



Natural Products as Potential Sources of Antidiabetic Drugs

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Authors' contributions

This work was carried out in collaboration between all authors. Author POO designed the study, participated in the literature search. Author EUO participated in searching the literature and writing the first draft of the manuscript. Author PFU participated in designing the work, searched the literature and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Natural products have played and continue to play an invaluable role in the treatment of various diseases and in drug discovery processes. It has remained a source of new compounds with diversified structural arrangements possessing interesting biological activities for various disease treatments. Drugs from natural products are usually considered to be safer, cheaper, easily available and sometimes more efficacious than purely synthetic ones. In recent years, scientists have been in search for safer and more

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potent drugs from natural sources particularly from medicinal plants. Diabetes is one of the chronic disorders which are associated with high mortality risk. The existing drugs have been identified with one or more adverse effects. In the present review, literature was surveyed to highlight the merits of natural products with regard to their role in diabetic management. Notwithstanding the seemingly decline in the natural product approach to drug discovery in favor of modern approaches such as combinatorial chemistry, literature survey has shown that a lot of research effort is still being directed to natural product in search for new antidiabetic agents. Several antidiabetic phytoconstituents have been isolated from medicinal plants and these were of chemically diversified nature which includes flavonoids, glycosides, terpenes, polysaccharides and polypeptides. Based on the merits of nature based medicines, the authors advocate the use of standardized crude forms of some of the natural drugs. Further researches geared towards exploiting the vast array of natural products in our environment and development of the isolated compounds to clinically useful drugs for diabetes management is advocated.

Keywords: Biological products; diabetes mellitus; herbal medicine; hypoglycemic agents; medicinal plants.

1. INTRODUCTION

Diabetes mellitus (DM) is a serious metabolic disorder which involves the endocrine system. Its major manifestations include disordered metabolism and inappropriate hyperglycemia [1]. The metabolic dysregulation associated with DM causes secondary pathophysiological changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. In the United States, DM is the leading cause of end-stage renal disease (ESRD), non-traumatic lower extremity amputations, and adult blindness [2]. According to an estimate, one person is detected with diabetes every 5s somewhere in the world, while someone dies of it every 10s [3]. Conventional agents are being used to control diabetes along with lifestyle management, though with certain limitations. Despite the enormity of this disorder, the drugs developed for its management, including the recently approved agents, are associated with several adverse effects. This has resulted to the continued search for antidiabetic agents by scientists.

Nature has afforded mankind a large array of drugs for the management of various diseases. Natural medicines have become the part of our daily diet like turmeric, cardamom, garlic, onion, ginger, tulsi, cloves, etc. Also, the use of plants as medicines has a long history in the treatment of various diseases. The earliest known records for the use of plants as drugs are from Mesopotamia in 2600 B.C. and these still are a significant part of traditional medicine and herbal remedies [4]. Beginning with the discovery of morphine as the first active alkaloid extracted from opium poppy plant in December 1804, the quest for isolation and discovery of active principles from the traditionally used natural products particularly medicinal plants took the momentum [4]. Several antidiabetic agents have been developed from natural sources. Plants have led to the development of metformin while animals afforded exenatide. Microorganisms have a wide variety of potentially active substances and have led to the discovery of the antidiabetic agents such as acarbose.

Despite the enormous potentials of natural products as sources of new drugs, there seems to be a decline in recent years, particularly within the pharmaceutical industry [5]. The reasons for this are complex, but can be summarized as being due to a combination of

factors, including the incompatibility of crude extracts with the high throughput assays used in the pharmaceutical industry, the cost of sample collection, problems with the lack of reproducibility and the presence of artifacts in some extracts, the difficulty in isolating active compounds, the long resupply times for active extracts, problems with large scale supply if a drug should emerge, the difficulty of complying with the Rio Treaty on Biodiversity, and last but not least, the diversion of resources to combinatorial chemical approaches to drug discovery [5]. However, there is evidence that some people now realize that the move to discontinue natural products research in favor of combinatorial chemistry may have been a mistake. The early combinatorial strategies were flawed and unproven, and have yet to deliver any blockbuster drugs [6]. Today, research and development (R&D) thrust in the pharmaceutical sector is focused on development of new drugs, innovative/indigenous processes for known drugs and development of plant-based drugs through investigation of leads obtained from the traditional systems of medicine as well other resources [7,8].

This review presents an appraisal of the natural products as source of medicines and lead compounds particularly with respect to antidiabetic agents. We have also presented some of the plants investigated with their antidiabetic principles isolated in the search for new antidiabetic agents from plants. The data were sourced by searching the Pub Med, Medline, Google scholar up to December 2013 using the keywords such as antidiabetic plants, antidiabetic plant constituents, hypoglycemic constituents of plants and natural product appraisal. Original and review works related to the subject were selected.

