A Perspective Review On Diabetes Mellitus And The Potential Antidiabetic Activity Of Medicinal Plants

Gargantiel, Maryglen, Faller, Erwin M.

Abstract : Plants have provided man with all his needs in terms of shelter, clothing, food, flavors and fragrances as not the smallest amount, medicines [1]. According to the estimation of the World Health Organization, 80% of the population in developing countries still depends on folk medicine for prevention or treatment of illnesses [2]. Chronic diseases have resulted from the radical change in the lifestyle choices of people over the century. [3] The use of herbal and traditional medicines may be a common practice because the option of traditional medicines within the treatment of lifestyle associated diseases (such as hypertension and diabetes mellitus) are found to be more practical due to its cheaper cost [4]. Diabetes mellitus is a public health problem which leads to serious complications over time [5]. Diabetes mellitus (DM), both insulin- dependent DM (IDDM) and non-insulin dependent DM (NIDDM) may be a common and high disorder throughout the planet. The use of traditional plant remedies has been practiced throughout the world for diabetes mellitus [6]. As mentioned in the review article of Bahare et. al in 2019[7] traditional knowledge of antidiabetic Asian plants were found in different countries in Southeast Asia like Iran; Malaysia; Philippines; Saudi Arabia; Sri Lanka and India, to name a few. A compiled review on the information about medicinal plants used for the treatment of diabetes mellitus was done comprehensively and was proven that plants are a potential source of anti-diabetic drugs through ethnobotanical information reports of several plants that may possess anti-diabetic potential. The present review aims to examine some of the important plant species and their constituents, showing their beneficial effects such as the potential antidiabetic activity that can be used in the management of diabetes.

Index Terms : Diabetes mellitus, fasting blood glucose, glibenclamide, hypoglycemic, insulin, medicinal plants, pancreatic β- cells

1 INTRODUCTION

According to the Diabetes care organization, the prevalence of diabetes for all age groups in the world was estimated at 2.8% in 2000 and 4.4% by 2030[8]. On long standing it results in many micro and macro vascular complications. Diabetes causes microvascular complications that bring damage to the kidneys, eyes, and the brain. In type-1 diabetes the primary signs of those complications may develop during adolescence, particularly if insulin is insufficient within the body. Similar complications may occur in the later life of patients with type-2 diabetes mellitus (T2DM) [3]. The increase in prevalence of type 2 diabetes has been greatest in low- and middle-income countries in the past few decades [14]. Sadly, T2DM is increasing at an alarming rate globally and therefore the Philippines is not any exception to the present as diabetes has affected around 4.6% (3.9 million) of Filipino population and the number is presumed to be doubled by 2030. (4) Proper planning and apportioning of resources should result from assessing the projected effects of the widespread presence of diabetes from the number of people it has affected then until now [6]. Currently, beside insulin, the foremost widely used medication for diabetes are oral hypoglycemic drugs including insulin sensitizers (biguanides, thiazolidinediones), insulin secretagogues (sulfonylureas, meglitinides), α-glucosidase inhibitors, incretin agonists and dipeptidyl peptidase-4 inhibitors [9]. Although early onset complications of diabetes can be controlled by oral hypoglycemic drugs/insulin treatment, serious late onsetcomplications emerge in many patients [10].Additionally, side effects such as abdominal pain, fluid retention in body extremities, and hypoglycemia come with the clinical use of some of the current drugs [9]. Therefore, investigation for new antidiabetic agents with more effectiveness and less side effects are still in pursuit.In diabetes, hyperglycemia generates reactive oxygen species (ROS), which successively cause lipid peroxidation and membrane damage and these free radicals play a crucial role within the production of secondary complications in diabetes mellitus (kidney, eye, blood vessel, and nerve damage) [11,12]. Antioxidants have been shown to prevent the destruction of ß- cells by inhibiting the peroxidation chain reaction and thus they may provide protection against the development of diabetes [13]. According to De Gruyter (2019) there are numerous studies that exhibit the potential of antioxidants in effectively neutralizing free radicals. Furthermore, it is also effective against diabetic complications [14].

2LITERATURE REVIEW

History: How Diabetes Started?

Prevalence of Diabetes as a disease approximately started since1550BC when an Egyptian doctor noticed an unknown rare disease that causes the patient to lose weight rapidly and urinate frequently. That was considered to be the first definition of diabetes milletus. In (30-90AC), Aristaeus, a Greek Physician coined the name Diabetes [15,16]. The symptoms were then recorded such as constant thirst (polydipsia), loss of weight and excessive urination (polyuria). This ‘diabetes’, which means ‘a flowing through’ condition has been understood as such, but during the Middle Ages this term was rarely mentioned. Avicenna, a famous Arabian Physician made reference to the disease. Complications and progression of the disease was described in details [17]. In order to establish the disease of the patient the color and odor of the urine were also examined. Qualitatively to know the characteristics of this urine output, some physicians even tasted their patients’ urine, and this seemingly led to the second name- mellitus, meaning ‘honey’ in Latin [18]. In the early 19th Century, in trying to detect excess sugar in the urine, chemical tests have been developed. Moses Barron, an American scientist in 1920 linked the Langerhans cells with the basis of diabetes mellitus. [19]. Barron in his study made mention about Frederick Banting, a doctor who conducted critical experiments relating the pancreas and diabetes. He revealed that an essential hormone named insulin, was produced in a structure named after the ‘islands’ of cells which was described by Langerhans. A Nobel Prize was awarded to Banting and one of his colleagues recognizing their achievement for this discovery. Development

and treatment of this disease has advanced drastically throughout the 20th century. Challenges on the prevention and management remained to be difficult for patient with diabetes milletus, but it made the life of an average diabetic to become both longer and easier due to innovative treatments which are being used these days [20]. Management of Diabetes Mellitus: The DiseaseThe diabetes can be measured by analyzing the blood sugar levels. A healthy man's blood sugar level on fasting should be 80 mg/dl and up to 160 mg/dl in postprandial state. Different test for diagnosed of diabetes in laboratory are finger prick blood sugar test, fasting blood sugar, glucose tolerance diagnostic test, glycohemoglobin [21]. Healthy eating, physical activity, and weight control are the center of any therapeutic program for patients in DM [22]. These lifestyle modifications not only lower blood glucose levels in the body, but also, they ameliorate many risk factors for cardiovascular disease, and help weight loss. However, most patients cannot have a good lifestyle [23], and so, if that happens patients must depend on medications for treatment. The conventional management of diabetes mellitus includes; insulin therapy, oral glucose-lowering agents such as sulfonylurea, biguanides, alpha-glucosidase inhibitors, thiazolidinediones, and meglitinides [24-29]. Importance of Medicinal Plants with Potential Antidiabetic Property for the Management of Diabetes mellitusNature stands as the prime example at emphasizing the concept of interdependence among species for food. Plant, animal and mineral byproducts have been the basis of the treatment of human disease since early history [3]. The demand for herbal medicines has been increasing. An ancient literature by Theophrastus has mentioned about 500 plants with medicinal use and about 800 plants have been used in native medicinal systems [30]. The hypoglycemic and antidiabetic effects of several plants used as traditional antidiabetic remedies have been proven, and the mechanisms of hypoglycemic activity of these plants have been studied effectively [15,16]. Currently the medicinal plants and herbs are being used in extract forms for their potential anti-diabetic activity. Various clinical studies confirmed that medicinal plants extracts show anti-diabetic activity and restoring the action of pancreatic β- cells [31]. The plants antihyperglycemic effects are ascribed to their capability to restore the pancreatic tissues' function by producing an increase in the output of insulin or intestinal inhibition of glucose absorption or how metabolites are facilitated in insulin dependent processes [32].

Figure 1

Acacia arabica [152]

Figure 2

Artemisia pallens [153]

3MATERIALS and METHODS

The information in this review was obtained from several articles made by different authors about the potential antidiabetic property of plants herbal products, but the most informative is the review on hypoglycemic properties of more than 300 plant species documented by Atta-Ar-Rahman. This review classifies the plants using the following categories: botanical name, country of origin, parts used, and nature of active ingredients. One such plant is Momordica charantia (Family: Cucurbitaceae). World Health Organization (WHO) have listed 21,000 plants, which are used for medicinal purposes throughout the world that has been studied and investigated [33]. The implied anti-diabetic effect of glycosides, alkaloids, terpenoids, flavonoids, carotenoids are found in most of the identified plants [32]. Plant families which are confirmed to show hypoglycemic activity include: Leguminosae, Lamiaceae, Liliaceae, Cucurbitaceae, Asteraceae, Moraceae, Rosaceae, Euphorbiaceae, Araliaceae, Polygalaceae, Asclepiadaceae, Meliaceae etc. [34].

Figure 3

Aegle marmelos [154]

Some of the important medicinal plants commonly used in traditional medicine of different civilizations and cultures having potential anti-diabetic activity is described showing information on its scientific name, common name, family, country of origin, constituents, focusing on recent studies confirming their efficacy and the parts of the plant used to treat diabetes. Acacia arabica (Leguminosae): A. arabica's fruit and gum have been used for the treatment of diabetes and other metabolic conditions in previous times. The study revealed that polyphenol extract fromA.arabica bark have antihyperglycemic activity and promotes reduction of body and white adipose tissue weight in mice with severe type-2 diabetes and obesity. Polyphenols as one of the metabolites found in acacia, has shown its valuable effect by increasing insulin sensitivity and energy expenditure-related mediators in type 2 diabetes which is indicative of its positive action in the management of diabetic metabolic syndrome [35]. Artemisia pallens (Compositae): The Methanolic extract of aerial parts of A. pallens, commonly known as davana are responsible for its anti-diabetic activity. A reported antihyperglycemic activity was shown in glucose fed hyperglycemic rats and also in alloxan induced diabetic rats using methanolic extract (100mg/ kg) given orally. Metabolites such as Cadinol α- Curarine, β-eudesmol, β-cubebene are said to be responsible for its anti- diabetic activity. Increase inhibition in glucose- reabsorption or increase peripheral glucose utilization is the mechanism of action of these metabolites found in A. pallens [36]. Aegle marmelos (Rutaceae): It is commonly called holyfruit tree, Bael or wood apple, an important medicinal tree native to Northern India [37]. It is inherited to India and parts of plant such as leaves, barks, roots and fruits are used in the Ayurveda and in various medicines which is used for cure of various diseases [34]. The antihyperglycemic activity of aqueous leaf extract is seen in streptozotocin induced diabetic rats [35]. Streptozotocin-induced diabetic Wistar rats were tested with oral administration of aqueous extract of A. marmelos fruit at a

