

GLOBAL CURRENT TRENDS IN NATURAL PRODUCTS FOR DIABETES MANAGEMENT: A REVIEW

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ABSTRACT

Diabetes mellitus is a major health problem in the world. There is no cure for diabetes. It is, therefore, essential to practice effective methods of the diagnosis, treatment, and management of diabetes. With the increase in a number of newer drugs for diabetes, there is the possibility of a wide range of side effects that vary from one drug to another. Hence, the need to explore oral antidiabetic drugs of natural origin with minimal side effects is highly essential. This review provides a scientific perspective on the usage and research of natural and Indian traditional remedies in the management of diabetes while also providing insight into the advances in our understanding of diabetic pathology.

Keywords: Diabetes, Hyperglycemia, Diabetic complications, Medicinal plants

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INTRODUCTION

DM (Diabetes mellitus) is one of the leading health problems in the world. More than 366 million people are affected with this metabolic disorder, and the projected prevalence is estimated to be 522 million by 2030 [1]. The burden of DM is high in developed and developing countries. DM now affects 7 % of the world's adult population. Data from the literature suggests that 8.3 % of the total population of the United States has diabetes, and 79 million adults have pre-diabetes [2]. The content of this review has been taken from various journal archiving services such as PubMed, Science Direct, Springer, and Scopus. The search criteria were limited to recent research in natural products for the management of DM.

Types of diabetes

DM is caused to the defects in insulin secretion, insulin action or both. Insulin deficiency, in turn, leads to chronic hyperglycemia (very high blood glucose levels) with disturbances in carbohydrate, fat and protein metabolism. Insulin dependent (IDDM) is type-1 DM and Non-Insulin dependent (NIDDM) is type-2 DM. DM in humans is a result of metabolic disturbances due to the dietary intake of excess carbohydrate and lipid [3]. Type-1 diabetes is most likely to occur in relatives of affected persons. It is associated with the autoimmune destruction of pancreatic β which leads to complete deficiency of insulin secretion [4]. Type-2 diabetes is a chronic and progressive syndrome, caused by the combination of resistance to insulin action and impaired insulin secretion. This results in more than 90 % of cases [5]. Glucose homeostasis is maintained by the liver, which also accumulates hepatic lipids. Hepatic lipids are the important factor for insulin resistance and decreased insulin secretion [6]. Type-2 DM leads to gradual changes in glucose homeostasis. Insulin acts as the principal treatment for both the type of DM [7]. All the diabetic complication is caused by the oxidative stress mechanism [8]. Pre-diabetes is a condition in which blood glucose levels are higher than normal but not high enough to be diagnosed as diabetes (i.e., Fasting blood glucose ≥ 100 mg/dl and ≤ 126 mg/dl) [3].

Diabetes in developing countries

Regions with high potential to DM are Asia and Africa, where the rates could rise to 2-3 folds than the present rates [9]. The International Diabetes Federation (IDF) predicted that 40.9 million of Indian populations is affected by DM. This may increase to 69.9 million by the year 2025 [10]. Diabetes is a major risk factor for cardiovascular disease, which is widely increasing in China [11]. Type-1 diabetes is low in Japan, compared to other populations in the world [12]. The diabetic population in various countries

according to 2011 censuses is China-90 million, India-61.3 million, United States of America-23.7 million, Brazil-12.4 million, Bangladesh-8.4 million, Mexico-16.4million, Russia-14.1 million, Egypt-7.3 million and Indonesia-7.3 million. The expected diabetic population in 2030 is China-129.7 million, India-101.2 million, United States of America-29.6 million, Brazil-19.6 million, Bangladesh-16.8 million, Mexico-16.4 million, Russia-14.1 million, Egypt-12.4 million, Indonesia-11.8 million and Pakistan-11.4 million [13]. Diabetes is rapidly increasing at alarming rates. Compared to type-1 DM, there is an increase in the rate type-2 DM [14]. Obesity and overweight are the main complications of insulin resistance [15, 16].

Reasons for onset of diabetes

The factor for a cardiovascular and metabolic disorder is high caloric intake, physical inactivity, sedentary lifestyle, consumption of energy-rich diet, obesity, higher life span [16]. Adipose tissue is the major site for lipid storage, which plays an important part in normal metabolic homeostasis and in the formation of disease like type-2 diabetes [17]. Factors like leptin tumor necrosis factor- α (TNF- α) and plasminogen activator inhibitor type-1 (PAI-1) are considered to be associated with the production of the pathophysiology of obesity [18, 19].