2. APPRAISAL OF NATURE-BASED DRUGS

The adverse effects and limitations of the orthodox medicines or synthetic drugs as enumerated above necessitate the search for safer and more efficacious drugs from natural sources particularly from plants. The natural sources of drugs include plants, animals, micro-organisms and marine life. However, most of the discussions in this review have emphasized more of plant based drugs. The following are the merits of nature-based agents for diabetes management.

2.1 Plant Based Medicines are Popular

It has been estimated that about 80-85% of population both in developed and developing countries rely on traditional medicine for their primarily health care needs and it is assumed that a major part of traditional therapy involves the use of plant extracts or their active principles [9-12]. In several countries, traditional medicine is still in vogue, and in fact, has been gaining more acceptability for treatment of chronic ailments. This is especially true for countries like India and China, which have a long tradition of fairly well-organized traditional therapy [13]. In Africa, a great number rely on traditional medicine because of the availability and high cost of the synthetic drugs. About 20% of the population of the US takes herbal products, often in the absence of good evidence of their effectiveness [14].

Many plants are used traditionally in the management of diabetes throughout the world [15]. Before the discovery of insulin by Banting and Best in 1922, the only options for diabetes treatment were those based on traditional practices [9,16] and they are still being used today because of the adverse effects and limitations of the conventional drugs as enumerated earlier.

2.2 Enormous Research Interest has been Attracted to Natural Drugs

The plant based drugs have been used from time immemorial in the treatment of various diseases including diabetes mellitus. Marles and Farnsworth estimated that more than 1000 plant species are being used as folk medicine for diabetes [17]. The attention of many investigators has been attracted to the research in medicinal plants since mid-1950s. Highly significant amount of research is going on several plants. Some have been investigated in clinical settings [13]. Review works on plants that have been investigated for their antidiabetic potentials in recent times have shown that enormous number of plants has been studied [18,19].

2.3 Efficacious

The efficacy and safety of some plants have been sufficiently validated by clinical use over thousands of years [20]. Literature search has shown that many of these plants investigated for antidiabetic potentials have been used for a long time in the traditional settings and scientific investigation further validated the claims [18,19]. Many of the plants have been found to be quite efficacious in the management of diabetes and its complications both in experimental animals and in clinical studies.

2.4 Safety-Less Side Effects

Some of the natural products particularly plants are have been used as food for many years and are considered safe. Plant drugs and herbal formulations are frequently considered to be less toxic and free from side effects than synthetic ones [21,22]. Medicinal plants are prescribed widely even when their biologically active compounds are unknown, because of their safety, effectiveness, and availability [23]. The synthetic drugs are associated with a number of adverse effects. For instance, the adverse effects of the conventional antidiabetic drugs such as cardiovascular risk, hepatotoxicity, weight gain, hypoglycemia etc. (Table 1) are low with plant based drugs. It has also been reported that the tremendous safety of Ayurvedic botanicals is very reassuring and forms the foundation of the much advocated "reverse pharmacology" approach [24] where clinical validation proceeds in parallel to other experimental studies.

2.5 Less Expensive

Medicinal plants are commonly available, thus they are considered to be of low cost [22]. In most traditional settings, plant based preparations are contemporaneously prepared from readily available plants. Even when prepared as herbal formulation on commercial basis, the cost is reduced compared with the synthetic products. The cost of drug research, development and advertisement add to the high cost of the conventional drugs. These activities are low in plant based drugs and cost can be further lowered by the simultaneous development in both experimental and clinical settings.

2.6 Easy Availability of Plants

An impressive array of plants is available in our environment and it is possible to cultivate some of them in botanical gardens for easier control. Besides providing the medicines, these plants protect our environment.

Table 1. Conventional antidiabetic drugs and their major adverse effects

S/N	Drug class	Example of drugs	Adverse effects
1	Insulin and analogues	Regular Insulin	Hypoglycemia, Weight gain, Insulin allergy, Lipodystrophy at injection sites
2	Sulphonylureas	Glibenclamide	Hypoglycaemia, Weight gain, Cardiovascular risk, rash, Cholestatic jaundice, Bone marrow damage, Photosensitivity
3	Meglitinides	Repaglinide	Hypoglycemia, Sensitivity reactions
4	Biguanides	Metformin	Gastrointestinal effects, Lactic acidosis
5	GLP-1 agonists	Exenatide	Gastrointestinal effects, Pancreatitis, risks for cancer and cardiovascular events
6	DPP-4 inhibitors	Saxagliptin	Pancreatitis, risk for cancer, acute hepatitis and kidney impairment
7	Thiazolidinedions	Pioglitazone	Hepatitis, Cardiovascular risk, Bladder cancer, Water retention and weight gain
8	Dual PPAR agonists	Saroglitazar	Gastritis, asthenia and pyrexia
9	Alpha-glucosidase inhibitors	Acarbose	Gastrointestinal effects, Hepatitis,
10	Amylin analogues	Pramlintide	Hypoglycemia, Allergy
11	SGLT 2 inhibitors	Canagliflozin	Glycosuria, Cardiovascular concern