dosage of 250 mg/kg body weight given in a twice a day dosing for 4 weeks, which resulted in significant reduction of blood sugar levels. This dosage showed effective results over the standard drug glibenclamide (39). Another study revealed that treatment with aqueous fruit and leaf extract of A. marmelos in a dose of 450 mg/kgadministered in 21 days, resulted in significant lowering of blood glucose and insulin levels accompanied with enhanced insulin sensitivity in neonatal type 2 diabetic model rats [39]. (Allium cepa) Onion and (Allium sativum) garlic (Liliaceae): Allium cepa is known only in cultivation but related wild species occur in Central Asia [36]. Onion (A. cepa) contains active hypoglycemic constituents. Garlic (A. sativum) also contains hypoglycemic organic sulfur compounds [40]. According to studies, fasting glucose concentration in both diabetic animals and human subjects are lowered by volatile oils in raw onion and garlic cloves where sulfur-containing compounds such asallyl propyl disulfide in onions and diallyl disulfide (allicin) are believed to be the active components. The disulfides in this plant lower glucose levels by competing with insulin for insulin -inactivating sites in the liver. Onion extracts reduce blood sugar levels in a dose-dependent manner [36]. A dosage of 400 mg capsule daily for A. cepa is the typical dose accepted while for fresh garlic, a general dose is 4 g or 8 mg for essential oil [41]. Aloe borbadensis/vera (Liliaceae): The dried sap (fluid) of vera commonly known as Ghikanvar is a traditional remedy used for diabetes in the Arabian Peninsula and Africa. A. borbadensis looks like a cactus plant with green blade shaped leaves that are heavy narrowing, hairy and filled with clear viscid gel. A preparation of the A. vera juice from an A. vera gel was made, which is a mucilaginous product obtained from the leaves of the plant [42]. The juice taken orally was shown to reduce fasting blood glucose and triglyceride levels in type 2 diabetic patients with or without combination of a conventional antidiabetic agent. The amount used is one tablespoon of A. vera juice with no significant adverse effects reported [43]. Oral administration of aqueous extract of A. vera in a dose of 150mg/kg per body weight significantly has shown lowering in the blood glucose level. A. vera gel isconsist of various therapeutic effects such as anti-diabetic, antioxidant, and increases the decrease level of glutathione by four times in diabetic rats [44]. Anacardium occidentale Linn. (Anacardiaceae): Anacardium occidentale is known as Cashew or Caju herb that originates from S. America – Brazil [45]. As folk medicine in African countries, mainly in Cameroon district, it is commonly used for the treatment of diabetes mellitus. Hypoglycemic and protective role of A. occidentale was reported in several literatures [46,47]. The investigation made using streptozotocin induced diabetic rats, revealed the antihyperglycemic and renal protective activities of the leaves of the herb. Thus, revealing the positive effect in reducing diabetes- induced functional and histological alterations in the kidneys. A histopathological study of A. occidentale revealed a decreased buildup of mucopolysaccharides in the kidneys of diabetic animal signifying its effectiveness as antidiabetic agent.[48] Annona squamosa Linn (Annonaceae): Custard apple is the common name in English and is known as sharifa in Hindi, and was cultivated throughout India. The pharmacological active ingredients are present in seeds, leaves and aerial parts of the plant [32]. The aqueous extract of this plant leaf has many antioxidant effects. Theblood glucose, hemoglobin, glycosylated hemoglobin, plasma insulin, antioxidant enzymes, lipid peroxidation in liver and kidneys were examined in STZ induced diabetic rats (Kootie, Farokhipour, Asadzadeh, Ashtary-larky, & Asadi-Samani, 2016). Literature review revealed that the aqueous extract of this plant is beneficial for regulating blood glucose levels and thus help improve plasma insulin and lipid metabolism. In addition, this extract is effective in preventing diabetic complications caused by lipid peroxidation and antioxidant systems in experimental diabetic rats (Kootie, et al, 2016) [49]. To strengthen the pharmacological activity of this plant, another research revealed that extract obtained from leaves of this plant is useful in maintaining healthy blood sugar and cholesterol levels [50]. Annona muricata L (Magnoliales: Annonaceae): A. muricata L., commonly known as soursop, graviola, guanabana, guayabano, paw- paw and sirsak [51,52], native to the warmest tropical areas in South and North America and is now widely distributed throughout tropical and subtropical parts of the world, including India, Malaysia and Nigeria [53]. Annonaceous acetogenins are the major constituents of A. muricata as revealed in the phytochemical studies performed during the investigation [54]. According to Garg, MK., in 2002, A. muricata Linn. leaf plant extract played important role in reduction of oxidative stress on pancreatic β cells of streptozotocin treated diabetic rats. The treatment increased the area of insulin immunoreactive β-cells and partially prevents degeneration of β-cells [55]. Several studies have corroborated these activities, including anticancer, anticonvulsant, anti-arthritic, antiparasitic, antimalarial, hepatoprotective and antidiabetic activities. Annona squamosa Linn. (Annonaceae): It iscommonly called custard apple in English and sharifa in Hindi, and widely cultivated throughout India. The pharmacological active ingredients are present in seeds, leaves and aerial parts of the plant [32]. The aqueous extract of this plant leaf has many antioxidant effects. The blood glucose, hemoglobin, glycosylated hemoglobin, plasma insulin, antioxidant enzymes, lipid peroxidation in liver and kidneys were examined in STZ induced diabetic rats. Blood glucose level has been controlled and improvement of plasma insulin and metabolism of lipid have been observed in the administration of the aqueous plant extract. In addition, this extract is effective in preventing diabetic complications caused by lipid peroxidation and antioxidant systems in experimental diabetic rats [49]. To strengthen the pharmacological activity of this plant, another research revealed that extract obtained from leaves of this plant is useful in maintaining healthy blood sugar and cholesterol levels in diabetic-induced rats [50]. Annona muricataL (Magnoliales: Annonaceae): A. muricata L., commonly known as soursop, graviola, guanabana, guayabano, paw- paw and sirsak [51,52], native to the warmest tropical areas in South and North America and is now widely scattered throughout the tropical and subtropical parts of the continent, including India, Malaysia and Nigeria. The study revealed the effects of methanolic extracts of Annona muricata (Linn) on the blood glucose level of streptozotocin-induced diabetic Wistar rats, which resulted to a reduce blood sugar upon administration of the methanolic extracts [53]. Several studies and investigations have verified these pharmacological activities, including anticancer, anticonvulsant, anti-arthritic, and antiparasitic potential activity of this plant. Antidesma bunius L. and Antidesma ghaesembilla Gaertn (Phyllantaceae): Antidesma bunius L., is also known as Bignay, buni, Chinese laurel, currant tree. This is found in Eastern Asia such as China, India, Myanmar, Thailand, Laos, Vietnam, Malaysia, Indonesia, Philippines, north of the

Australian mainland (New Guinea), and some part in northern Australia to the Pacific Islands. The α-glucosidase inhibitory activity of the plant was evaluated by using the stem barksand leaves. Ethyl acetate (EtOAc) fraction of buni stem barks and methanol (MeOH) fraction of buni leaves showed the highest α-glucosidase inhibitory activity [48]. The plant A. ghaesembilla Gaertn is a native species found in Ilocos Norte, Philippines [4]. It is commonly known as Binayuyo (Tag.) and black currant tree and is found in southern China, Myanmar, Thailand, Cambodia, Laos, Vietnam, Malaysia, Indonesia, New Guinea, Australia, Philippines. The study showed the antioxidant and hypoglycemic activity of the crude methanolic extract of A. ghaesembillla. Significant hypoglycemic potential with dose dependent decrease in blood glucose was shown in the result. The crude extract also showed moderate to strong antioxidant potential attributed to the presence of polyphenolic compounds and its ability to scavenge free radicals [4,49]. Boswellia carterii and B. serrata (Burseraceae): This is commonly known as Frankincense, of which the oleo- gum resin found from the trees were considered ancient drugs that possesses anti-diabetic activity in traditional medicine. The hypoglycemic activity in mice with type-1 diabetes, via inhibiting pro-inflammatory cytokines associated with induction of autoimmune process in pancreatic islet was observed in B. serrata oleo-gum. Metabolites found as its active constituents are 11-Keto-β-boswellic acid and O-acetyl-11- Keto-β-boswellic acid linked to its antidiabetic property [35]. Suppression of pancreatic islet tissue atrophy and apoptosis of periinsular cells mediated by anti-caspase 3 are among its main antidiabetic mechanisms [32]. In addition, another study revealed that B. carterii oleo-gum resin displayed antidiabetic potentiality through an intensification in serum insulin, renewal of the β-cells of Langerhans islets as well as increasing glycogenesis and reducing glycogenolysis in rats with alloxan-induced type 1 diabetes [33]. Bougainvillea spectabilis Linn. (Nyctaginaceae): B. spectabilis Wild is commonly known as bougainvillea, great bougainvillea, (local Indian names: booganbel, cherei, baganbilas, booganvel, bougainvillea, kagithala puvvu [57]. Significant hypoglycemic activity at different doses and intervals were found in the stem bark extract of A. spectabilis. The study revealed that stem bark extract was 22.2% more potent than standard oral hypoglycemic drug, glibenclamide at 0.2 mg/kg. Another study revealed the blood glucose lowering potential of B. spectabilis Wild leaf extract in streptozotocin-induced type I diabetic albino rats. The ethanolic extract of the leaves showed antihyperglycemic activity probably due to increased uptake of glucose by enhanced glycogenesis in the liver and also due to increase in insulin sensitivity [58]. Chemical constituents were isolated using Column chromatography of fractions B and C affording four compounds identified aspinitol, β-sitosterol,quercetinand quercetin-3-O-α-rhamnopyranoside. The isolation of the metabolites pinitol, β-sitosterol, quercetin and quercetin-3-O- α-L-rhamnopyranoside were done for the first time using the stem bark of B. spectabilis Wild. Thus, verifying that the antidiabetic metabolite, pinitol, was successfully isolated from the stem bark of B. spectabilis Wild [59]. Brassica juncea ((L.) Czern: This is a species of mustard plant described as peppery, crispy, and mustard green known to be as leaf mustards. This was commonly known as Mustasa in the Philippines. In India, it is known as Rhai, widely used as spice in various food items. Aqueous seed extract has blood sugar lowering activity which was observed in alloxan-induced diabetic rats [60]. Another investigation of aqueous seed extract in STZ-induced diabetic male albino rat revealed a potent hypoglycemic activity. Reported doses of extract which showed hypoglycemic activity were at the level of 250, 350, 450 mg/kg [61]. Oral administration of mustard exerts significant hypoglycemic activity. The hypoglycemic effect of Rhai was attributed to stimulation of glycogen synthetase and suppression of various glycogenic enzymes [62]. Caesalpinia bonducella (Leguminosae): It is commonly called Chinese cinnamon. The hypoglycemic activity of the plant in aqueous and ethanolic extract was reported to be effective in chronic type II diabetic model with increase in secretion of insulin. Bargenin, caesalpinine A, α and β amyrin lupeol increases the release of insulin from pancreatic cell [63]. Another study revealed that the hypoglycemia produced by the aqueous extract was of prolonged duration as compared to ethanolic extract. These results suggest that the seeds of C. bonducella possessed an antidiabetic property and can be of used for the treatment of diabetes [64]. Catharanthus roseus Linn. (Apocynaceae): This is commonly known as Madagascar periwinkle, bright eyes, graveyard plant, cape periwinkle, pink periwinkle, and rose periwinkle, a flowering plant species in Apocynaceae family. InTamil, India it is called as nithyakalyani, an ornamental shrub that is widely distributed around the world. The increase in serum insulin level and restoration of β- cells were evident in aqueous extract treated rats [65]. Another study revealed that treatment of diabetic animals with extracts resulted in significant decrease in serum LDL level. This change is linked with the flavonoids present in the ethanol extract of C. roseus showing significant reduction in the level of LDL as reported. [66]. In the study of Al-Shaqha (2015), C. roseus was found to be more effective in reducing fasting blood glucose level, and increased GLUT-2 mRNA and GLUT-4 mRNA concentrations [67]. Significant study on the administration of C. roseus leaf powder at a dose of 100 mg/kg b.w. has shown to lower the plasma glucose and increased the plasma insulin after 15 days of administration in STZ induced diabetic rats [68]. Another report indicated the blood glucose lowering activity in the alcoholic extract of the leaves of C. roseus. The herb has prophylactic activity against the necrotic actions of alloxan monohydrate as revealed by several studies [69-71]. Centella asiatica (Apiaceae):C. asiatica is commonly called as centella, and vallarai in Tamil, India and was found also in other countries in Southeast Asia including the Philippines, which is known as takip-kohol or Gotu kola. The methanolic extract of C. asiatica have been proven to possess antidiabetic activity in various animals [72,73]. C.asiatica plant extract has shown a significant decrease in the blood glucose, cholesterol and triglycerides upon administration to alloxan-induced diabetic rats [74]. According to literature, the possible mechanism of antihyperglycemic activity of C. asiatica is to reduce carbohydrate breakdown, and glucose fiber binding, which in turn reduces the glucose absorption through the gastrointestinal tract [75]. Cinnamomum zeylanicum (Lauraceae): Ceylon cinnamon is the common name of this bushy evergreen tree of the laurel family (Lauraceae). The spice derived from its bark, is indigenous to Sri Lanka (formerly Ceylon), and is also known to be cultivated in South America and the West Indies [59]. Cinnamaldehyde is a compound isolated from the bark of C. zeylanicum. Cinnamaldehyde compound taken orally in the dose of 20 mg/kg significantly decreased the HbA1C, serum total cholesterol, triglyceride levels and at the same time markedly increased plasma insulin,