Mechanism

In DM insulin stimulates glucose transporter in skeletal muscle and fat; it also suppresses hepatic glucose production. These mechanisms affect the β cells of the pancreas by producing sufficient amounts of insulin to balance peripheral insulin resistance [20]. DM is a major risk factor for cardiovascular disease. Recent evidence proves that diabetes is related to a vascular complication, which could be due to oxidative stress. Increased production of reactive oxygen species (ROS) is formed due to the coupling of oxidative stress [21]. This also results in imbalance production of the body, antioxidant defense system. Reduced EDR (Endothelium Dependent Relaxation) and enhanced receptor-mediated contractions are the vascular complication which is associated with DM [22]. Oxidative stress is formed by hyperglycemia which is due to increase mitochondrial production of the superoxide anion, non-enzymatic glycation of proteins and glucose antioxidant. Stress-sensitive signaling pathways are activated by oxidative stress [23].

Glucose homeostasis is maintained by two primary hormones namely, insulin and glucagon, which tightly control blood glucose concentrations following ingestion of a carbohydrate-rich meal. Starch molecules which are digested in the upper gastrointestinal tract are hydrolyzed into monosaccharide and later absorbed into

the blood stream through various glucose transporters (GLUT). GLUT-2 transports glucose into pancreatic β cells of the islets of Langerhans. Insulin is secreted by the oxidation of glucose through a mechanism of adenosine triphosphate (ATP)-sensitive potassium channels, membrane depolarization followed by voltage-dependent calcium influx and subsequent exocytosis of insulin granules [24].

Insulin reduces blood glucose level by (i) translocation of GLUT-4 vesicles to the plasma membrane; insulin enhances the uptake of glucose in peripheral tissues, (ii) helps utilization or storage of glucose in the liver and (iii) promoting lipogenesis and inhibiting lipolysis in (WAT) white adipose tissues [25]. When blood glucose concentration declines, glucagon is secreted from α -cells of pancreatic islets.

Glucagon raises blood glucose level by (i) enhancing glucose production and releasing it in a liver and (ii) releasing Free Fatty Acids (FFAs) and increasing lipolysis from adipose tissue. This can affect glucose homeostasis by targeting glucose-regulating processes in the pancreas, liver, skeletal muscle or adipose tissue [26].

Diabetic complications

At the early stage of DM, biomarkers of oxidative stress are elevated in the liver [27]. Diabetes could cause cataract at a younger age [28]. In the end stage of diabetes, patients will be influenced by diabetic nephropathy which is a worldwide renal disease. Diabetic nephropathy is a defect in the glomerular filtration rate; characterized by glomerular hyperfiltration, increase urinary albumin excretion, glomerular, tubular epithelial hypertrophy and mesangial expansion with the accumulation of Extracellular Matrix Proteins (EXM) and increased basement membrane thickness [29, 30]. Initial treatment for early stage diabetic patients is to change the lifestyle [31].

Organs affected

DM leads to defects in insulin production and release of insulin or even improper action of insulin in various organs. The lens of the eye is one of the highly affected body parts in DM. This is because the extracellular glucose diffuses into the lens and it cannot be controlled by insulin [32]. Diabetic hyperglycemia can cause aggravated ischemic brain damages [25]. Type-2 DM leads to cognitive impairment [33–35]. DM is a harmful disorder that can lead to atherosclerosis, renal, nervous system and ocular damages [36]. DM can also result in significant morbidity and mortality with micro and macrovascular complication [37].

Synthetic drug used clinically

Several classes of approved oral anti-diabetic drugs are available for the treatment and management of DM. Demerits of most drugs are undesirable side effects, drug interaction, and cost. Currently, several researchers are involved in identifying novel targets that can improve disorders of DM. Thus, glucocorticoid (GCs) are the potent antagonists of insulin action and promoters of gluconeogenesis in the liver, leading to increasing in blood glucose concentration [38]. Insulin can be directly stimulated by oral hypoglycemic agents that are released in blood concentration [38]. Insulin can be directly stimulated by oral hypoglycemic agents that are released from β -cells such as sulfonylurea-based drugs. However, this insulin secretion from islets is enough to overcome peripheral insulin resistance and normalize blood glucose level in type-2 patients [7]. The important classes of oral hypoglycemic drugs are thiazolidinediones (TZDs), biguanides, α -glucosidase inhibitor and sulphanyl ureas [39]. The TZDs are used commonly, but they cause undesirable side effects like weight gain, fluid retention and heart failure. The biguanide metformin is not a complete therapy on its own because it mainly acts in the liver rather than muscle and this does not cause weight gain [40]. Some recently approved drugs such as dipeptidyl peptidase-IV inhibitors, glucagon like peptide-1 agonists and amylin analogs are also used in the treatment of diabetes [41]. One of the therapeutic approaches to decrease postprandial hyperglycemia is by absorption of glucose via inhibition of carbohydrate-hydrolyzing enzymes such as glucosidase in the intestine [42].