2.7 Many Plant-Based Formulations are now Available

The plants can be properly standardized at all levels of manufacture, ranging from plant selection and procurement to high performance liquid chromatography (HPLC) analysis. They could be prepared using modern ways in form of tablets/capsules, suspensions, solutions, powder etc. In the past few decades, a new trend in the preparation and marketing of drugs based on medicinal plants has become increasing important in several European countries. These preparations, labeled herbal drugs or phytomedicines are carefully standardized, and their efficacy and safety for a specific application demonstrated, and are dispensed just like the allopathic preparations [13]. In India, Ayurvedic formulations are governed by well-described pharmacological principles of preparation, compactibility and administration [20]. A lot of herbal formulations containing a number of antidiabetic drugs have been evaluated and are being marketed presently. Some formulations are included in pharmacopoeia. In the US, the National Center for Complementary and Alternative Medicine (NCCAM) actively supports such works. In Nigeria, some plant based formulations are approved and registered by the drug regulatory body, the National Agency for Food, Drug Administration and Control (NAFDAC).

Also many researchers have advocated the use of traditional and orthodox medicines in clinical settings. Chopra et al. [20] has suggested that in a scientific context, critical questions of standardization and defining clinical indications need to be answered through modern experiments and clinical studies. New paradigms need defining and testing, so both systems can be used in parallel or tandem in given clinical situations. This practice is

obtainable in Ghana where herbal medicines are the integral part of the healthcare delivery system.

2.8 WHO Supports Herbal Medicines

The World Health Organization (WHO) supports and encourages the utilization of herbal remedies for the treatment of various diseases including diabetes [25]. WHO considers plant treatments to be effective, non-toxic, with less or no side effects and excellent candidates for oral therapy [26]. Part of the support for plant based medicines is the preparation of WHO Monograph on Selected Medicinal Plants and similar publications [27].

2.9 Holistic Treatment

In using plant formulation, man is viewed not in isolation but against the big picture of the universe. He is treated holistically. The plant-based total approach package seems to provide the body's milieu interior with an opportunity to heal. Some are based on strengthening the immune system, healing and rejuvenating especially in chronic diseases such as diabetes, arthritis while some are nutritive [20].

In addition, compounds from natural sources are considered more "druglike" than the synthetic ones. A statistical comparison between compounds isolated from natural sources and drugs shows that there is more similarity between natural compounds and drugs in several areas (LogP, number of chiral centers, number of nitrogen atoms, number of oxygen atoms, percent of aromatic rings) than between synthetic compounds and drugs [6]. This is due to the fact that most natural products have built-in chirality, whereas most synthetic compounds are achiral. Though combinatorial synthesis is now producing molecules that are drug-like in terms of size and property, these molecules, in contrast to natural products, have not evolved to interact with biomolecules [28].

2.10 Many Bioactive Compounds are of Natural Origin

Phytochemicals or compounds from other natural sources can be used as drugs or could serve as "lead" molecules for the synthesis of bioactive compounds. Also from some of the lead molecules, new analogs with greater synthetic accessibility could be derived. In the early development of modern medicine, biologically active compounds from higher plants played a vital role in providing medicines to combat pain and diseases, most of these were culled from plants traditionally used for that purpose in one culture or another. Today the search for bioactives from nature-plants, animals, or microflora, continues to play an important role in fashioning new therapeutic agents [13]. Many drugs used today are from plants or are derived from plants. Approx one-half of all licensed drugs that we were registered worldwide in the 25y period prior to 2007 were natural products or their synthetic derivatives [29]. A review article on the sources of new drugs about 30 year period from 1981 to 2010 shows that a large percentage came from natural sources. According to the authors, "although combinatorial chemistry techniques have succeeded as methods of optimization of many recently approved agents, we were able to identify only one de novo combinatorial compound approved as a drug in this 30-year time frame" [30]. In a recent review thesis on the origin of all drugs approved between 2010 and 2012, it was discovered that a high percentage of recently approved drugs are either natural products (bacteria, fungi, plants and marine life), semi-synthetic derivatives thereof or natural product mimics [31]. Few of the bioactive compounds isolated from natural sources include morphine and

codeine which are alkaloids derived from *Papaver somniferum* and used for pains and cough. Also such drugs such as quinine, artemisinin (antimalarial), digoxin (congestive heart failure) etc. are from plants. Examples of plant-derived clinically used anticancer agents include vinblastine and vincristine, etoposide and teniposide, taxol and docetaxel, and topotecan and irinotecan. It was also reported that among 19 natural product based drugs which were approved for marketing worldwide in between the year 2005 to April 2010, seven were classified as natural products, 10 semi-synthetic natural products and 2 natural product-derived drugs [32].

