Diabetes Res. Clin. Pract. 157, 107843.
Sahnoun, M., Saibi, W., Brini, F., Bejar, S., 2018. Apigenin isolated from *A. americana* encodes Human and *Aspergillus oryzae* S2 α-amylase inhibitions: credible approach for antifungal and antidiabetic therapies. J. Food Sci. Technol. 55 (4), 1489–1498.
Salau, V.F., Erukainure, O.L., Koorbanally, N.A., Islam, M.S., 2020. Kolaviron modulates dysregulated metabolism in oxidative pancreatic injury and inhibits intestinal glucose absorption with concomitant stimulation of muscle glucose uptake. Arch. Physiol. Biochem. https://doi.org/10.1080/13813455.2020.1806331.
Sekii, Y., Han, J., Isoda, H., Bouaziz, M., Dhouib, A., Sayadi, S., Shigemori, H., 2015. Two isorhamnetin glycosides from *Arthrocnemum glaucum* that inhibit adipogenesis in 3T3-L1 adipocytes. Chem. Nat. Comp. 51 (2), 338–340.
Sohn, J.H., Kim, T.Y., 2010. Recent update on pathogenesis of nonalcoholic fatty liver disease. Korean J. Med. 79, 461–474.
Soladoye, M.O., Chukwuma, E.C., Owa, F.P., 2012. An 'Avalanche' of plant species for the traditional cure of diabetes mellitus in South-Western Nigeria. J. Nat. Prod. Plant Res. 2, 60–72.
Stark, T.D., Mtui, D.J., Balemba, O.B., 2013. Ethnopharmacological survey of plants used in the traditional treatment of gastrointestinal pain, inflammation and diarrhea in Africa: future perspectives for integration into modern medicine. Animals 3 (1), 158–227.
Su, C., Yang, C., Gong, M., Ke, Y., Yuan, P., Wang, X., Li, M., Feng, W., 2019. Antidiabetic activity and potential mechanism of amentoflavone in diabetic mice. Molecules 24 (11), 2184.
Tadera, K., Minami, Y., Takamatsu, K., Matsuoka, T., 2006. Inhibition of α-glucosidase and α-amylase by flavonoids. J. Nutr. Sci. Vitaminol. 52, 149–153.

Toma, A., Makonnen, E., Debella, A., Tesfaye, B., 2012. Antihyperglycemic effect on chronic administration of butanol fraction of ethanol extract of *Moringa stenopetala* leaves in alloxan induced diabetic mice. Asian Pac. J. Trop. Biomed. 2 (3), S1606–S1610.

Toma, A., Makonnen, E., Mekonnen, Y., Debella, A., Adisakwattana, S., 2015. Antidiabetic activities of aqueous ethanol and n-butanol fraction of *Moringa stenopetala* leaves in streptozotocin-induced diabetic rats. BMC Complement. Alternat. Med. 15 (1), 1–8.

Tundis, R., Loizzo, M.R., Menichini, F., 2010. Natural products as α-amylase and α-glucosidase inhibitors and their hypoglycaemic potential in the treatment of diabetes: an update. Mini Rev. Med. Chem. 10, 315–331.

Tyagi, S., Gupta, P., Saini, A.S., Kaushal, C., Sharma, S., 2011. The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases. J. Adv. Pharm. Technol. Res. 2 (4), 236.

Verma, M., Gupta, S.J., Chaudhary, A., Garg, V.K., 2017. Protein tyrosine phosphatase 1B inhibitors as antidiabetic agents-A brief review. Bioorg. Chem. 70, 267–283.

Wade, F., Belhaj, K., Poizat, C., 2018. Protein tyrosine phosphatases in cardiac physiology and pathophysiology. Heart Fail. Rev. 23 (2), 261–272.

Wang, C.H., Wang, C.C., Wei, Y.H., 2010. Mitochondrial dysfunction in insulin insensitivity: implication of mitochondrial role in type 2 diabetes. Ann. N. Y. Acad. Sci. 1201 (1), 157–165.

Wang, G., Chen, M., Wang, J., Peng, Y., Li, L., Xie, Z., Deng, B., Chen, S., Li, W., 2017. Synthesis, biological evaluation and molecular docking studies of chromone hydrazone derivatives as α-glucosidase inhibitors. Bioorg. Med. Chem. Lett. 27 (13), 2957–2961.

Waterman, PG, Hussain, RA, 1983. Systematic significance of xanthones, benzophenones and biflavonoids in Garcinia. Biochem. Syst. Ecol. 11, 21–28.

Zhang, J., Zhou, J., Zhang, T., Niu, Z., Wang, J., Guo, J., Li, Z., Zhang, Z., 2019. Facile fabrication of an amentoflavone-loaded micelle system for oral delivery to improve bioavailability and hypoglycemic effects in KKAy mice. ACS Appl. Mater. Interfaces 11 (13), 12904–12913.

Zheng, X.K., Su, C.F., Zhang, L., Gao, A.S., Ke, Y.Y., Yuan, P.P., Wang, Y.Z., Feng, W.S., 2013. Anti-diabetic activity of amentoflavone in *Selaginella tamariscina* in diabetic mice. Chin. J. Exp. Tradit. Med. Formulae(17), 62 2013.

Zhou, J, Wu, G, Sun, M, Onakpa, M.M, Yao, G, Zhao, M, Chet, C.T, 2019. Modified diterpenoids from the tuber of *Icacina oliviformis* as protein tyrosine phosphatase 1B inhibitors. Org. Chem. Front 355–367.