Complication

The absence of controlling normal blood glucose levels is the main disadvantage of sulfonylurea-based drugs [43, 44]. Anti-diabetic drugs can lead to various toxicities which are due to the continuous use of long-term therapy. Moreover, the high cost of these drugs is another issue for the patients in developed and developing countries. Hence, to reduce the side effect now drug discovery is focusing on natural plant sources. Recent research involves in finding of new compounds with therapeutic properties from chemical and pharmacological studies of medicinal plants [45].

Need for natural remedies

Natural products and their derivatives have been a successful source of bioactive molecules in medicines much before the discovery of modern therapeutics in the post-genomic era. Traditional medicine from natural products is being used in treating human diseases for many years, and it is considered effective and safe [46]. Flavonoids are one of the most studied natural products which are found predominantly in several comestible fruits as part of daily food consumption [47]. Most of the studies on herbal and natural products have reported for the better anti-diabetic effects with lower cost and fewer side effects than synthetic drugs. Most anti-diabetic herbs can improve β -cell function and increase the secretion of insulin from the islets of Langerhans, which have high antioxidant power [48].

Consumption of fruits and vegetables can decrease the incidence of type-2 diabetes which is rich in polyphenol [49]. Plants contain biologically active substances such as hypoglycemic, hypolipidemic and antioxidant agents, which play an important role in the discovery of new therapeutic [50]. India is composed of about 45,000 plant species, and most of them have medicinal properties. Out of them, many herbal drugs reported having anti-diabetic activity in the Ayurvedic medicine of India [51].

Flavonoids are capable of interacting with more than one target. The flavonoids or bioflavonoids are consisting of about 4000 compounds that occur in both flowering and non-flowering plants [52]. Recent investigations prove the anti-diabetic properties of flavonoids. In type-2 diabetes flavonoids can act against the progression of insulin resistance by reducing oxidative stress-induced tissue damage which therefore preserves the function of β -cells [53]. It is a part of the human diet which contains various properties including antioxidant, anti-inflammatory, antibacterial, anti-tumor, anti-allergic and anti-mutagenic properties [54, 55]. It is also proved to have beneficial effects in cardiovascular disease by overproduction of reactive oxygen species [56]. Flavonoids are also described as glucosidase inhibitors. Glucosidase inhibitors are the active agents for diabetes therapy [57]. Flavones have the presence of hydroxyl groups, especially in C-30, C-40 and C-7, and also the double bond between C-2 and C-3, which could increase the anti-diabetic activity [47].

Flavonoids represent a large class of at least 6,000 phenolic compounds found in fruits, vegetables, herbs, cocoa, chocolate, tea, soy, red wine and other plant food and beverage products. Structurally flavonoids consist of two aromatic rings (A and B chain) which are linked by 3 carbon chains that form an oxygenated heterocyclic ring (C ring) [58]. Flavonoids are bioactive phenols with low molecular weight and play a major role in cell synthesis [59]. Medicinal plants are widely used by the population of developing countries as an alternative therapy. In India, hundreds of plants are used traditionally for the management of DM. Unfortunately, only a few of such Indian medicinal plants have received scientific scrutiny [60].

Common Indian medicinal plants and their metabolites with antidiabetic activity

In recent years, researchers are focusing on polyphenolic compounds, due to their beneficial properties in cardiovascular disease. Polyphenolic compounds have pharmacological effects such as anti-inflammatory, antioxidant, antiviral and anticarcinogenic agents [47]. Quercetin is widely found flavonoid in the human diet [56]. Quercetin helps in glucose absorption, which is investigated and proved by National Institutes of Health Clinical Center [47].

Polygonatum odoratum consist of a dried rhizome which is called as *Rhizoma Polygonatti odorati*. This is highly cultivated in the southern area of china, which is known as Yu Zhu. It is a well-known herbal medicine among the Chinese which is commonly used for promoting secretion of fluid, removing dryness and quenching thirst in China. This is traditionally used as the treatment for DM. As a treatment for DM, it is administered orally as a single herb or with other medicinal plants after decoction in water. It is also cooked along with meats or porridges as health foods, which is widely practiced in southern China [61].