Approved antidiabetic agents derived from various natural sources include the following:

2.10.1 Antidiabetic drugs derived from plants

Metformin, the mainstay drug in treatment of type 2 diabetes, is derived from the guanidines which were obtained from *Galegine officinalis* [33]. Other investigations in the search for antidiabetic principles from plants are discussed in more details in section 3.

2.10.2 Antidiabetic drugs derived from animals

2.10.2.1 Insulin

The discovery of insulin from animals marked a major breakthrough in the treatment of diabetes. Historically, in 1921, in Ontario Canada, a young surgeon Frederick Banting, and his assistant Charles Best, kept a severely diabetic dog alive for 70 days by injecting it with a murky concoction of canine pancreas extract. Banting and co-workers later administered a more refined extract of insulin to Leonard Thompson, a young boy dying of diabetes. Within 24 hours, Leonard's dangerously high blood sugars had dropped to near normal levels [34].

2.10.2.2 Exenatide

Exenatide, a 39-amino-acid peptide, is a synthetic version of exendin-4, a hormone found in the saliva of the Gila monster (*Heloderma suspectum*) that was first isolated by Dr. John Eng in 1992 [35]. This drug has been approved for the management of type 2 diabetes mellitus.

2.10.3 Antidiabetic drugs derived from micro-organisms

Acarbose is a pseudo-oligosaccharide isolated from the culture broths of various actinomycetes. It is an alpha-glucosidase inhibitor used in type 2 diabetes.

2.11 Some Compounds cannot be Synthesized

Plants and other organisms produce many biologically active substances for defense and other purposes [36]. These substances are often so complex that they would never be prepared synthetically as drug candidates. Isolation from natural sources is the only feasible way to access them.

2.12 Drug Targets can be Identified Through Natural Products

Natural product compounds not only serve as drugs or templates for drugs, but in many instances lead to the discovery and better understanding of targets and pathways involved in

the disease process. Also, natural products play an important role in chemical biology. They help in elucidating the complex cellular mechanisms, including signal transduction and cell cycle regulation, leading to the identification of important targets for therapeutic interventions [37]. The identification of the anti-inflammatory mechanism of aspirin action led to the discovery of the cyclo-oxygenase isozymes (COX)-1 and -2, which are being used in the development of novel anti-inflammatory drugs [38].

3. PLANTS AS POTENTIAL SOURCES OF ANTIDIABETIC AGENTS

The following plants have been investigated scientifically and their putative hypoglycemic active agents isolated and evaluated. Some of the investigations and their findings have been discussed briefly while the rest are presented in Table 2. The chemical structures of some isolated phytoconstituents with antidiabetic properties are presented in Fig. 1.

Other plants with identified hypoglycemic active principles are listed in Table 2.