hepatic glycogen and high-density lipoprotein cholesterol levels in STZ- induced diabetic rats [77]. In another study, it revealed restoration of the plasma enzyme reduction in blood glucose level in alloxan-induced diabetic rats [78]. Phenolic extract of cinnamon (C. zeylanicum) shows the insulin potentiating activity, and is important for in-vivo glucose control and insulin sensitivity in humans. Furthermore, it showed increase in lipid metabolism and antioxidant status. shows increase in lipid metabolism and antioxidant status. It contains alkaloids, proteins, tannins, cardiac glycosides and saponins as its primary metabolites [79]. Citrus sinensis (L.) Osbeck (Rutaceae) is commonly known as sweet orange. A study has shown that a dose-dependent hypoglycemic activity in male rats with induced diabetes had a significant result with the administration of peel extract of this worldwide served table fruit showed. This is in addition to its anti-thyroidal and insulin stimulatory properties [80]. An investigation on the effects of four different concentrations of peel extract from C. sinensis (CS) or Punica granatum (PG)showed an increased glucose lowering and antiperoxidative activities at 25 mg/kg of CS and 200 mg/kg of PG administered in male mice. Subsequent phytochemical analysis indicated that the high content of total polyphenols in the test peels might be related to the antidiabetic and antiperoxidative effects of the test peels [81]. According to the study of Kingue et al (2017), the stem bark of aqueous extract of C. sinensis is able to reduce postprandial glycaemia by slowing down the absorption of glucose, challenging the efficacy of glibenclamide, an anti-diabetic drug [82]. Coccinia indica Wight & Arn. (Cucurbitaceae): It is commonly known as Kundru, Kovai in Tamil, [83] widely used in traditional treatment of diabetes mellitus in sub- Saharan Africa and Southeast Asia. Pectin isolated from the fruits of C. indica has hypoglycemic activity [34]. The plant's alcoholic extract was found to be effective in decreasing blood glucose level, and the extract was subjected to further fractionation to evaluate its biochemical parameters effecting diabetes and results suggested toluene as an active fraction. The exact action of these principles may be due to their β-cell restorative properties against alloxan induced damage [84]. Triterpenes present in the extract acts like insulin [85]. Coffea arabica (Rubiaceae): Coffea arabica (LINN.) is a medium- size tree of Rubiacea family. The plants can live up to 25 yrs. and grows to a height of 6-15m. In the first century it was cultivated in Arabic countries later in Iran and India. Main producers currently are Brazil and Columbia [86]. The study revealed that the aqueous extract of Coffea arabica reduces blood glucose levels as tested in alloxan-induced diabetic rats [87]. Several recently published cohort studies suggest a significant reduced risk of type 2 diabetes in coffee drinkers [88]. As similar results have been found with decaffeinated coffee [89], compounds in coffee other than caffeine have been proposed as being potentially responsible for the reduced risk [90]. Coriandrum sativum L. (Apiaceae): C. sativum L. is commonly known as Chinese-parsley, Chinese parsley, coriander, used as food ingredient possessing medicinal as well as nutritional properties [91]. Anti-diabetic activity of the aqueous extract of this plant was examined in STZ-induced diabetic rats. The doses of extract at 500 and 250 mg/kg produced a significant reduction in blood glucose levels in the experimental group, compared to the control group. In addition, the dose of 500 mg/kg was the maximally effective [92]. Another study revealed that administration of ethanolic stem and leaves extract of coriander to alloxan-induced diabetic Wistar rats at a dosage of 200 mg/kg/b.w. resulted in hepatoprotective, hypoglycemic, hypolipidemic activities with improved antioxidant potential [93]. Similar studies on the hypoglycemic activities of C. sativum have been investigated by other researchers showing positive results in clinical testing [94,95]. Curcuma longa (Zingiberoside). Turmeric is the common name of C. longa and the bioactive molecule present in the plant rhizome is known as Curcumin. It has diverse pharmacological and biological effects that have been described by both in-vitro and in-vivo study, and include antioxidant, cardio-protective, anti-inflammatory, anti- microbial, nephro-protective, anti-neoplastic, hepato-protective, immunomodulatory, hypoglycemic and anti-rheumatic effects [96]. In animal models, curcumin extract delays diabetes development, improves β-cell functions, prevents β-cell death, and decreases insulin resistance. The reducing effect of enzymes responsible for converting dietary carbohydrates into glucose, led to a decrease in blood glucose level. Curcumin shows reduction in blood glucose, hemoglobin, and glaciated hemoglobin levels as tested in animal studies. The bioactive molecules found in turmeric exhibits hypoglycemic action in both type I and type II diabetes (known as Ferulic acid or 4-hydroxy-3-methoxy- cinnamic acid). Some amide compound derived from ferulic acid has evidence for insulin secretion from pancreatic beta cells [97]. In another study, Kuroda, M et. al (2008), revealed that turmeric (C. longa L. rhizomes) ethanolic extract have shown significant suppression in the increase of blood glucose level in type 2 DM induced KK-Ay mice. The main constituents of the extract were identifiedascurcumin,desmethoxycurcumin,
bisdemethoxycurcumin, and ar- turmerone, which had also PPAR-γ ligand-binding activity. These results indicate that turmeric is a promising ingredient of functional food for the prevention and/or amelioration of type 2 diabetes and that curcumin, desmethoxycurcumin, bisdemethoxycurcumin, and ar-turmerone mainly contribute to the effects via PPAR-γ activation [98]. Eugenia jambolana (Lam)E. jambolana known as Jamun, [99] has been widely used in Indian traditional medicine for the remedy of various ailments. Different parts of E. jambolana such as the kernel, leaves, and septum have a significant antihyperglycemic effect when compared with glibenclamide, a standard antidiabetic drug as tested in streptozotocin-induced diabetic male albino rats [100]. In addition, oral administration of EJ significantly ($p<0.05$) decreased serum total cholesterol, LDL-cholesterol, VLDL-cholesterol, triglycerides and at the same time markedly increased serum insulin and HDL-cholesterol levels [101]. Glycyrrhiza glabra (Fabaceae):Glycyrrhiza glabra, commonly known as liquorice, is a well-known traditional herbal remedy and the roots have been administered as antidiabetic drug from ancient time [102]. Significant constituents isolated from licorice include flavonoids, iso flavonoids, saponins, triterpenes and the most imperative is Glycyrrhizin. Due to these elements, it has important pharmacological activities such as antioxidant, antibacterial, antiviral, antidiabetic and anti-inflammatory as well [103]. Root extract of G. glabra exhibited antidiabetic and lipid- lowering activities when administered to albino mice at low doses [104,105]. Antidiabetic activity of long-term treatment with glycyrrhizin was examined on non-insulin-dependent diabetic mice. According to Sen et al., it revealed that glycyrrhizin effectiveness was comparable to the well-known antidiabetic drug glibenclamide and they observed that the STZ diabetic efficacy was significantly stimulated by glycyrrhizin as it regulated glucose-intolerant behavior and

blood glucose levels, enhanced glycohemoglobin, cholesterol, and triglyceride levels, and reduced the level of serum insulin, including the numbers of pancreatic islet cell as well as pancreas and kidney tissue abnormalities due to diabetes [104]. Gymnemasylvestre (Asclepiadaceae):G.sylvestre commonly called podapatri, is a large woody, much branched climber with pubescent young parts in dry forest up to 600 m height [106]. Gymnemic acids— a group of triterpenoid saponins was isolated and identified successfully as the major bioactive ingredient of G. sylvestre. Several studies have reported that the main biological activity of this plant is antidiabetic activity. It is rich in phytochemicals such as alkaloids, flavonoids, saponins, carbohydrates and phenols with highest concentration of saponins being 5.5% [107]. In the investigation of S. Sathya et al., the aqueous extract of G. sylvestre leaf informed hypoglycemic activity in normal and alloxan-induced diabetic rats [108] by reducing glucose concentration. Other research on G. sylvestre, proposed that the aqueous extract could stimulate the release of insulin in vitro by permeabilizing the cell [109]. Hibiscus rosa sinensis (Malvaceae): It is commonly called china rose. Alcoholic leaf extract (250mg/kg/p. o) given for seven consecutive days has shown hypoglycemic activity in hyperglycemic rats [110]. Several investigations were done to assess the effect of aqueous extract of H. rosa sinensis leaves on blood glucose level and glucose tolerance using Wistar rats. By comparison with the standard drug, the results clearly indicated that tolbutamide improves the glucose tolerance by 91% and the aqueous extract does so only by 47%. At 250 mg kg (-1), the efficacy of the extract was 51.5% of tolbutamide (100mg kg (-1)). These data suggest that hypoglycemic activity of H. rosa sinensis leaf extract is comparable to tolbutamide and not to glibenclamide treatment [111]. The ethanolic extract of H. rosa-sinensis (L) flowers has significant anti-diabetic activity in hyperlipidemic rat models. Hence, it can be used as a healing factor or in the supportive treatment to existing therapy for the treatment of diabetes in hyperlipidemic conditions [112]. Mangifera indica (Anacardiaceae): It is commonly known as mango. The anti-diabetic properties of Mangifera indica leaves were evaluated in glucose induced normoglycemic, hyperglycemic, and streptozotocin induced diabetic rats. The aqueous extract of this plant leaf decreased the glucose level in normoglycemic and glucose induced hyperglycemia, however it did not demonstrate any effects on the STZ-induced diabetic mice group. The hypoglycemic effects of the extract are comparable with an oral dose of chlorpropamide under the same conditions [113]. The anti-diabetic activity of the extract in this study is probably due to reduced intestinal absorption of glucose [114]. In Nigerian folk medicine, the leaves of this plant are used as an antidiabetic agent. The aqueous extract of M. indica have shown a hypoglycemic activity as manifested by an intestinal reduction of the absorption of glucose [115]. Momordica charantia (Cucurbitaceae). It is commonly known as bitter melon (karela), bitter gourd and Pagakkai in Tamil, India. Aside from using it as food (vegetable), M. charantia is also used as an herbal remedy in folk medicine. Its bioactivities, such as anti-inflammatory activity, anti- oxidant activity, anti-viral activity, anti-cancer activity, anti- bacterial activity, etc. and especially anti-diabetic activity [116]. The active constituents of Momordica charantia are momordic I and momordic II, cucurbitacin B. It is used in the treatment of diabetes. It consists of lectin which has insulin like activity. Lectin is a non-protein molecule which is linked to an insulin receptor, which is responsible for decreasing the blood sugar level by acting on peripheral tissues [117]. The fruits, seeds and callus of Momordica charantia contain some insulin-like proteins [118] which are homologous to human insulin, and it produced consistent hypoglycemic effect when tested on rats, gerbils, langurs and human beings [119]. M. charantia was believed to be a treatment for diabetes mellitus for thousands of years in India and China [120]. Consumption of dried powder of M. charantia fruit revealed reduction in fasting blood sugar of 10 Type 2-Diabetes mellitus patients with no history of previous medication and 10-T2DM patients with history of taking oral hypoglycemic agents. The aqueous and alcoholic extracts of M. charantia fruit revealed the same effect [121]. Morus alba (Moraceae): is commonly known as Mulberry. Since time immemorial, the leaf has been known to have hypoglycemic effects used in folk medicines. In Asia mulberry leaf is used as tea to complement the treatment of diabetes mellitus [122]. According to the study of Mundra, M. et al (2007), as observed in the testing of the control and type-2 diabetic subjects for 120 minutes, co-ingestion of mulberry extract with 75 g sucrose significantly reduced the increase in blood glucose [123]. The mulberry-induced reduction in blood glucose presumably reflects the ability of mulberry to inhibit intestinal sucrase [124]. Another study showed that induced-sucrose malabsorption was observed with the used of this mulberry supplement, indicating that there is an increased level of Hydrogen in the tissues. Both animal and clinical studies have demonstrated that the phytochemicals in white mulberry make the plant a viable alpha-glucosidase inhibitor. Study showed that products made from white mulberry can effectively contribute to the decrease in glucose levels after carbohydrate consumption, although large-scale trials need to be conducted to confirm these findings and provide clinical guidelines for their use [125]. In another study of Abdulrahman, S et al in 2017, they concluded the M. alba stem bark extracts produced significant antidiabetic and antioxidant effect which might be due to the presence of bioactive components such as phenolic and flavonoid content in the extract [126]. All the studies made warrant the need for further evaluation in certain other models of diabetes. Panax ginseng Linn. (Araliaceae): The root has been used clinically in the treatment of type II diabetes throughout Asian countries. The antihyperglycemic activity of P. ginseng roots have been tested both in-vitro and in-vivo in animal studies and clinical trials that supported its claim. The bioactive molecule ginsenoside plays important role in antihyperglycemic action and other constituents has distinct pharmacological effect on energy metabolism [127]. Several studies revealed the ginseng mode of action of attenuating the blood glucose level is by way of diminution of beta cell function and insulin resistance [128-130]. In another study it revealed that, the ethanol: aqueous (80: 20, v/v) ginseng root extract possesses a protective and shielding effect against the apoptosis of beta cells in the MIN6N8 cell line [131]. The mechanism in the antihyperglycemic activity of ginseng extract is associated with improved peroxisome proliferator activated receptor gamma expression and AMP-activated protein kinase phosphorylation in liver and muscle. Oral administration of P. ginseng root improves insulin sensitivity and may be used as an adjuvant therapy for treating diabetic patients with insulin resistance [132-134]. Psidium guajava (Myrtaceae). A hot water extract of P. guajava unripe fruit peel (400 mg/kg) significantly decreased the triglyceride, total cholesterol,