Drug discovery is focusing on 'new anti-diabetic drugs' with a lower price and higher safety and efficacy, which could be a novel treatment for DM by the combination of antioxidant compounds [48, 62]. Recently, it has been reported that the activity of glucose-induced insulin release from pancreatic β -cells by anthocyanidins and anthocyanins. The dimethoxy ether and the glycoside of leucopelargonidin are obtained from the bark of the Indian banyan tree. *Ficus bengalensis* is possessed significant hypolipidemic, hypoglycemic and serum insulin-raising effects in moderate diabetic rats with close similarities to the effects of glibenclamide [49]. Fasting blood glucose levels can be reduced by TFP (*Polygona tumodratum*). This can also prevent and reduce hyperglycemia in alloxan and high-fat-diet-induced type-2 diabetic rats [61]. Several experimental trials prove that the consumption of flavonoid-rich foods such as tea and onion can increase the plasma levels in the diabetic patient. A study from Finland has recently demonstrated that the intakes of flavonoids like quercetin and myricetin are inversely associated with risk of type-2 DM [63].

Medicinal plants

We have listed few medicinal plants used traditionally in Indian Ayurvedic medicine for the treatment and management of DM. The selection criteria include (i) use in Indian Ayurvedic medicine (ii) ethnopharmacological significance (iii) bioactive phytochemicals with antidiabetic potential and (iv) commercial availability.

Eugenia jambolana

Anthocyanins (ACs) are commonly found in various fruits, vegetables, flowers and grains and to some extent in leaves, stems, and roots. It belongs to a group of phenolic compounds. *Eugenia jambolana* is commonly known as Indian Blackberry or Jamun. Chemopreventive potential of ACs, anthocyanidins (ACdn) and polyphenolics are extracted from fruit pulp of this plant. The pulp of Jamun fruit consists of major ACs namely cyaniding 3,5-diglucoiside (Cy3,5), dolphin idin-3,5-diglucoiside (Dp3,5), malvidin-3,5-diglucoiside (Mv3,5), petunidin-3,5-diglucoiside (Pt3,5) and peonidin-3,5-diglucoiside (Pe3,5). This plant is held against the treatment of cancer [64].

Syzygium alternifolium

Syzygium alternifolium (SA) are locally termed as Mogi or Adavinerudu, which comes under the plant family Myrtaceae. Laboratory study has reported that seeds of SA have the activity of anti-hyperglycemic. Fever and skin related disease can be treated by SA. Aqueous extract of SA seeds can cure alloxan-induced diabetic rats at the dosage of 750 mg/kg b. w, which possesses anti-hyperglycemic activity. Maximum activity of anti-hyperglycemic (83 %) could be produced from the aqueous extract of SA seeds. Drugs from the extracted seeds can normalize the function of DM without causing hypoglycemia. Its activity is observed even from the first hour of treatment. The anti-hyperglycemic activity could form even at a lower dose (50 mg/kg b. w.) than the aqueous extract of other fractions and glibenclamide. During treatment, no hypoglycemic condition was observed in the treated diabetic rats [65].

Curcuma longa

Curcuma longa has the activity like antibacterial, hypolipidemic, anti-diabetic, anti-inflammatory, antioxidant and anticancer. Quercetin is reported to possess the property like reduction of blood glucose, promotion of Langerhans islets regeneration and increasing insulin release which demonstrated its antidiabetic activity both *in vitro* and *in vivo*. The *C. longa* consists of an active ingredient like diferuloylmethane or 1, 6-heptadiene-3, 5-dione-1, 7-bis (4-

hydroxy-3-methoxyphenyl). In India and China, *C. longa* is used as a traditional medicine over a long period [48].

Aloe vera

The extracted gel from *Aloe vera* is most commonly used as healthcare product [48]. It is also reported having beneficial therapeutic effects of DM [66]. *A. vera* gel consists of active ingredients like minerals, amino acids, polyphenols, and polysaccharides. The major polysaccharides in *A. vera* are glucose and mannose [67]. *A. vera* has been reported to possess the hypoglycemic effects [66]. Anti-diabetic activity of *A. vera* is observed by oral administration of its juice in a tablespoon twice a day for at least 2 w. The continuous administration of *A. vera* juice is reported to reduce the blood sugar and triglyceride level, but cholesterol levels are not affected. The results prove the potential use of *A. vera* juice as an anti-diabetic agent [68].