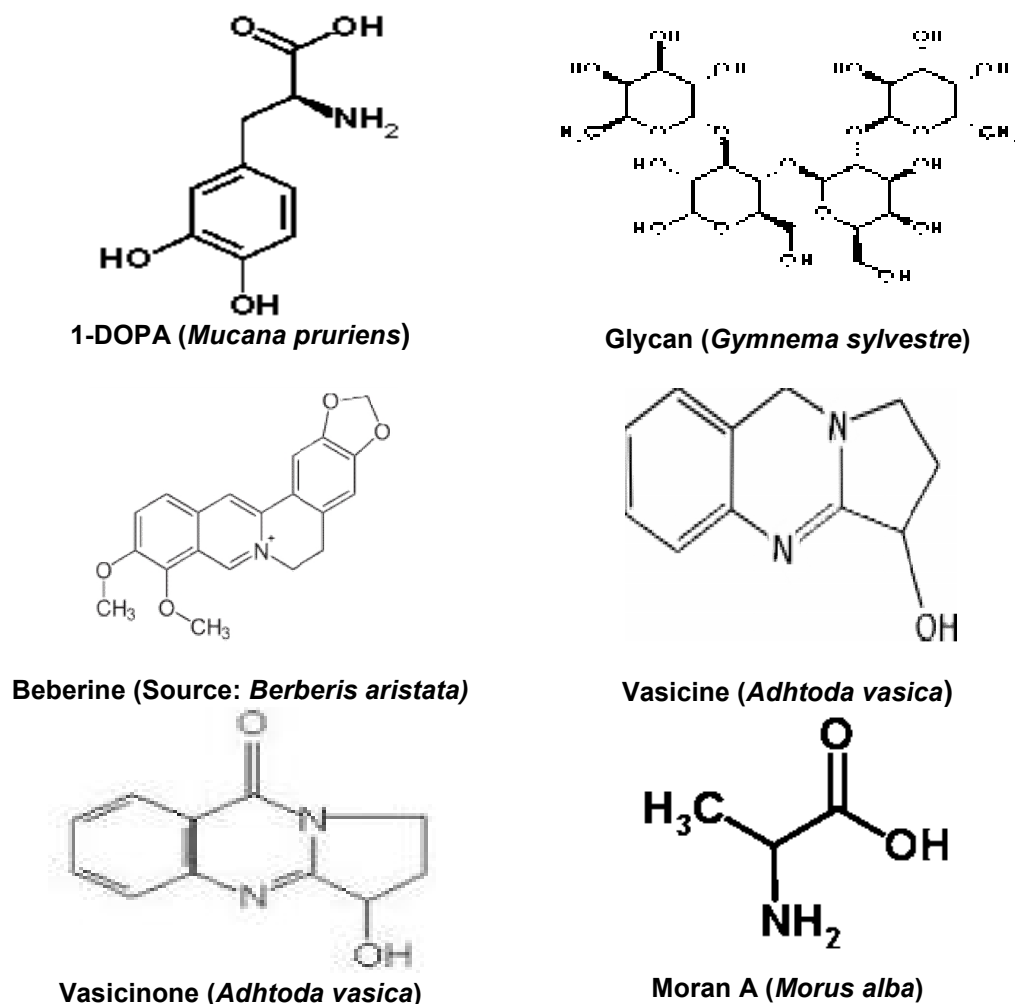


Fig. 1. Chemical structures of some isolated antidiabetic phytoconstituents

Table 2. Antidiabetic medicinal plants with their isolated active principles

S/n	Botanical name (common name)	Family	Main constituents/part of plant	Ref
1	<i>Abelmoschus moschatus</i> Medik	Malvaceae	Myricelin	[64]
2	<i>Acanthopanax senticosus</i>	Araliaceae	Saponin/leaves	[65]
3	<i>Bryonia alba</i>	Cucurbitaceae	trihydroxyoctadecadienoic acids/roots	[66]
4	<i>Chamaemelum nobile</i>	Compositae	A 3 hydroxy-3-methylglutaric acid (HMG) containing flavonoids, glucoside chamaemeloside	[67]
5	<i>Citrullus colocynthis</i> (Linn.) Schrad (Bitter gourd)	Cucurbitaceae	Beta-pyrazol-1 yalanine, the major free amino acid derivative/seeds; Saponin glycosides/rind	[68,69]
6	<i>Coccina indica</i> Wight & Am. (Ivy Gourd)	Cucurbitaceae	Pectin/fruit	[70]
7	<i>Croton cajucara</i> Benth	Euphorbiaceae	Trans dehydro-crotonin (t-DCTN), a 19-nor-clerodane diterpene/bark	[71]
8	<i>Cuminum nigrum</i>	Apiaceae	Flavonoid/seeds	[72]
9	<i>Equisetum myriochaetum</i>	Equisetaceae	Three kaempferol glucosides and one caffeoyl glucoside	[73]
10	<i>Eriobotrya japonica</i> Lindl. (Loquat)	Rosaceae	Sesquiterpene glycoside and polyhydroxylated triterpenoids	[74]
11	<i>Ficus bengalensis</i> L. (Banyan)	Moraceae	A dimethoxy derivative of perlargonidin 3-O-alpha-L rhamnoside, Glycoside of leucopelargonidin and dimethoxy ether of leucopelargonidin-3-O-alpha-L rhamnoside /bark	[75,76]
12	<i>Galega officinalis</i> L. (Goat's Rue)	Leguminosea	Galgine	[77]
13	<i>Kalopanax pictum</i> Thumb.	Araliaceae	Hederagenin gly-cosides and phenolic Glycosides/stem bark	[78]
14	<i>Kochia scoparia</i> L. (Tonburi ; Summer cypress)	Chenopodiaceae	Momordin IC and its 2'-O-beta-D-glucopyranoside together with three saponins named scoparianosides A, B and C.	[79]
15	<i>Lagerstroemia speciosa</i> Pers. (Queen crape-myrtle)	Lythraceae	Two terpenoides: colosolic acid and maslinic acid.	[80]
16	<i>Larrea tridentata</i> (Creosote bush)	Zygophyllaceae	Masoprocol (nordihydroguaiaretic acid)	[81]
17	<i>Malva verticillata</i>	Malvacées	Polysaccharide/seeds	[82]
18	<i>Morus insigni</i> L.	Moraceae	Two new compounds	[83]