alkaline phosphatase, aspartate amino transferase, alanine amino transferase and creatinine levels of STZ induced diabetic rats [135]. In the study of Mukhtar HM et al.in 2006, results showed that ethanol stem bark extract exhibited statistically significant hypoglycemic activity in alloxan-induced hyperglycemic rats but was devoid of significant hypoglycemic effect in normal and normal glucose loaded rats (OGTT) [136]. Another study of Kamala, M et. al (2011) revealed that plant P. guajava Linn. (Guava) has an ethnomedical history as it has various activities especially functionally against the hyperglycemia. Hence, the review article gave an idea of the effect of leaf extracts of P. guajava on diabetes. It is believed that the study of such medicinal plants might offer a natural key to unlock a Diabetologist pharmacy in future [137]. Tinospora cardifolia (Menispermaceae): This is an herbaceous vine indigenous to the tropical areas of India, Myanmar and Sri Lanka and is commonly known as Guduchi. A study showed that oral administration of an aqueous T. cordifolia root extract resulted in a significant reduction in blood glucose and brain lipids when administered in alloxan-diabetic rats. The dosage of 400 mg/kg aqueous extract could elicit a significant antihyperglycemic effect in different animal models, however its effect is equivalent to only one unit/kg of insulin [138,139]. It contains the active ingredient diterpene compounds which consists tinosporone, tinosporic acid, Syringen, berberine and giloin (142). Root extract of T. cardifolia (50-200mg/kg) shows decrease in blood and urine sugar in streptozotocin induced diabetic rats during oral administration for 6 weeks [140-142] Solanum xanthocarpum (Solanaceae): The methanolic extract of both the leaves (field and in vitro raised) of S. xanthocarpum given at a dose of 200 mg/kg given orally, showed significant reduction in the blood glucose level, urea, uric acid and creatinine level with a good observation in the increased serum level of insulin in alloxan induced diabetic rats [143]. In another study, the extract was found to possess significant hypoglycemic activity when compared with the reference standard glibenclamide. The in-vitro study on glucose utilization by isolated rat hemidiaphragm suggests that the aqueous extract may have direct insulin like activity which enhances the peripheral utilization of glucose and have extra pancreatic effect. The toxicity studies report safety usage of the plant extract [144]. Zea mays L. (Poaceae): It is commonly known as corn, Maize powder, corn silk polysaccharides, and Z. mays saponins were studied for their hypoglycemic activities in normal and alloxan/ STZ-diabetic rats and mice. Their hypoglycemic activities were established already [145]. Treatment of diabetic rats with the extract/fractions caused a reduction in FBG with the dichloromethane fraction having the highest activity. The extract/fractions also caused increases in serum insulin levels [146]. The results of GC-MS and enzymatic investigations support the usage of a traditional anti-diabetic herb [147]. It is worthy to state further that the corn silk extracts can be subjected to further studies as potential anti-diabetic agents with selective inhibition against glucoamylase and α-glucosidase based on the proven evidence of potent and selective inhibitory potentials the plant has [148]. Zingiber officinale Roscoe (Zingiberaceae): commonly known as ginger is considered to be an important spice with innumerable health benefits. The rhizomes of ginger have been used traditionally for the treatment of hypertension, diabetes, arthritis, sprain, muscular aches, sore throats, fever, cramps, gingivitis, toothache, asthma, and infectious diseases [149]. It is a medicinal plant and spice extensively used in the control of diabetes [150]. The study demonstrated that Z. officinale consumption in 70 T2DM patients (aged 30–70 years, BMI between 20 and 35 kg/m2, and HbA1C between 7 and 10%) significantly reduced FBG, HbA1C, insulin, HOMA, TG, TC, CRP, and PGE2 compared to the placebo group, suggesting an improvement of insulin sensitivity and the prevention of complications in T2DM patients [151].

Figure 4

Aloe-Vera-Aloe-Barbadensis[155]

Figure 5

Anacardium occidentale [156]

Figure 6

Annona muricata [157]

TOXICITY STUDIES
List of Some Antidiabetic Plants with their Toxicological Studies

S. No	Botanical Name	Plant Part used in Dosage form	Pharmacological Activity	Toxicological studies	Reference
1	Acacia arabica (Leguminosae)	Powdered Seed	Antidiabetic	Safe in doses of 2, 3 and 4 gm/kg body-weight to normal and alloxan-diabetic rabbits	Wadood, Abdul;Wadood, Noreen &Wahid Shah, S. A., 1989[160]
2	Allium cepa (Liliaceae)	ripe onion juice	Antidiabetic	Tolerated dose of ripe onion juice was above 25 mL/kg body weight	Lee, C. W., Lee, H. S., Cha, Y. J., Joo, W. H., Kang,

					D. O., & Moon, J. Y. 2013.[161]
3	Aloe vera (Liliaceae)	lyophilized aloe gel	Antidiabetic	LD50 is over 5 g/kg body weight	Charles, B., (1981). [162]
4	Anacardium occidentale Linn. (Anacardiaceae):	Leaves in ethanolic extract	Antidiabetic	No lethality at a dose level of 100 mg/kg body weight	Jaiswal, Y. S., Tatke, P. A., Gabhe, S. Y., & Vaidya, A. B. (2016).[163]
5	Annona squamosa Linn Annonaceae)	Leaves in ethanolic extract	Antidiabetic	No acute toxicity was observed at 800mg/kg and 1600mg/kg doses. At 5000mg/kg body weight dose 100% fatality was recorded within 24 hours.	Saeed, Farah; Ahmad, Mansoor. (2017) [164]
6	Annona muricata Linn (Annonaceae):	Bark, roots and leaves Leaves in methanolic extract Bark and leaves	Antidiabetic Anti-hyperglycemic Antihypertensive, vasodilator, anti-spasmodic and cardio depressant	LD_{50} > 5 g/kg for aqueous extracts while methanolic and ethanolic extracts of leaves, flowers and pulp had a LD_{50} of >2 g/kg, considered non-toxic according to the guidelines of OECD.[160]	Vasquez M R.1990.[165] Adeyemi, D. O., Komolafe, O. A. et.al (2008).[166] Feng PC, Haynes Lj, et al. (1962) [167] O.V. Sousa, G.D. Vieira, JJRGd Pinho, C.H. Yamamoto, M.S. Alves. (2010) [168]
7	Antidesma ghaesembilla Gaertn (Phyllantaceae)	Leaves in methanolic extract	Hypoglycemic and antioxidant	Data showed no mortality and is nontoxic up to 5000mg/kg bw.	Gargantiel, M.F. and Ysrael, M. C. (2014) [4]
8	Boswellia serrata (Burseraceae)	Gummy oleoresin	Antidiabetic and other metabolic syndrome	Data showed no toxic effect up to 500 mg/kg	Singh P, ChackoKM, Aggarwal ML.et al. (2012) [169,170]
9	Bougainvillea spectabilis Linn. (Nyctaginaceae)	Apical leaves in aqueous extract	Antidiabetic and Antioxidant	Data showed restoration of the kidney and liver functions to normal and proven to be nontoxic.	Pratibha C., Sunil Mahajan, M.et al.(2015) [171]
10	Caesalpinia bonducella (Leguminosae)	Leaves in aqueous extract	Antidiabetic and Antioxidant	Maximum dose of 2000 mg/kg showed no toxic effect.	Vijay Patel M. and Meena Joshi. (2019) [172]
11	Catharanthus roseus Linn (Apocynaceae)	Leaf powder suspension/extract	Antidiabetic	No mortality at the highest dose of 10,000mg/kg body weight of the extract.	Ukoha AI, Okereke SC, Arunsi UO, et al. (2017) [173]
12	Centella asiatica (Apiaceae)	Leaf extract	Antidiabetic	Data showed no toxic effect to doses up to 2000 mg/kg b.w.	Giribabu, N., Srinivasarao, N., et. al (2014).[174]
13	Cinnamomum zeylanicum (Lauraceae)	Leaves in alcoholic extract	Antidiabetic	Study showed no acute or chronic toxicity or mortality.	Shah,A.H. et al. (1998) [175]
14	Coffea arabica (Rubiaceae)	Ethanolic seed extract	Antidiabetic	Data showed the acute toxicity test of the seed extract resulted to be nontoxic when administered orally to mice. The LD50 value was more than 2gm/kg bod weight.	Bisht, S. and Sisodia, S.S. (2011) [176]
15	Glycyrrhiza glabra (Fabaceae)	Root extract	Antidiabetic	Study showed that calculation via the “Karber,” Arithmetic Method the LD50 was observed at the dose of 833.3 mg/kg body weight.	Sharma, V., Agrawal, R. C., and Shrivastava, VK. (2003).[177]

Toxicity studies have not been conducted for most of the plants mentioned in this review article, however, acute toxicity tests per OECD have been shown in some articles. Most of the plants in these reviews have been used for many centuries as folkloric medicines and sometimes as regular constituents of the diet, thus, it is assumed that they do not have many side effects. The continuing consumption of hefty amounts of traditional medicines and preparations must always be taken with

caution. According to the study of Coria-Téllez, Ana V. et.al (2018) large quantities of extract of Momordica charantia (bitter gourd) induced testicular lesion in dogs [178]. The presence of alkaloids from Catharanthus roseus when taken in large amounts caused cytotoxic effects and adverse reactions such as the increased risk of infection andneurological effects [179] Reduce or abolish taste sensation of sweetness or bitterness is the adverse effect of Gymnema sylvestre (gurmar)

CONCLUSION:

According to the report of the World Health Organization, in 1985 about 30 million people have been estimated to suffer from diabetes and the number is increasing each day reaching more than 171 million in 2000. It is further anticipated that the number will increase to over 366 million by 2030, mostly targeting developing countries, especially those in the bracket of middle-aged to senior citizens (between 45 and 64 years) [181]. Several synthetic pharmaceutical drugs have been a result of advancement in modern medicine such as biguanides, thiazolidinediones, biguanides, and insulin proven to possessed antidiabetic properties. But these drugs are often associated with several complications such as nephrological disorders, fatigue, gastrointestinal discomfort (upset stomach, diarrhea, vomiting), hypoglycemia, etc. Many medicinal plant treatments for diabetes are used throughout the world. Based on several literatures, the plants mentioned in this study are proven to possess natural antioxidants and used as an effective herbal medicine in diabetes mellitus due to their bioactive compounds, such as flavonoids, tannins, phenolic, and alkaloids that improve the performance of pancreatic tissues by enhancing insulin secretion or reducing the intestinal absorption of glucose. This paper has presented various anti-diabetic plants that have been pharmacologically tested and shown to be of some value in the treatment and as prophylaxis for Diabetes Mellitus. The effects of these plants may delay the development of diabetic complications according to some studies and correct the metabolic abnormalities. Furthermore, it has been noted that there are several possible mechanisms through which these herbs can act to control the blood glucose level. The mechanisms of action can be related, generally, to the ability of the plant in question (or its active principle) to lower plasma glucose level by interfering with some processes involved in glucose homeostasis. In the present review, interest is focused on looking at the results of the experimental studies performed on hypoglycemic activities of plants and their bioactive components in some regions in Asia and other parts of the world. The type of diabetes is described briefly along with the related physiological disorders and accessible herbs that can be utilized for antidiabetic activity. Finally, this review article presents the profiles of plants with hypoglycemic properties, reported in the literature. This may be useful to health professionals, scientists, and scholars to develop evidence-based alternative medicine or dosage formulations to cure different kinds of diabetes problems using herbal preparation. Extracts isolated and derived substances from different natural resources play a very significant role to design medicine and treat the hyperglycemic problems in diabetes mellitus. Thus, the researcher can conclude that the mentioned medicinal plants can be used for the treatment and prophylaxis of diabetes and the plants have the wide possibility for further research. Conflicts of Interest: The author declares no conflict of interest.

REFERENCES:

[1] Gurib-Fakim, A. (2006) Medicinal plants: Traditions of yesterday and drugs of tomorrow. Molecular Aspects of Medicine 27 (2006) 1–93

[2] Ngan, T., Bao, P. and Ly L. (2020) Bioactive Compounds in Anti-Diabetic Plants: From HerbalMedicine to Modern Drug Discovery. Biology 2020, 9, 252doi:10.3390/biology909025 www.mdpi.com/journal/biology

[3] Mohana Lakshmi, S., Sandhya Rani, K. S., and Usha Kiran Reddy, T (2012). A Review on Diabetes Milletus and The Herbal Plants Used for Its Treatment. Asian Journal of Pharmaceutical and Clinical Research. Vol 5, Issue 4, 2012 ISSN - 0974-2441

[4] Gargantiel, M.F. and Ysrael, M. C. (2014) Antioxidant Activity and Hypoglycemic Potential of Antidesma Ghaesembilla Gaertn (Phyllantaceae), IJSTR©2014 www.ijstr.org

[5] Ghorbani, Ahmad (2013). Best herbs for managing diabetes: A review of clinical studies. Brazilian Journal of Pharmaceutical Sciences vol. 49, n. 3.

[6] Durgeshnandani, S., Chandraprakash, D., Mehendra Kumar, D., et.al (2014) Anti Diabetic Potential of Herbal Plants and Polyherbal Formulation. International Journal of Phytotherapy Research, ISSN 2278 – 5701.www.earthjournals.org Volume 4 Issue 3, 2014 28

[7] Bahare, S.; Ata, Athar; Anil Kumar, Nanjangud V.et al. 2019, Antidiabetic Potential of Medicinal Plants and Their Active Components. Biomolecules 2019, 9, 551; doi:10.3390/biom9100551(online) (retrieved 14, March 2021) from https://www.ncbi.nlm.nih.gov/pmc/articles/ PMC6843349/pdf/biomolecules-09-00551

[8] Sonal, Narhe, Sandip, Kshirsagar S, and Vishal, Patil S. (2018) Review on Medicinal Herbs Used for Diabetes. International Journal of Pharmaceutical and Clinical Research. 10(8): 224-228 ISSN- 0975 1556 Review Article @ www.ijpcr.com

[9] Lorenzati, B.; Zucco, C.; Miglietta, S.; Lamberti, F.; Bruno, G. (2010). Oral hypoglycemic drugs: pathophysiological basis of their mechanism of action. Pharmaceuticals, v.3, p.3005-3020, 2010.

[10] Tzoulaki, I., Molokhia, M., Curcin, V. et al. (2009) Risk of cardiovascular disease and all-cause mortality among patients with type 2 diabetes prescribed oral antidiabetic drugs: retrospective cohort study using UK general practice research database. BMJ, v.339, p.b4731, 2009.

[11] Mutalik, S., Sulochana, B., Chetana, M., et. al. (2003) Preliminary studies on acute and sub-acute toxicity of an antidiabetic herbal preparation, Dianex. Indian Journal of Experimental Biology. 2003; 4:316- 320.

[12] Piyush, M.P, Natvarlal, M.P., Ramesh, K.G. (2006) Holistic classification of herbal antidiabetics: A review. Pharma Times, 2006; 38: 19-25.

[13] Roglic, G. and Norris, S.L. 2018. Medicines for treatment intensification in type 2 diabetes and type of insulin in type 1 and type 2 diabetes in low-resource settings: synopsis of the world health organization guidelines on second- and third-line medicines and

type of insulin for the control of blood glucose levels in nonpregnant adults with diabetes mellitus Ann. Intern.Med., 169 (2018), pp. 394-397
[14] Ghosh R.K., Gupta I.: Indian J. Anim. Health19, 145 (1980).
[15] Chattopadhyay R.R., Sarkar S.K., Ganguli S., et al.: Indian J. Physiol. Pharmacol. 35, 145 (1991).
[16] Moran A, Palmas W, Field L, et al. Cardiovascular autonomic neuropathy is associated with microalbuminuria in older patients with type 2 diabetes. Diabetes care 2004; 27: 972-977.
[17] Huang C, Kim Y, Caramori ML, et al. Cellular basis of diabetic nephropathy: II. The transforming growth factor-beta system and diabetic nephropathy lesions in type 1 diabetes. Diabetes 2002; 51: 3577-3581.
[18] Henschen, F. (April 1969). "On the term diabetes in the works of Aretaeus and Galen". Medical History. 13 (2): 190–192. doi:10.1017/s0025727300014277. ISSN 0025-7273. PMC 1033927. PMID 4890048
[19] Ram Prakash Rastogi, Bhola Nath Dhawan. Anticancer and antiviral activities in Indian medicinal plants: a review. Drug development research 1990; 19(1): 1-12. Bayer T, Breu W, Seligmann O, Wray V, Wagner H. Biologically Active Thiosulfates and Alpha Sulfinyl Disulfides from Allium-Cepa. Ind J Med Res 1989; 28:2373-8.
[20] Aggarwal, N.; Aggarwal, S. A Review of Recent Investigations on Medicinal Herbs Possessing Antidiabetic Properties. J. Nutr. Disord. Ther. 2011.
[21] Sidhu, M.C.; Sharma, T. Medicinal Plants from Twelve Families Having Antidiabetic Activity: A Review. Am.J. PharmTech Res. 2013, 3, 36–52 Edition; http://www.vision2020uk.org.uk/idfdiabetes- atlas-7thedition.
[22] Khan, M.U. Lifestyle Modification in the Prevention of Type II Diabetes Mellitus. Oman Med. J. 2012,27, 170–171.
[23] Bastaki S. Diabetes mellitus and its treatment. Int J Diabetes Metabolism 2005; 13:111-34.
[24] Garg MK. Current perspective in insulin therapy in the management of diabetes mellitus. J Indian Med Assoc 2002; 100:194-5, 202.
[25] Raing HP, Dale MM, Ritter JM. The endocrine pancreas and the control of blood glucose. In: Pharmacology. 4th ed. Edinburgh, London, New York, Philadelphia, Sydney, Toronto: Churchill Livingstone; 2000. p. 389-98.
[26] Fuhlendorff J, Rorsman P, Kofod H, Brand CL, Rolin B, MacKay P, et al. Stimulation of insulin release by repaglinide and glibenclamide involves both common and distinct processes. Diabetes 1998; 47:345-51.
[27] Kelly DE. Effects of weight loss on glucose homeostasis in NIDDM. Diabetes Rev 1995; 3:366-77.
[28] Shukla N, Angelini GD, Jeremy JY, et al. Homocysteine as a risk factor for nephropathy and retinopathy in type 2 diabetes. Diabetologia 2003; 46; 766-772.
[29] Gupta R. Bajpai KG, Johri S, Saxenaa M. An overview of Indian novel traditional medicinal plants with antidiabetic potentials. Complementary and Alternative.Medicines;2008(5):1–17.
[30] Malviya, Neelesh; Jain, Sanjay and Malviya, Sapna. 2010. Antidiabetic Potential of Medicinal Plants. Acta Poloniae Pharmaceutica ñ Drug Research, Vol. 67 No. 2 pp. 113ñ118.
[31] Swaroopa, P.; Jaya Sankar Reddy, V.; Mallapu Koshma, Y. et. al.2017. Review on Antidiabetic Activity on Medicinal Plants. International Journal of Pharmacological Research ISSN: 2277-3312 (Online) Journal DOI: https://doi.org/10.7439/ijpr
[32] Farnsworth, N.R. and Bingel, A.S. (1977): Problems and prospects of discovery new drugs from higher plants by pharmacological screening. Springer Verlag, Berlin.1-22.
[33] Hosein Farzaei, Mohammad; Rahimi, Roja Farzaei, Fatemeh et.al. 2015.Traditional Medicinal Herbs for the Management of Diabetes and its Complications: An Evidence-Based Review. International Journal of Pharmacology 11 (7): 874-887, ISSN 1811-7775
[34] Subramoniam, A., Pushpangadan, P., Rajasekharan, S., et.al. 1996. Effects of Artemisia pallens Wall on blood glucose levels in normal and alloxan-induced diabetic rats. Journal of Ethnopharmacology 1996; 50:13–17.
[35] Baliga MS, Bhat HP, Joseph N, Fazal F (2011) Phytochemistry and medicinal uses of the Bael fruit (Aegle marmelos Correa): a concise review. Food Res Int 44:7:1768–1775. https ://doi. org/10.1016/j.foodres.2011.02.008
[36] Kamalakkannan N, Prince PSM (2005) The effect of Aegle marmelos fruit extract in streptozotocin diabetes: a histopathological study. J Herb Pharmacother5(3):87– 96.https://doi.org/10.1080/J157v 05n03 08
[37] Mudi SR, Akhter M, Biswas SK, Muttalib MA, Choudhury S, Rokeya B, Ali L (2017) Effect of aqueous extract of Aegle marmelos fruit and leaf on glycemic, insulinemic and lipidemic status of type 2 diabetic model rats. J Complement Integr Med. https ://doi. org/10.1515/jcim-2016-0111
[38] Rawi SM, Abdelmoneim A, Ahmed OM. Studies on the effect of garlic oil and glibenclamide on alloxan diabetic rats. Egypt J Zoology 1998; 30:211-28.
[39] Sharma KK, Gupta RK, Gupta S, Samuel KC. Antihyperglycemic effect of onion: Effect on fasting blood sugar and induced hyperglycemia in man. Indian J Med Res 1977; 65:422-9.
[40] Malvi R, Jain S, Khatri S, Patel A, Mishra S. A Review on Antidiabetic Medicinal Plants and Marketed Herbal Formulations International Journal of Pharmaceutical & Biological Archives;2011(2):1344–1355.
[41] Dey L, Attele AS, Yuan CS. Alternative therapies for type 2 diabetes. Altern Med Rev 2002; 7:45-58.
[42] Bordoloi R, Dutta KN. Review on Herbs Used in the Treatment of Diabetes mellitus. Journal of Pharmaceutical, Chemical and Biological. Sciences;2014(2):86–92. Anacardium occidentale - L., online retrieval 04, March 2021@https://pfaf.org/user/Plant.aspx
[43] Kamtchouing P., Sokeng D.S., Moundipa P.F., et al.: J. Ethnopharmacology. 62, 95 (1998).
[44] Sokeng S.D., Kamtchouing P., Watcho P., et al.: Diabetes Res. 36, 1 (2001). Antidesma bunius - (L.) Spreng. - L., online retrieval 04, March2021@https://pfaf.org/user/Plant.aspx?