Hibiscus sabdariffa

The genus Hibiscus (Malvaceae) includes more than 300 species of perennial or annual herbs, shrubs or tree. *Hibiscus sabdariffa* L. (Hs) are found in tropical and subtropical zones of both hemispheres. They composed of three types namely red, dark red and green which are grown for its fibers and calyces. The commonly used type is red calyces. Extract of Hibiscus inhibits the activity of α -amylase, blocking sugars and starch absorption, which helps to reduce weight; this has been demonstrated by *in vitro* and *in vivo* studies [69]. Study on Hs has reported the anti-spermatogenic, androgenic, anti-tumor and anticonvulsant activities of the flowers. Heart disorders can also be treated by this flower. Anti-diabetic activity among DM in rural population is also reported in *Hibiscus rosasinensis* [70].

In India, Africa and Mexico, the leaves of Hs are used traditionally for their diuretic, choleric, febrifugal and hypotensive effects. In China the seeds of Hs are used for making oil and the plant is invoked as traditional medicine. In Egypt, cardiac and nerve disease is treated by the leaves of Hs. This can enhance the production of urine (diuresis) and help in lowering the body temperature. Powdered leaves and seeds are used in meals, which are widely practiced in West Africa. It is also used in pharmaceutical and food industries. In North Africa, abscesses and external wounds are treated by the leaf pulp and the calyces are used as the treatment of sore throats and coughs, as well as genital problems. This also helps in decreasing the viscosity of the blood and stimulating intestinal peristalsis. In Senegal, it is employed to hypotensive. It is utilized to relieve pain in indigestion and urination. The roots are believed to have emollient and stomachic properties, in Brazil. In the folk medicine of China, high blood pressure and liver disorders are treated by Hs plant extract. In Nigeria, the decoration of the seeds is traditionally used for the poor letdown, maternal mortality and to increase or induce lactation in cases of inadequate milk production. Sour hibiscus tea is reported as a traditional treatment for hypertension in Iran [69].

Polyphenol extract of Hs was studied in type-2 diabetic rat models which prove its protective effects. It reduces hyperinsulinemia and hyperglycemia at the dosage of 200 mg/kg b.w., which demonstrated its anti-insulin properties. It contributes to reducing serum triacylglycerol, cholesterol and the ratio of low-density lipoprotein (LDL) and high-density lipoprotein (HDL). It also decreases plasma advanced glycation end products formation and lipid peroxidation [69].

Bacopa monnieri

Bacopa monnieri is used along with a kudzu relieving hangover, fever and flu. It also improves liver function, enhancing the detoxification process, regulating cardiac functions and aiding weight loss [71]. This plant is reported to manage DM [72].

Embilica officinalis

Embilica officinalis lies in the family Euphorbiaceae. In traditional Indian medicine, all the parts of plants, including fruits, seed, leaves, root, bark and flower are used for various herbal preparations. Leaves of *E. officinalis* is has been used for antipyretic and anti-

inflammatory treatments. A study on the antioxidant potential and hypoglycemic effects of *E. officinalis* is reported producing anti-diabetic action against streptozotocin-induced diabetic rats. This on continuing treatment for a period of 45 d produces a significant decrease in blood levels in diabetic rats, which is comparable to that of standard and diabetic control group. *E. officinalis* leaves are proved to be used as a natural alternative remedy for the treatment of diabetes [73]. In Ayurveda medicine, *E. officinalis* is used to promote health and longevity by increasing defense against disease [54, 62]. *E. officinalis* consist of vitamin C, which is used as scavenging free radicals [49]. *E. officinalis* is reported reducing the fasting serum glucose level compared to the baseline level. This also improves oral glucose tolerance in type-2 diabetic rats, but it does not change the total cholesterol level. *E. officinalis* is proved to have anti-diabetic and antioxidant properties on treatment for type-2 diabetic rats and has not formed any toxic effect [74].

Momordica charantia

Momordica charantia belongs to the family Cucurbitaceae, which is commonly known as kugua, karela, bitter gourd or bitter melon. It is a tropical plant known to have hypoglycemic which could be used for diabetic studies in herbal medicine [54]. It can be utilized to treat infections like antiviral, antibacterial and anthelmintic [62]. It has anti-fertility effects on male animals [56, 75]. Cucurbitaceae (*M. charantia* L) is used as a traditional medicine by the Chinese people. Pharmacological studies have possessed its anti-diabetic, anti-tumor and antiviral activities. The crude extract of *M. charantia* has the property of lowering the blood glucose levels. The active ingredients of *M. charantia* are called as triterpenoids, which has reported showing anti-diabetic activity [76].