S/n	Botanical name (common name)	Family	Main constituents/part of plant	Ref
			mulberrofuran U and moracin (M-3-O-β-D glucopyranoside) together with 6 known compounds.	
19	<i>Myrcia multiflora</i> DC	Myrtaceae	A new flavanone glucosides (myrciacitrins I and II) and new acetophenone glucosides (myrciaphenones A and B)	[84]
20	<i>Olea europea</i> L. (olive)	Oleaceae	Oleuropeoside/leaf	[85]
21	<i>Otholobium pubescens</i>	Fabaceae	Bakuchiol	[86]
22	<i>Paeonia lactiflora</i> Pall.	Ranunculaceae	Paeoniflorin and 8-debenzoylpaeoniflorin (glycosides)/root	[87]
23	<i>Panax ginseng</i> Mey. (Asiatic)	Araliaceae	Ginseng polypeptides (GPP)/roots	[88,89]
24	<i>Pandanus odoratus</i> Ridl. (Toei-hom)	Pandanaceae	known compound, 4-hydroxybenzoic acid	[90]
25	<i>Polygala senega</i> (L.) var. <i>Latifolia</i> Torrey & Gray. (<i>Senega radix</i>)	Polygalaceae	A triterpenoid glycoside named senegin II ; The E and Z-senegasaponins a and b/rhizomes; Saponins, named E-senegasaponin C and Z-senegasaponin C together with Z-senegins II, II and IV/root	[91-93]
26	<i>Pterocarpus marsupium</i>	Leguminosea	Marsupsin, pterosupin and pterostilbene (Phenolics) and also (-)Epicatechin	[94]
27	<i>Rhodiola sachalinensis</i>	Crassulaceae	Polysaccharides	[95]
28	<i>Salacia oblonga</i> Wall	Hippocrateaceae	Two biologically active fractions have been isolated.	[96]
29	<i>Securigera securidacea</i> L.	Fabaceae	A new cardenolide (-)-14-methoxy-hyrcanoside with five new dihydrobenzofuran derivatives (securigran I to V)/seeds	[97]
30	<i>Swertia chirayita</i> (Roxb)	Gentianaceae	Swerchirin(1,8-dihydroxy-3,5-dimethoxyxanthone)	[98,99]
31	<i>Swertia japonica</i> Blum Bijdr(Javanica)	Gentianaceae	Bellidifolin (a known xanthone)	[100]
32	<i>Tillandsia usneoides</i> L. (Spanish Moss)	Bromeliaceae	3-Hydroxy-3-methyl-glutaric acid (HMG)	[101]
33	<i>Trigonella foenum graecum</i> L. (Fenugreek)	Leguminosea	Steroidal saponins	[102]
34	<i>Xanthocercis zambesiaca</i>	Leguminaceae	Four compounds (fagomine, 4-O-beta-D-gluco-pyranosylfagomine, 3-O-beta-Dglucopyranosylfagomine, and 3 epifagomine)/leaves and roots	[103]
35	<i>Zizyphus spina-christi</i> L. (Christ-Thoron)	Rhamnaceae	Christinin-A, (saponin glycoside)	[104]

3.1 *Achyrocline satureioides* (Lam.) DC (Asteraceae)

This is known as Macela and it is a medicinal plant regarded as symbol of Rio Grand do Sul state in Brazil. The aerial part was reported to possess antioxidant and hepatoprotective property [39]. A new prenylated dibenzofuran, achyrofuran, derived from the plant significantly lowers blood glucose levels when administered orally at 20mg/kg q.d [40].

3.2 *Allium cepa* L. (onion): (Liliaceae)

This is the most widely cultivated species of the genus *Allium*. *A. cepa* is exclusively known from cultivation and its wild original form is not known. Onions contain phenolics and flavonoids that have potential anti-inflammatory, antidiabetic, anti-cholesterol, anticancer and antioxidant properties. Post-prandial glucose levels were significantly controlled when diabetic patients were given single oral dose of 50 g of onion juice [41]. A sulfur containing amino acid, S-methyl cysteine sulphoxide (SMCS) administered daily (200 mg/kg for 45 days) in alloxan induced diabetic rats significantly controlled the blood glucose and the lipid profile [42].

3.3 *Acrocomia mexicana* (Arecaceae)

This is a palm of the ancient Mesoamericans. Coyolosa, a new tetrahydropyrane was isolated from a methanol extract of the roots of the plant. The extract when administered i.p. at 2.5 to 40 mg/kg body weight, exhibits a dose-dependent significant blood sugar lowering effect in healthy and alloxan-induced diabetic mice [43].

3.4 *Aesculus hippocastanum* L. (Sapindaceae)

This is a large deciduous tree commonly known as horse-chestnut or conker tree. Five triterpene oligoglycosides named escins-Ia, Ib, IIa, IIb and IIIa were isolated from the seeds of the plant. These compounds exhibit hypoglycemic activity but the hypoglycemic activities of escins IIa and IIb were greater [44,45].