[45] Sidhu, M.C.; Sharma, T. Medicinal Plants from Twelve Families Having Antidiabetic Activity: A Review. Am. J. PharmTech Res. 2013, 3, 36–52 Edition; http://www.vision2020uk.org.uk/idfdiabetes - atlas-7th edition.
[46] Colberg, S.R.; Sigal, R.J.; Yardley, J.E.; Riddell, M.C.; Dunstan, D.W.; Dempsey, P.C.; Horton, E.S.; Castorino, K.; Tate, D.F. Physical activity/ Exercise and Diabetes: A Position Statement of the American Diabetes Association. Diabetes Care 2016, 39, 2065–2079.
[47] Khan, M.U. Lifestyle Modification in the Prevention of Type II Diabetes Mellitus. Oman Med. J. 2012,27, 170–171. [CrossRef] [PubMed]
[48] Bastaki S. Diabetes mellitus and its treatment. Int J Diabetes Metab 2005; 13:111-34.
[49] Garg MK. Current perspective in insulin therapy in the management of diabetes mellitus. J Indian Med Assoc 2002; 100:194-5, 202.
[50] Raing HP, Dale MM, Ritter JM. The endocrine pancreas and the control of blood glucose. In: Pharmacology. 4th ed. Edinburgh, London, New York, Philadelphia, Sydney, Toronto: Churchill Livingstone; 2000. p. 389-98.
[51] DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. Ann Intern Med 1999; 131:281-303.
[52] Sunil, Jawla and Kumar, Yathesh 2012. Hypoglycemic activity of Bougainvillea spectabilis stem bark in normal and alloxan-induced diabetic rats. Asian Pacific Journal of Tropical Biomedicine 2(2) DOI: 10.1016/S2221- 1691(12)60337-2
[53] Purohit A., Sharma A. 2006. Indian Drugs 43, 538
[54] Jawla, Sunil; Kumar, Yatendra, Yar and Sardar Khan, Mohammad. 2013 Isolation of Antidiabetic Principle from Bougainvillea spectabilis Willd (Nyctaginaceae) Stem Bark. Tropical Journal of Pharmaceutical Research October 2013; 12 (5): 761-765 ISSN: 1596-5996 (print); 1596-9827 (electronic)
[55] Arumugam G, Manjula P, Paari N. A review: Antidiabetic medicinal plants used for diabetes mellitus. Journal of acute diseases; 2013.
[56] Thirumalai T, Therasa VS, Elumalai EK, David E. Hypoglycemic effect of Brassica juncea (seeds) on streptozotocin induced diabetic male albino rat. Asian Pac JTrop Biomed 2011; 4: 323-325.
[57] Sunil, Jawla and Kumar, Yathesh 2012. Hypoglycemic activity of Bougainvillea spectabilis stem bark in normal and alloxan-induced diabetic rats. Asian Pacific Journal of Tropical Biomedicine 2(2) DOI: 10.1016/S2221- 1691(12)60337-2
[58] Sharm SR, Dwivedi SK, Swarup D (1997). Hypoglycemic, antihyperglycemic and hypolipidemic activities of Caesalpinia bonducella seeds in rats. J. Ethnopharmacology., 58: 39-44.
[59] Sharma, S.R.; Dwivedi, S.K. and Swarup, D.1997. Hypoglycemic, antihyperglycemic and hypolipidemic activities of Caesalpinia bonducella seeds in rats. Journal of Ethnopharmacology 58 (1997) 39–44
[60] Kelly DE. Effects of weight loss on glucose homeostasis in NIDDM. Diabetes Rev 1995; 3:366-77.
[61] Gupta R. Bajpai KG, Johri S, Saxenaa M. An overview of Indian novel traditional medicinal plants with antidiabetic potentials. Complementary and Alternative.Medicines;2008(5):1–17.
[62] Malviya, Neelesh; Jain, Sanjay and Malviya, Sapna. 2010. Antidiabetic Potential of Medicinal Plants. Acta Poloniae Pharmaceutica ñ Drug Research, Vol. 67 No. 2 pp. 113ñ118.
[63] Swaroopa, P.; Jaya Sankar Reddy, V.; Mallapu Koshma, Y. et. al.2017. Review on Antidiabetic Activity on Medicinal Plants. International Journal of Pharmacological Research ISSN: 2277-3312 (Online) Journal DOI:
[64] Farnsworth, N.R. and Bingel, A.S. (1977): Problems and prospects of discovery new drugs from higher plants by pharmacological screening. Springer Verlag, Berlin.1-22.
[65] Hosein Farzaei, Mohammad; Rahimi, Roja Farzaei, Fatemeh et.al. 2015.Traditional Medicinal Herbs for the Management of Diabetes and its Complications: An Evidence-Based Review. International Journal of Pharmacology 11 (7): 874-887, ISSN 1811-7775
[66] Subramoniam, A., Pushpangadan, P., Rajasekharan, S., et.al. 1996. Effects of Artemisia pallens Wall on blood glucose levels in normal and alloxan-induced diabetic rats. Journal of Ethnopharmacology 1996; 50:13–17.
[67] Parvaiz, M.; Hussain, K.; Khalid, S and Hussnain, N. 2014. A review: Medicinal importance of Glycyrrhiza glabra L. (Fabaceae Family) Global Journal of Pharmacology8(1):8-13DOI: 10.5829/idosi.gjp.2014.8. 1.81179
[68] Parmar, Hemendra Singh and Kar, Anand.2007. Antidiabetic potential of Citrus sinensis and Punica granatum peel extracts in alloxan treated male mice. DO10.1002/biof.5520310102 JO - Bio Factors (Oxford, England) (online)(retrieved 10,March 2021)
[69] Gayathri V, Lekshmi P, Padmanabhan RN. Anti-diabetes activity of ethanol extract of Centella asiatica (L) Urban (Whole Plant) is Streptozotocin-induced diabetic rats, isolation of an active fraction and toxicity evaluation of the extract. Int J Med Arom Plants. 2011; 1(3):278-286.
[70] Emran TB, Dutta M, Uddin MMN, Nath AK, Uddin MZ. Antidiabetic potential of the leaf extract of Centella asiatica in alloxan induced diabetic rats. J Biol Sci. 2015; 4(1):51-59.
[71] Ranasinghe, P., Galappaththy, P., Constantine, G.R. et al. Cinnamomum zeylanicum (Ceylon cinnamon) as a potential pharmaceutical agent for type-2 diabetes mellitus: study protocol for a randomized controlled trial. Trials18,446(2017). https://doi.org/10.1186/ s13063-017-2192-0
[72] Elavarasi S & Saravanan K, Ethnobotanical study of plants used to treat diabetes by tribal people of Kolli Hills, Namakkal District, Tamil Nadu, Southern India, Int. J. Pharm Tech Res, 4(2012) 404.
[73] Subash Babu P, Prabuseenivasan S & Ignacimuthu S, Cinnamaldehyde – A potential antidiabetic agent, Phytomedicine, 14 (2007) 15.
[74] Shehata, A.M., J. Jauch, L. Quintanilla-Martinez and H.P.T. Ammon, 2012. 11-Keto-β-boswellic acid inhibits infiltration of lymphocytes into pancreatic islets in NOD-mice. Diabetologie Stoffwechsel, Vol.

7. 10.1055/s-0032-1314454
[75] Wild S., Roglic G., Green A., et al.: Diabetes Care 27, 1047 (2004).
[76] Mustafa S.B., Akram M., Muhammad Asif H., et.al.2019 Antihyperglycemic activity of hydroalcoholic extracts of selective medicinal plants Curcuma longa, Lavandula stoechas, Aegle marmelos, and Glycyrrhiza glabra and their polyherbal preparation in Alloxan- induced diabetic mice. Dose Response.2019;17: 1559325819852503.doi:10.1177/1559325819852503 . [PMC free article] [PubMed]
[77] J.K. Grover et al, (2002), "Medicinal Plants of India With Anti-Diabetic Potential" Journal of Ethnopharmacology; 81;81/100. 161 Upasani et al., J. Pharm. BioSci. 4(2013)157-161.
[78] Chauhan PK, Pandey IP, Dhatwalia VK. Evaluation of the Antidiabetic Effect of Ethanolic and Methanolic Extract of Centella asiatica Leaves Extract on Alloxan Induced Diabetic Rats. Advan Biol Res. 2010; 4(1):27- 30.
[79] Sakurai T, Nishimura T, Otake N, Xinsheng Y, Abe K, Zeida M et al. novel triterpenoid saponins with insulin- like activity from Aesculus assamica Griff. Bioorg Med Chem Lett. 2002; 11(12):807-10.
[80] Karthikeyan J, Kavitha V, Abirami T and Bavani G. 2017.Medicinal plants and diabetes mellitus: A review; Journal of Pharmacognosy and Phytochemistry 2017; 6(4): 1270-1279
[81] Aboudi, Amal Al and Afifi, Fatma U. (2011) Plants used for the treatment of diabetes in Jordan: A review of scientific evidence, Pharmaceutical Biology,49:3,221-239, DOI:10.3109/13880209 .2010.501802 (online) (retrieved14, March2021) fromhttps://doi.org/10.3109/ 13880209.2010.501802
[82] Stehmann JR, Brandao MGL. Medicinal plants of Lavras Novas (Minas Gerias, Brazil). Fitoterapia 1995; 56(6): 515-520
[83] Florián, J.C et al. 2013 Emir. J. Food Agric. 2013. 25 (10):772-777 http://www.ejfa.info/ (online) (retrieved 17, March 2021)
[84] Greenberg JA, Axen KV, Schnoll R, Boozer CN. Coffee, tea and diabetes: the role of weight loss and caffeine. Int J Obes (Lond) 2005; 29:1121–1129
[85] Wu T, Willett WC, Hankinson SE, Giovannucci E: Caffeinated coffee, decaffeinated coffee, and caffeine in relation to plasma C-peptide levels, a marker of insulin secretion, in U.S. women. Diabetes Care 2005; 28: 1390–1396.
[86] King H, Aubert R, Herman W. Global burden of diabetes, 1995-2025. Prevalence, numerical estimates and projections. Diabetes Care 1998; 21: 141-143.
[87] Chatterjee, I. Chakravarty, A.K. and GomesaA. (2006): Br. J. Ethnopharmacology 106(1); 38-42.
[88] Laribi B. Kouki K, M'Hamdi M, Bettaieb T (2015) Coriander (Coriandrum sativum L.) and its bioactive constituents. Fitoterapia 103:9–26. https://doi.org/10.1016/j.fitot e.2015.03.012
[89] Naquvi KJ, Ali M, Ahmad J. Antidiabetic activity of aqueous extract of Coriandrum sativum L. fruits in streptozotocin induced rats. Indian J Exp Biol. 2004; 42(9): 909-12.
[90] Sreelatha S, Inbavalli R (2012) Antioxidant, antihyperglycemic, and antihyperlipidemic effects of Coriandrum sativum leaf and stem in alloxan-induced diabeticrats. J Food Sci. https ://doi.org/10.1111/j.1750- 3841.2012.02755.
[91] C. J. Nolan, P. Damm, and M. Prentki, "Type 2 diabetes across generations: from pathophysiology to prevention and management," The Lancet 2011; (378)9786,169181.
[92] Wahl, S.P. and Chunekar, K.C. (1964) Pharmacological studies on Gymenma sylvestre. J. Sci.Res., Banaras Hindu University 15,205-207
[93] Pivari, F., Mingione, A., Brasacchio, C., & Soldati, L. (2019). Curcumin and Type 2 Diabetes Mellitus: Prevention and Treatment. Nutrients, 11(8), 1837. https://doi.org/10.3390/nu11081837
[94] Dwivedi CP, Daspaul S. Antidiabetic herbal drugs and polyherbal formulation used for diabetes: A review. The journal of phytopharmacology;2013(2):44–51.
[95] Das AV, Padayatti PS Paulose CS (1996). Effect of leaf extract of Aegle marmelose (L.) Correa ex Roxb. on histological and ultrastructural changes in tissues of streptozotocin induced diabetic rats. Ind. J. Exp. Biol., 34: 341-345.
[96] Van Dam RM. Coffee and type 2 diabetes: from beans to beta cells. Nutr Metab Cardiovasc Dis 2006; 16: 69 – 77.
[97] Li L, Adams LS, Chen S, Killian C, Ahmed A, Seeram NP. Eugenia jambolana Lam. berry extract inhibits growth and induces apoptosis of human breast cancer but not non-tumorigenic breast cells. J Agric FoodChem.2009;57(3): 826-831.doi:10.1021/jf803407q
[98] Mathew PT and Augusti KT. Hypoglycemic effects of onion, Allium cepa Linn, on diabetes mellitus-apreliminary report. Indian Journal of Physiology and Pharmacology 1975; 19: 213-217.
[99] Aderibigbe A, Emudianughe T, Lawal B. Evaluation of the antidiabetic action of Mangifera indica in mice. Phytotherapy research. 2001; 15(5): 456-8. doi: 10.1002/ptr.859, PMID: 11507745.
[100] Sen, S., M. Roy and A.S. Chakraborti, 2011. Ameliorative effects of glycyrrhizin on streptozotocin-induced diabetes in rats. J. Pharm. Pharmacol., 63: 287- 296.
[101] Rawi SM, Abdelmoneim A, Ahmed OM. Studies on the effect of garlic oil and glibenclamide on alloxan diabetic rats. Egypt J Zool 1998; 30:211-28.
[102] Parmar HS, Kar A. (2008). Medicinal values of fruit peels from Citrus sinensis, Punica granatum and Musa paradisiacal with respect to alterations in tissue lipid peroxidation and serum concentration of glucose, insulin and thyroid hormones. J Med Food, 11, 376–381
[103] Chinaka, O.N., O.O. Julius and V.A. Onyeka, 2014. Hypoglycemic, hypolipidemic and anti-free radical effects of ethyl acetate extract of Bridelia micrantha (Hoechst) baill. (Euphorbiaceae) leaves in streptozotocin induced diabetic wistar rats. Am. J. Drug Discov. Dev., 3: 254-262.
[104] Khan, F.; Sarker, M.M.R.; Ming, L.C.; Mohamed, I.N.; Zhao, C.; Sheikh, B.Y.; Tsong, H.F.; Rashid, M.A. Comprehensive Review on Phytochemicals,