Anona squamosa

Anona squamosa belongs to a family Annonaceae. It has the properties of insecticide, anti-ovulatory and abortifacient. This is generally used as an alternative therapy in many countries. In Brazil, the extract of *A. squamosa* seed is used to promote abortion [77].

Bauhinia forficata

Bauhinia forficata (Brazilian Orchid tree) is a type of evergreen tree, which is commonly used as a medicine for DM. Phytochemicals experiments helped to isolate a compound from *B. forficata* roots, bark and stems, which could be used against DM. Kaempferol and quercetin O-glycosides, are the compounds which are separated from this tree. Currently, drug discovery is going on in the leaf extract of kaempferitrin to find a novel drug for DM [78]. In Brazil, this is used as an herbal drug for the treatment of diabetes where it is known as "cow hoof" [52].

Allium sativum

The common name of *Allium sativum* is garlic, which has been used as a medicinal plant since ancient times. They are highly cultivated in Iran. Garlic is used for the therapeutic purpose in the form of garlic oil, garlic powder and pills. This is reported to lower the blood pressure and helps in improving lipid profile [79].

Centaurea cyanus

It is a common class of phenolic compounds, which consist of 8000 flavonoids and 500 anthocyanins. This has the protective effects like antioxidant, anti-allergic, anti-diabetic, anti-inflammatory, antiviral, anti-proliferative, anti-mutagenic, anti-microbial, anti-carcinogenic, microcirculation improvement, protection from cardiovascular damage, allergy protection, peripheral capillary fragility prevention and vision improvement [49].

Morus alba

The leaves and root bark of the white mulberry tree (*Morus alba* L.) is said to be the source of phytotherapeutics. They are typically used for the treatment of type-2 diabetes. Antidiabetic activity of mulberry extract is proved by *in vivo* animals and human studies [80].

Averrhoa carambola

In Brazil, *Averrhoa carambola* is used as the generic medicine to balance glucose levels [81].

Trigonella foenum

Trigonella foenum is an annual herb, which belongs to the family Leguminosae; this grows abundantly in the Mediterranean region. Fenugreek seeds are employed in traditional Indian and Chinese medicine as a treatment for gastric disorders. Pharmacological studies have proved its properties like anti-diabetic, anti-inflammatory, antibacterial, hypocholesterolemic effects, hypolipidemic and neuroprotective potential. Seeds of *T. foenum* consist of secondary metabolites namely: polysaccharides, flavonoids, steroidal saponins and alkaloids [82–88]. Its seed is traditionally used in the treatment of type-2 DM in India, Egypt, Asia, Southern Europe and North Africa. Their seeds are certified as a generally recognized as safe (GRAS) by the US Food and Drug Administration (US FDA). The seeds are traditionally reported regulating hormones in the male. In India, extracts of this seed along with jaggery is given to females after the childbirth, which enhances the muscle strength. Their seed is reported to form lean body mass and helps in lowering cholesterol [84–88]. *T. foenum* extract is used to reduce the fat content in the body [85]. Their seeds are considered to have rich steroidal compounds [89,90]. The extracted gum is reported to have prebiotic effects which are used in animal husbandry as nutritional supplements and as a stabilizer for food industry [84]. Egypt, the seeds are used for bread making, herbal tea and also eaten after germination [85]. Their seeds are considered as Ayurvedic medicine, Traditional Chinese, and Arabic medicine. Their seeds are used as a galactagogue which is a milk producing agent that helps the nursing mothers to increase breast milk. Experiments on animal models have reported that the seed of *Trigonella foenum* is known to reduce serum glucose and helps in improving the glucose tolerance [87].

Terminalia bellirica

Terminalia bellirica has bio-actives which possess antibacterial, antiviral and anti-inflammatory properties. They are the popular Ayurvedic formulation. Some experimental studies on Triphala and *T. bellirica* are reported to reduce the LDL oxidation [91].