3.5 *Allium sativum* L. (Garlic): (Liliaceae)

This plant is a specie in the onion genus, *Allium*. It is native to central Asia but used for long as seasoning agent in the Mediterranean region, Asia, Africa and Europe. It is used traditionally to relieve cold, management of diabetes, cardiovascular benefits, reducing cholesterol levels, among other uses. Oral administration of the garlic extract significantly decreases serum glucose, total cholesterol, triglycerides, urea, uric acid, creatinine, AST and ALT levels, while increases serum insulin in diabetic rats but not in normal rats when compared with antidiabetic drug glibenclamide [46]. S-allyl cysteine sulphoxide (SACS), a sulphur-containing amino acid of *A. sativum* that is the precursor of allicin and garlic oil shows significant antidiabetic effects in alloxan diabetic rats [47].

3.6 *Annona squamosa* L. (Annonaceae)

This is a small well-branched tree or shrub which grows at lower altitudes. Oral administration of the aqueous extract of leaves to diabetic rats for 30 days significantly reduces the levels of blood glucose, lipids, but increased the activities of plasma insulin and antioxidant enzymes indicating the hypoglycemic effect, potential in preventing diabetes

complications and antioxidant effects [48]. Isolated juercetin-3-O-glucoside from the leaves exhibits anti-hyperglycemic and antioxidant activities in animals [49].

3.7 *Aralia elata* (Miq.) Seem (*Araliaceae*)

This is a deciduous woody tree also known as Japanese Angelica tree. Elatosides E which was isolated from the root cortex of the plant displays blood sugar lowering effect in an oral glucose tolerance test (OGTT) in rats. Similarly, elatosides G, H, and I exhibit potent hypoglycaemic activity [50]. Oleanolic acid and nine oleanolic acid glycosides isolated from the root cortex of this plant also shows hypoglycemic activity [51].

3.8 *Astragalus membranaceus* Bunge (*Fisch.*) (*Leguminosae*)

A new glycoside of cycloartane-type triterpene isolated from the root of the plant (AGS-IV) produces hypoglycemia and exerts a protective effect in neuropathy in STZ-induced diabetic rats [52].

3.9 *Balanites aegyptiaca* Delile (*Simarubiaceae*)

Aqueous extract of mesocarps of the fruits administered orally exhibits antidiabetic activity in STZ-induced diabetic mice. Two new steroidal saponins were isolated. Combination of the two new saponins isolated from the extract produces significant antidiabetic activity while the individual saponins shows no antidiabetic activity [53].

3.10 *Beta vulgaris* Var *Cicla* L. (*Chenopodiaceae*)

The plant extract displays the ability of preventing or at least retarding the development of some diabetic complications by inhibiting the increase in the non-enzymatic glycosylation of skin proteins and blood glucose [54]. Betavulgarosides II, III and IV isolated from the root of the plant produce hypoglycaemic effect in an OGTT in rats [55].

3.11 *Bidens pilosa* Sch. Bip. Var. *Radiata* (*Asteraceae*)

This (common name: Beggar-ticks, Cobbler's pegs) is a flowering plant which is native to the Americas but introduced in other regions, including Asia and the Pacific Island. It is considered a weed in some tropical regions but a source of food or medicine in some other parts of the world. Two known polyacetylenic glucosides, 2-beta-D-glucopyranosyloxyl-1-hydroxy-6(E)-tidecene-7, 9, 11-triylne (1) and 3-beta-Dglucopyranosyloxyl-1-hydroxy-6(E)-tetradecene-8, 10, 12- triylne (2), were isolated from the aerial part of the plant. A 3:2 mixture of glucosides 1 and 2 produce significant hypoglycemic effect in diabetic mice model [56].

3.12 *Bombax ceiba* L. *Malvaceae*

This is commonly known as cotton tree, like other trees in the genus. It is a tropical tree, native to Cape York and tropical Asia with a straight trunk and the leaves are deciduous. Shamimin, a C-flavonol glucoside from the plant, produces a significant blood glucose reduction in rats [57].

3.13 *Bumelia sartorum* Mart Sapotaceae

This plant is used in ethnomedicine especially Brazilian traditional medicine in diabetes and inflammatory disorders. Bassic acid, an unsaturated triterpene acid isolated from an ethanolic extract of the root bark exhibits hypoglycaemic effect in alloxan-induced diabetic rats. The hypoglycemic potential was also demonstrated *in vitro* using isolated rat diaphragm [58]. Assessment of the hypoglycemic effect of the plant extract rich in polyphenols and the possible mechanism of action was also made. Hypoglycemia is produced by the polyphenol rich extracts while sarco/endoplasmic reticulum Ca²⁺-ATPase (SERCA) inhibition may be one of the possible mechanisms involved in glucose decrease [59].