Pharmacological and Clinical Potentials of Gymnemasylvestre.Front. Pharmacol. 2019, 10, 1223. [CrossRef]

[105] Shanmugasundaram ER, Rajeswari G, Baskaran K, Rajesh Kumar BR, Radha Shanmugasundaran K, Kizar Ahmath B. Use of Gymnema sylvestre leaf extract in the control of blood glucose in insulin-dependent diabetes mellitus. J Ethnopharmacol 1990; 30: 281-294.

[106] Sathya, S.; Kokilavani, R.; Gurusamy, K. Hypoglycemic effect of Gymnema sylvestre (retz.,) R. Br leaf in normal and alloxan induced diabetic rats. Anc. Sci. Life 2008, 28, 12–14.

[107] Persaud, S.J.; Al-Majed, H.; Raman, A.; Jones, P.M. Gymnema sylvestre stimulates insulin release in vitro by increased membrane permeability. J. Endocrinol. 1999, 163, 207–212. [Cross Ref] [PubMed]

[108] Malvi R, Jain S, Khatri S, Patel A, Mishra S. A Review on Antidiabetic Medicinal Plants and Marketed Herbal Formulations International Journal of Pharmaceutical & Biological Archives;2011(2):1344– 1355.

[109] Dey L, Attele AS, Yuan CS. Alternative therapies for type 2 diabetes. Altern Med Rev 2002; 7:45-58.

[110] Eidi M, Eidi A, Saeidi A, Molanaei S, Sadeghipour A, Bahar M, Bahar K (2009) Effect of coriander seed (Coriandrum sativumL.) ethanol extract on insulin release from pancreatic beta cells in streptozotocin- induced diabetic rats. Phytotherapy Res23(3):404– 406.https://doi.org/10.1002/ptr. 2642

[111] Wild S., Roglic G., Green A., et al.: Diabetes Care 27, 1047 (2004).

[112] Md Yaheya Md Ismail et al (2010), “Role of Spices in Diabetes Mellitus”, Research Journal of Pharmaceutical, Biological and Chemical Sciences; 1 (3); July – September; 30.

[113] Saeed, F.; Afzaal, M.; Niaz, B.; Arshad, M.U.; Tufail, T.; Hussain, M.B.; Javed, A. Bitter melon (Momordica charantia): A natural healthy vegetable. Int. J. Food Prop. 2018, 21, 1270–1290. [CrossRef]

[114] Abhijeet Ghosh and Dr.Abhijit Dutta.2017 2017 IJEDR | Volume 5, Issue 4 | ISSN: 2321-9939

[115] Sharma KK, Gupta RK, Gupta S, Samuel KC. Antihyperglycemic effect of onion: Effect on fasting blood sugar and induced hyperglycemia in man. Indian J Med Res 1977; 65:422-9.

[116] Bordoloi R, Dutta KN. Review on Herbs Used in the Treatment of Diabetes mellitus. Journal of Pharmaceutical, Chemical and Biological. Sciences;2014(2):86–92.

[117] Arumugam G, Manjula P, Paari N. A review: Antidiabetic medicinal plants used for diabetes mellitus. Journal of acute diseases; 2013.

[118] Waheed, A.; Miana, G.A.; Sharafatullah, T.; Ahmad, S.I. Clinical Investigation of Hypoglycemic Effect of Unripe Fruit on Momordica Charantia In Type-2 (NIDDM) diabetes mellitus. Pakistan J. Pharmacol., v.25, p.7-12, 2008.

[119] Fuangchan, A.; Sonthisombat, P.; Seubnukarn, T.; Ch a n o u a n, T.; Chotchaisuwat, P.; Sirigulsatien, V.; Ingkaninan, K.; Plianbangchang, P.; Haines, S.T. Hypoglycemic Effect of Bitter Melon Compared with Metformin in Newly Diagnosed Type 2 Diabetes Patients. J. Ethnopharmacology., V.134, P.422-428, 2011.

[120] Tian, S.; Tang, M; and Zhao, B; 2016. Current anti- diabetes mechanisms and clinical trials using Morus albaL. Journal of Chinese medical Sciences, (retrieved 25, March 2021@https://doi.org/10.1016/ j. jtcms.2016.04.001

[121] Mudra, M; BA, Fang, N. E M. D; Zhong, L.MD; Furne, J.; and Levitt, M.MD.2007. Influence of Mulberry Leaf Extract on the Blood Glucose and Breath Hydrogen Response to Ingestion of 75 g Sucrose by Type 2 Diabetic and Control Subjects. Diabetes Care 2007May;30(5):1272-1274.https://doi.org/10.2337/ dc06 -2120

[122] Oku T, Yamada M, Nakamura M, Sadamori N, Nakamura S: Inhibitory effects of extractives from leaves of Morus alba on human and rat small intestinal disaccharidase activity. Br J Nutr 95:933–938, 2006PubMedGoogle Scholar

[123] Young Ju, and Morgan Kim.Anti-diabetic Potentials of White Mulberry. retrieved28, March2021@ https://www.pubs.ext.vt.edu/ content/dam/pubs_ext_vt_edu/HNFE/hnfe-518/HNFE- 518.pdf

[124] Alanazi, A.S.Md.; Anwar. Md.; and Alam, N.2017. Hypoglycemic and Antioxidant Effect of Morus alba L. Stem Bark Extracts in Streptozotocin-Induced Diabetes in Rats. Journal of Applied Pharmacy. DOI: 10.21065/1920-4159.1000234

[125] John L.S., John T. A., Lawrence A. L., et al.: J.Am. Coll. Nutr. 22, 524 (2003).

[126] H. J. Lee, Y. H. Lee, S. K. Park et al., “Korean red ginseng (Panax ginseng) improves insulin sensitivity and attenuates the development of diabetes in Otsuka Long- Evans Tokushima fatty rats,” Metabolism, vol. 58, no. 8, pp. 1170–1177, 2009.

[127] F. Chen, Y. Chen, X. Kang, Z. Zhou, Z. Zhang, and D. Liu, “Anti-apoptotic function and mechanism of ginseng saponins in Rattus pancreatic β-cells,“Biological& Pharmaceutical Bulletin, vol. 35, no. 9, pp. 1568–1573, 2012.

[128] H. Y. Kim and K. Kim, “Regulation of signaling molecules associated with insulin action, insulin secretion and pancreatic β-cell mass in the hypoglycemic effects of Korean red ginseng in Goto-Kakizaki rats,” Journal of Ethnopharmacology, vol. 142, no. 1, pp. 53–58, 2012.

[129] Tanira MO. Anti-diabetic medicinal plants: A review of the present status and future directions. Int J Diabetes Mellit 1994; 2:15-22.

[130] Bnouham M, Ziyyat A, Mekhfi H, Tahri A, Legssyer A. Medicinal plants with potential antidiabetic activity-A review of ten years of herbal medicine research (1990-2000). Int J Diabetes Metab 2006; 14:1

[131] Mishra R, Shuaib M, Shravan, Mishra PS. A review on herbal antidiabetic drugs. Journal of Applied Pharmaceutical Science. 2011; 1(6): 235-237.