Murraya koenigii

Murraya koenigii is used as traditional Indian medicine and also in Ayurveda and Siddha system [92,93]. This belongs to the family Rutaceae, which is widely distributed in southern Asia [93, 94]. Leaves, bark and roots of this plant are used in the treatment of dyspepsia, dysentery, chronic fever, mental disorder, diarrhea, nausea, and diarrhea. The boiled leaves are recommended for the treatment of hiccups and hoarseness. Leaves are applied externally to treat eruptions [92]. The leaves of this plant which is termed as curry leaves have been used as herbs in South Indian food [94]. Leaves are used in the treatment of piles, vomiting, itching, fresh cuts, inflammation, dysentery, and dropsy. *M. koenigii* is reported forming hypolipidemic activity. It is also suggested for treating a mild form of diabetes. Their leaves are rich in pharmacological agents like carbazole, alkaloids, flavonoids, furan coumarins, terpenoid and tannins [95]. This is also used as an analgesic, anesthetic agent and to cure eczema, rheumatism, and dropsy. Juice of *M. koenigii* is used to relieve the pain in kidney. They are reported to have anti-oxidative, anti-tumor, anti-mutagenic and anti-inflammatory properties [93, 96]. In Ayurvedic medicine, the extract of the plant is used for the treatment of hysteria, hypertension, cough, hepatitis, rheumatism, skin eruption and poisonous bites. People use its stem for cleaning the teeth which help in strengthening the gums. The extract of this leaf is reported to improve the renal function [93].

Urtica pilulifera

Urtica pilulifera belong to the family Urticaceae, which is found widely in Palestinian and Sinai areas. Leaves of *U. pilulifera* are used for making tea, which also traditionally used for blood purification and to maintain hemostatic. This plant is reported to have the properties like a diuretic, antiasthmatic, anti-inflammatory, hypoglycemic and hemostatic. The extract of this plant is used in treating the symptoms caused by lower urinary tract infection. *U. pilulifera* is reported to have non-toxic, mutagenic and embryogenic

effects. An experimental study on streptozotocin-induced type-2 diabetic rats has possessed pancreatic oxidative stress and inflammation in high-fat diet [97]. *U. diocia* and *U. urens* are used in the treatment of hyperthyroidism, eczema, hemorrhoids, bronchitis, cancer and rheumatism. In folk medicine, *U. urens* is used as a traditional medicine in Turkey [98].

Urtica diocia

Urtica diocia is used against DM, which is also proved through pharmacological screening [98]. *U. diocia* is used by ancient Egyptians as a relief for arthritis and lumbago. This plant is also used as a medicine for rheumatism and muscular paralysis. Leaf extract of this plant is considered to have the anti-inflammatory property. The juice of these leaves is known to decrease body weight and systolic blood pressure. The extract of this plant is reported to have antioxidant properties in rat [99]. This species is cultivated commercially for the pharmaceutical purpose [100].

Cichorium intybus

Cichorium intybus is widely grown in northwestern Europe. The roots of this plant are considered to have the rich source of dietary fiber inulin. In France and Japan, the roots are used for the preparation of coffee, as there is no caffeine in it. The inulin produced from it is a good replacement of dietary fat, which will help to reduce calorie intake [101,102].

Ocimum garatissimum

Ocimum garatissimum is mainly originated from Africa. The extract of this plant is reported to have antioxidant [103] and anti-diabetic activity [104, 105]. A study on healthy and diabetic mice has possessed the hypoglycemic effect of *O. garatissimum* [104].

Other medicinal plants

Acacia nilotica belongs to the family Leguminosae. This has been observed to possess antibacterial, antioxidant and antidiabetic properties. People use its branches as tooth stick for cleansing the teeth [106].

Ajuga bracteosa belongs to the family Amiaceae. This has the properties like anticancer, anti-malaria, antimicrobial, antidiabetic, antioxidant, diuretic and stimulant users. The dried parts of the plant are used for ulcer, colic and jaundice [107].

Bombax ceiba belongs to the family Malvaceae. The properties found in this plants are anti-microbial, antioxidant, anti-inflammatory, anti-obesity and anti-diabetic. Buds of this flower are used as the treatment for digestive problems [108, 109].

Calotropis procera is under the family Asclepiadaceae. This has the properties like anticancer, antifeedant, anti-fertility, antimicrobial, antioxidant, anti-inflammatory, anti-diabetic and hemolytic uses. The leaves are warmed and tied over the wounds for quick healing. The latex of stem and leaves are used to remove worms from the teeth and to treat skin disease [110].

Carissa opacais are used as an antioxidant, antimicrobial, antidiabetic and antitumor agent. They belong to the family Apocynaceae. Hepatitis and jaundice can be treated by the extraction. Fruits are used as a digestive stimulant [103].

Cassia fistula belongs to the family Leguminosae. This has the properties like abortifacient, anti-allergenic, anti-diabetic, anti-inflammatory, antioxidant, hypoglycemic and astringent. The pulp of the fruit is used against constipation. Leaves are used as fodder; dried branches are used as fuels, and the pulp of the fruits is also used to relieve constipation in cattle [111].