3.14 *Gymnema sylvestre* r. br. Ex schult (Asclepiadaceae)

This is a woody plant found in tropical forests of India and Africa and used in diabetes management. The hypoglycemic action of *Gymnema* leaves was first documented in the in 1930 [60]. The leaf extract was demonstrated to possess a significant antidiabetic and a hypolipidemic activity in alloxan induced and normal fasting rats in a 30-day chronic studies [61]. *G. sylvestre* crude extracts and its isolated compound, dihydroxy gymnemic triacetate, also exhibit hypoglycemic effect against streptozotocin induced diabetic rats [62].

3.15 *Leucaena leucocephala* (LMK) Dewit (Fabaceae)

This is small, fast-growing mimosoid tree native to southern Mexico and northern Central America but now naturalized throughout the tropics. The young pods are edible and eaten in Indonesia and Thailand. A study was conducted on antidiabetic effect of the fractions of methanol extract from *L. leucocephala* seeds using alloxan-induced rats. Result showed that *L. leucocephala* seeds has antidiabetic activities and their bioactive compounds constitute glycoside compounds with monosaccharide galactose clusters and many other saccharides [63].

4. OTHER POTENTIAL SOURCES OF ANTIDIABETIC AGENTS

Studies have shown that with chromium supplements there might be an improvement in glucose metabolism in individuals with diabetes, although the evidence for this effect remains weak [105]. Vanadyl sulfate, a salt of vanadium, is still in preliminary studies [106]. There is tentative research that thiamine may prevent some diabetic complications however more research is needed [107].

5. SUMMARY AND CONCLUSION

In the present review work, we have presented the merits of nature-based medicines and various drugs that have been developed from the natural sources. The advantages of natural-based drugs over synthetic counterparts (such as lesser side effects, efficacy, availability, lower cost, etc.) have been emphasized. Some of these natural medicines are better extracted and used in crude form as is the common practice in traditional settings. This is advantageous as it makes for holistic treatment. In addition, the combined effect of the constituent agents could be better than a single agent acting alone. It is necessary that some of the natural extracts especially plants extracts are processed and standardized, using modern tools, as herbal formulations for commercialization and use in clinical settings.

This is already obtainable in some countries. However, caution is to be exercised to identify possible drug herb interactions.

Besides the use of crude drugs from natural sources, this work has also presented the natural products as sources of some of the drugs approved for various clinical indications. This has been due to the untiring efforts of scientists over the years in the field of drug discovery from natural products. Mishra and Tiwari [32] have observed that there have been remarkable achievements in the field of 'natural products drug discovery' during last three decades and several compounds having profound biological activities have been searched out with the help of modern and sophisticated techniques.

Having seen the merits of natural products, we went further in presenting some of the natural sources of antidiabetic drugs including plants, animals, micro-organisms and other inorganic or organic sources. However, more emphasis was laid on the medicinal plants that have been experimentally investigated for antidiabetic potentials with their antidiabetic principles isolated and evaluated. Few of them are briefly described while the rest are summarized in Table 2. Other review works have also emphasized the importance of medicinal plants as sources of antidiabetic agents [108,109]. Various classes of phytoconstituents have been isolated including saponins, fatty acids, flavonoids, glucosides, amino acids, terpenes, amino acids, polypeptides and polysaccharides. Notwithstanding the numerous isolated compounds, only about 5–15% of nearly 250 000 higher plants and less than 1% of the microbial world have been explored so far chemically—the vast majority of these sources remains untapped [110].

Some of these agents have been demonstrated to exhibit antidiabetic activity through various mechanisms. For instance, several reports have shown that flavonoids, steroids/terpenoids, phenolic acids are bioactive antidiabetic principles [111-114]. Polysaccharides increase the level of serum insulin, reduce the blood glucose level and enhance tolerance to glucose [115]. Investigation into the detailed mechanism of action of some of the isolated constituents was not however reported. Moreover, at this point none of the isolated compounds as listed in Table 2 are clear antidiabetic drug candidates, but this is not the end of the story yet. Given the multi-stage process involved in drug discovery and development, it is hoped that further chemical, pharmacological and toxicological assessment of the isolated compounds could afford more potent and safer antidiabetic agents which would be better than the existing drugs.

In conclusion, given that majority of the world population rely on traditional medicine for the treatment of various diseases and given the enormity of drugs that have been developed from natural products, we advocate more emphasis on the use of natural products either in the form of standardized crude formulation or purified compounds. The conventional drugs and the herbal remedies could, after scientific investigation about potential drug-herb interactions, be used together in the management of chronic diseases such as diabetes. In the search for more potent and safer antidiabetic agents from natural sources, medicinal plants offer a chief source of lead compounds. These may serve as commercially significant entities themselves or may provide lead structures for the development of modified derivatives possessing enhanced activity and/or reduced toxicity. Therefore, more research effort is therefore needed to explore the vast array of natural sources of the drugs especially plants for the benefit of mankind.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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