[132] Vitaminol. (Tokyo), 53: 482-88. Improvement of insulin resistance by panax ginseng in fructose-rich

chowfed rats. Horm. Metab Res., 37: 146-51.
[133] H. Y. Kim and K. Kim, “Protective effect of ginseng on cytokine-induced apoptosis in pancreatic β-cells,” Journal of Agricultural and Food Chemistry, vol. 55, no. 8, pp. 2816–2823, 2007.
[134] Kamala, M.; Banu, M.S.; Vijaya Anand, A.; and Beena, W.S. (2011). Antidiabetic Potential of Psidium guajava Leaf extract: A review / Journal of Pharmacy Research 2011,4(6),1588-1589. ISSN: 0974-6943.
[135] Chandraprakash et al, Indian herbal medicines used for treatment of dementia: an overview, world journal of pharmaceutical research, volume 3, issue 6, 344-382.
[136] Rai PK, Jaiswal D, Mehta S, Watal G, Anti-hyperglycemic potential of Psidium guajava raw fruit peel. Indian J Med Res. 2009; 129: 561-565.
[137] Ozougwu JC. Anti-diabetic effects of Allium cepa (onions) aqueous extracts on alloxan-induced diabetic Rattus novergicus. Journal of Medicinal Plants Research;2011(5):1134–1139.
[138] Dwivedi CP, Daspaul S. Antidiabetic herbal drugs and polyherbal formulation used for diabetes: A review. The journal of phytopharmacology; 2013(2): 44–51.
[139] Nugroho AE, Andrie M, Warditiani NK, Siswanto E, Pramono S, Lukitaningsih E. Antidiabetic and antihyperlipidemic effect of Andrographis paniculata (Burm. f.) Nees and andrographolide in high-fructose-fat-fed rats. Indian journal of pharmacology 2012;44 (3):377–381.
[140] Khan BA, Abraham A, Leelamma S. Hypoglycemic action
[141] of Murraya koeingii (curry leaf) and Brassica juncea (mustard): mechanism of action. Indian Journal of Biochemistry and Biophysics;1995 (32):106–108.
[142] Seema P V, Sudha B, Padayatti S P, Abraham A, Raghu K G & Paulose C S, Kinetic studies of purified malate dehydrogenase in liver of streptozotocin-diabetic rats and the effect of leaf extract of Aegle marmelos (L.) Corr, Indian J Exp Biol, 34 (1996) 600.
[143] Kar DM, Maharana L, Pattnaik S, Dash GK. Studies on
[144] hypoglycemic activity of Solanum xanthocarpum Schrad. & Wendl. fruit extract in rats. J Ethnopharmacology. 2006Nov24;108(2): 251-6.doi: 10.1016/j.jep.2006. 05.016. Epub 2006 May 26. PMID: 16829003.
[145] Haq Nawaz, Saima Muzaffar, Momna Aslam and Shakeel Ahmad (October 10th 2018). Phytochemical Composition: Antioxidant Potential and Biological Activities of Corn, Corn - Production and Human Health in Changing Climate, Amanullah and Shah Fahad, Intech Open, DOI: 10.5772/intechopen.79648.
[146] JudeEfiomOkokon& Mandu Emmanuel Nyong (2018) Antidiabetic and hypolipidemic activities of Zea mays husk extract and fractions, Journal of Herbs, Spices & Medicinal Plants, 24:2, 134-150, DOI: 10.1080/10496475.2017.1423146
[147] Govindappa M, Chandrappa CP and Sadananda TS (2014) In vitro Antidiabetic Activity of Three Fractions of Methanol Extracts of Loranthus Micranthus, Identification of Phytoconstituents by GC-MS and Possible Mechanism Identified by GEMDOCK Method. Asian J Biomed Pharm Sci 4: 34-44.
[148] Adewole, E.; Ojo, A.; Omoaghe, AO.; Enye, LA.; and Jamshed, I. (2018) Antidiabetic potential of corn silk extracts, identification and drug properties of bioactive compound. Trends Med, 2018 doi: 10.15761/TiM.1000166
[149] Wannes WA, Marzouk B. Research progress of Tunisian medicinal plants used for acute diabetes. Journal of Acute Disease2016;5(5):357–363.
[150] Arablou, T.; Aryaeian, N.; Valizadeh, M.; Sharifi, F.; Hosseini, A.; Djalali, M. The effect of ginger consumption on glycemic status, lipid profile and some inflammatory markers in patients with type 2 diabetes mellitus. Int. J. Food Sci. Nutr. 2014, 65, 515–520.
[151] Mahluji, S.; Attari, V.E.; Mobasseri, M.; Payahoo, L.; Ostadrahimi, A.; Golzari, S.E.J. E_ects of ginger (Zingiber occinale) on plasma glucose level, hba1c and insulin sensitivity in type 2 diabetic patients. Int. J. Food Sci. Nutr. 2013, 64, 682–686.
[152] Adewole S.O., Caxton-Martins E.A. Morphological changes and hypoglycemic effects of Annona muricata Linn. (Annonaceae) leaf aqueous extract on pancreatic B-cells of streptozotocin-treated diabetic rats. Afr. J. Biomed. Res. 2006; 9:173–187. doi:10.4314/ ajbr. v9i3.48903.[GoogleScholar]http://www.epharmacognosy.com/2012/10/acacia-acacia-arabica-lam-willd.html
[153] http://www.epharmacognosy.com/2012/10/acacia-acacia-arabica-lam-willd.html
[154] https://www.marziaclinic.com/en/ingrediente/davana-2/
[155] https://urbantropicals.com/product/ancient-asian-bael-fruit-tree-aegle-marmelos/
[156] https://www.pngitem.com/middle/JRhmi_9-aloe-vera-aloe-barbadensis-miller-hd-png/
[157] https://ayushvedah.com/druginfo.php?drugid=738&info=cultivation
[158] https://www.flickriver.com/photos/blackdiamondimages/5489854399/
[159] https://www.flickr.com/photos/sharonwills/30649799443
[160] https://www.monaconatureencyclopedia.com/annona-muricata/?lang=en
[161] Wadood, Abdul; Wadood, Noreen & Wahid Shah, S. A., 1989Effects of acacia arabica and Caralluma edulis on Blood Glucose level of Normal and Alloxan Diabetic rats. ISSN (Print): 0030-9982; ISSN (Linking): 0030-9982- August 1989, Volume 39, Issue 8[Google Scholar]
[162] Lee, C. W., Lee, H. S., Cha, Y. J., Joo, W. H., Kang, D. O., & Moon, J. Y. (2013). In vivo Investigation of Anti-diabetic Properties of Ripe Onion Juice in Normal and Streptozotocin-induced Diabetic Rats. Preventive nutrition and food science, 18(3), 169–174. https://doi.org/10.3746/pnf.2013.18.3.169
[163] Charles, B., 1981. Acute Oral Toxicity Study. Dawson Research Corporation, DRC 2765. [Ref list]
[164] Jaiswal, Y. S., Tatke, P. A., Gabhe, S. Y., & Vaidya, A. B. (2016). Antidiabetic activity of extracts of Anacardium occidentale Linn. leaves on n-streptozotocin diabetic rats. Journal of traditional and complementary medicine, 7(4),421–427.https://doi.org/10.1016/j.jtcme.2016.11.007

[165] Saeed, Farah -; Ahmad, Mansoor. Anti-diabetic and acute toxicity studies of Annona squamosa L. ethanolic leaves extract. International Journal of Phytomedicine, [S.l.], v. 9, n. 4, p. 642-647, dec. 2017. ISSN 0975-0185. Availableat:<https://www.arjournals.org/index.php/ijpm/ article/view/2182>.Dateaccessed: 11May.2021.doi: http://dx.doi.org/10.5138/ 09750185.2182.

[166] Vasquez M R. Useful Plants of Amazonian Peru Second Draft. USA: Filed with USDA's National Agricultural Library; 1990. [Google Scholar] [Ref list]

[167] Adeyemi, D. O., Komolafe, O. A., Adewole, O. S., Obuotor, E. M., & Adenowo, T. K. (2008). Anti hyperglycemic activities of Annona muricata (Linn). African journal of traditional, complementary, and alternative medicines: AJTCAM, 6(1), 62–69.

[168] Feng PC, Haynes Lj, Magnus Ke, Plimmer Jr, Sherratt HS. J Pharm Pharmacol. 1962 Sep; 14():556-61. [PubMed] [Ref list]

[169] O.V. Sousa, G.D. Vieira, JJRGd Pinho, C.H. Yamamoto, M.S. Alves 2010.Antinociceptive and anti-inflammatory activities of the ethanol extract of Annona muricata L. leaves in animal models Int J Mol Sci, 11 (5), pp. 2067-2078. Google Scholar

[170] Singh P, Chacko KM, Aggarwal ML, Bhat B, Khandal RK, Sultana S, Kuruvilla BT. A-90 Day Gavage Safety Assessment of Boswellia serrata in Rats. Toxicology Int. 2012 Sep; 19(3):273-8. [PubMed]

[171] Mahdian, D., Abbaszadeh-Goudarzi, K., Raoofi, A., Dadashizadeh, G., Abroudi, M., Zarepour, E., & Hosseinzadeh, H. (2020). Effect of Boswellia species on the metabolic syndrome: A review. Iranian journal of basic medical sciences, 23(11), 1374–1381. https://doi.org/10.22038/ijbms.2020.42115.9957

[172] Pratibha C., Sunil Mahajan, M., Archana, K., Sadhana S., Bechan S.H. M., Goswamy, B., and Prasad, G. B. K. (2015). Bougainvillea spectabilis Exhibits Antihyperglycemic and Antioxidant Activities in Experimental Diabetes. Journal of Evidence-Based Complementary & Alternative Medicine 2016, Vol. 21(3) 177-185. DOI: 10.1177/2156587215595152.

[173] Vijay Patel M. and Meena Joshi. 2019. Antidiabetic Activity of Aqueous Extract of Caesalpinia Bonducella Leaves in Streptozotocin Induced Diabetic Rats. European Journal of Pharmaceutical and Medical Research. ejpmr, 2020,7(2), 362-367. ISSN 2394-3211

[174] Ukoha AI, Okereke SC, Arunsi UO, et al. Sub-lethal assessment of aqueous dried leaf extract of Catharanthus roseus (Linn.) g. don in male albino rats. MOJ Toxicology. 2017;3(5):128–133. DOI: 10.15406/mojt.2017.03.00068.

[175] Giribabu, N., Srinivasarao, N., Swapna, S., Rekha, S.S., Muniandy, S., and Salleh, N.2014. Centella asiatica Attenuates Diabetes Induced Hippocampal Changes in Experimental Diabetic Rats. EvidenceBased and Complementary Medicine. Volume 2014 |Article ID 592062https://doi.org/ 10.1155/ 2014/592062.

[176] Shah, A.H. et al .1998. Toxicity studies in mice of common spices, Cinnamomum zeylanicum bark and Piper longum fruits Plant Foods for Human Nutrition, 52: 231-239.

[177] Bisht, S. and Sisodia, S.S.,2011. Protective Role of Coffee Beans in Diabetes Mellitus Model of Rats. Journal of Pharmacy Research 2011,4(10),3717-3720. ISSN: 0974-6943.Availableonlinethroughhttp://jprsolutions.Info

[178] Sharma, V., Agrawal, R. C., and Shrivastava, VK. 2003. Assessment of median lethal dose and anti-mutagenic effects of Glycyrrhiza glabra root extract against chemically induced micronucleus formation in Swiss albino mice. International Journal of Basic & Clinical Pharmacology.OnlineISSN2279-0780/doi:10.5455/2319-2003.ijbcp20140407.

[179] Coria-Téllez, Ana V.; Montalvo-Gónzalez, Efigenia.; Yahia, Elhadi M.and Obledo-Vázquez, EvaN.2018. Annona muricata: A comprehensive review on its traditional medicinal uses, phytochemicals, pharmacological activities, mechanisms of action and toxicity. Arabian Journal of Chemistry.Vol.11, issue 5 July 2018, Pages 662-691. (retrieved 07, March 2021) from https://www.sciencedirect.com/science/article/pii/S1878535216000058? via%3Dihu

[180] Adewole S.O., Ezekiel A., Martins C.: Afr. J. Biomed. Res. 9, 173 (2006).

[181] Sharm SR, Dwivedi SK, Swarup D (1997). Hypoglycemic, antihyperglycemic and hypolipidemic activities of Caesalpinia bonducella seeds in rats. J. Ethnopharmacology., 58: 39-44.

[182] Sharma, S.R.; Dwivedi, S.K. and Swarup, D.1997.Hypoglycaemic, antihyperglycemic and hypolipidemic activities of Caesalpinia bonducella seeds in rats. Journal of Ethnopharmacology 58 (1997) 39–44

[183] (Ranasinghe, P., Galappaththy, P., Constantine, G.R. et al. Cinnamomum zeylanicum (Ceylon cinnamon) as a potential pharmaceutical agent for type-2 diabetes mellitus: study protocol for a randomized controlled trial. Trials18,446(2017). https://doi.org/10.1186/s13063-017-21