Cuscuta reflexa belongs to the family Convolvulaceae. The whole plant is used as antioxidant, antimicrobial, antidiabetic, analgesic, anti-fertility, anti-lice and anti-anemia. They are also used to treat skin disease [112].

Clematis grata comes under the family Ranunculaceae. The extract of this plant is the rich source of antioxidant, antimicrobial, antidiabetic and expectorant agent. The leaves are chopped and smelled, which is the treatment of nausea [103, 113].

Cynodon dactylon belongs to the family Poaceae. They are the rich source of anti-diabetic, antioxidant, and immune modulator, diuretic and anti-emetic. Aerial parts are made as paste, and it is applied on skin infection, injuries and eczema [114].

Cyperus kyllingia are proved to have the anti-diabetic properties. The roots showed significant anti-diabetic activity on oral administration of 750 mg/kg b.w. of cured root and 120 mg/kg b.w. of root extract [115].

Cyperus iria comes under the family Cyperaceae. They are used as antioxidant, antibacterial and Antidiabetic agent [103].

Cyperus rotundus belongs to the family Cyperaceae. They have properties like anti-diabetic, anti-diarrhoeal, cytoprotective, antimutagenic, antioxidant, anti-malaria, anti-inflammatory, antipyretic and analgesic agent. Stomach diseases can be cured by the rhizome of this plant [116].

Dicliptera roxburghianna comes under the family name Acanthaceae. They are reported to have the property of antioxidant, antimicrobial and anti-diabetic. Extract of the plant is used to avoid sun stroke in buffaloes [117, 118].

Eruca sativa belongs to the family Brassicaceae. Activities observed from the extract of this plant are antitumor, antidiabetic, antihypertensive, antioxidant and antibacterial. Extract of this plant is used as a blood purifier, oil for cooking, massage and remove dandruff in hair [119,120].

Flacourtia indica comes under the family Flacourtiaceae. They are used as antioxidant, antimicrobial and anti-diabetic agents. Fruits of this plant are used against diabetes [121].

Fumaria indica belong to the family Fumariaceae. The properties found in this plant are antioxidant, antimicrobial, antidiabetic and analgesic [122–125].

Galium aparine has the family name of Rubiaceae. This has the properties like antioxidant, antimicrobial and anti-diabetic. Their leaves are used in the treatment of jaundice. A paste of the leaves is used as the antiseptic which is externally applied on wounds [125].

Hedera nepalensis belongs to the family Araliaceae. The various properties found in this species are antipyretic and anti-diabetic. Juice from the leaves is used as anti-diabetic agent [126].

Ipomoea purpurea comes in the family name of Convolvulaceae. They are used as the antimicrobial, antioxidant and antidiabetic agent. They are used in the treatment of bronchitis [103].

Linum usitatissimum comes under the family name Linaceae. They consist of various properties like antimicrobial, antioxidant, antidiabetic, anti-hyperlipidemic, antioxidant, antidiabetic, anti-arthritis, anti-asthmatic, anti-allergic, anti-inflammatory and also used for heart disease [127].

Mallotus philippensis belongs to the family Euphorbiaceae. Anti-diabetic, antioxidant, are antimicrobial are the properties that are found in this plant. The crushed fruits are used orally to treat bloody diarrhea [128, 129].

Malvastrum coromandelianum comes under the family name of Malvaceae. This has properties like anti-diabetic, antioxidant and antimicrobial. Crushed leaves are used to treat DM. Seeds are used for curing leprosy [104].

Mentha longifolia belong to the family Lamiaceae. The various uses of this plant are anti-diabetic, antioxidant and anti-microbial activities. This herb is used in treating cholera and digestive problems [103].

Prunella vulgaris belongs to the family Lamiaceae. The various properties of this plant are antioxidant, antiviral, immunomodulatory, proliferative and anti-diabetic. The seeds can be used in the treatment of antipyretic, laxative and diuretic. This helps in treating inflammation, disease of the heart, difficulty in breathing and weakness of eyesight. This is also useful in curing fever and cough [130].

CONCLUSION

The rate of diabetes is increasing due to changing food habits and increased uses of synthetic food products. Therefore, a reversion to increased usage of naturally obtained food products and food supplements would increase the resistance of the population to both diabetes incidence and diabetic complications.

CONFLICTS OF INTERESTS

The authors declare no conflicts of interest.

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