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REVIEW

Alternative Medicine in Diabetes – Role of Angiogenesis, Oxidative Stress, and Chronic Inflammation

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■ Abstract

Diabetes is a chronic metabolic disorder that is characterized by hyperglycemia due to lack of or resistance to insulin. Patients with diabetes are frequently afflicted with ischemic vascular disease and impaired wound healing. Type 2 diabetes (T2D) is known to accelerate atherosclerotic processes, endothelial cell dysfunction, glycosylation of extracellular matrix proteins, and vascular denervation. Herbal medicines and naturally occurring substances may positively affect diabetes management, and could thus be utilized as cost-effective means of supporting treatment in developing countries. Natural treatments have been used in these countries for a long time to treat diabetes. The present review analyses the features of aberrant angiogenesis, abnormalities in growth factors, oxidative stress, and metabolic derangements relevant to diabetes, and how herbal substances and their active chemical constituents may counteract these events. Evidence for possible biochemical effectiveness and limitations of herbal medicines are given, as well as details regarding the role of cytokines and nitric oxide.

Keywords: diabetes · herbal medicine · anthocyanidins · antidiabetic agent · endothelial cell · VEGF · cinnamon · figs

1. Introduction

Diabetes is a chronic metabolic disorder characterized by hyperglycemia and hyperlipidemia [1, 2]; it causes both impaired insulin secretion and insulin action [3]. The disease decreases life expectancy and negatively impacts quality of life by physiological, psychological, and social challenges. It is regarded the third-largest "destroyer" of human health through the development of micro- and macrovascular diseases, including neuropathy, nephropathy, and cerebro- and cardiovascular diseases [4-8].

Hyperglycemia is caused by both type 1 and type 2 diabetes, both of which cause endothelial cell dysfunction (ECD) by its different glycooxidative end-products [9]. One of the essential components of type 2 diabetes is insulin resistance, which is assumed to cause ECD through dyslipidemia and oxidative stress [4]. Obesity may cause inflammation in endothelial cells, and is thus linked to ECD and type 2 diabetes; it is regarded as an individual risk factor for the development of vascular complications [10, 11]. Obesity has been found to accelerate ECD in the presence of resistance to insulin more than in its absence [12, 13].

The prevalence of diabetes is increasing worldwide, affecting people in both developed and developing countries. The expected number of patients to be affected is estimated to reach 366 million by the year 2030 [14]. In most countries, 95% of diabetes patients are afflicted with type 2 diabetes. This trend is constantly carrying forward. The disease is reaching epidemic magnitudes and potentially evolving into a leading cause of morbidity and mortality in the near future due to the devastating micro- and macrovascular complications associated with it [15].

Abbreviations:
aFGF – acidic fibroblast growth factor
Ang – angiopoietin
APDS – allyl propyl disulfide
bFGF – basic fibroblast growth factor
ECD – endothelial cell dysfunction
ECM – extracellular matrix
EGFR – pidermal growth factor receptor
ETC – electron transport chain
FDA - Food and Drug Administration
GFR – glomerular filtration rate
GLP-1 – glucagon-like peptide 1
GRAS – generally recognized as safe
HGF – hepatocyte growth factor
HIF-α – hypoxic-inducible factors α
PD-ECGF – platelet-derived endothelial cell growth factor
PDGF – platelet-derived growth factor
PlGF – placental growth factor
PPARγ – peroxisome proliferator-activated receptor γ
PTP – protein tyrosine phosphatases
PTP1B – protein tyrosine phosphatase 1B
ROS – reactive oxygen species
SDF-1 – stromal-derived factor 1
T2D – type 2 diabetes
UGDP – University Group Diabetes Program
UKPDS – United Kingdom Prospective Diabetes Study
VCAM-1 – vascular cell adhesion protein 1
VEGF – vascular endothelial growth factor
VHL – von Hippel-Lindau

While available antidiabetic pharmacological agents have shown good success in controlling hyperglycemia, research has focused on novel antidiabetic agents with different mechanisms of action to better prevent hypoglycemic episodes and late vascular complications [16]. The array of treatment options is continuously expanding, with new options for type 1 and 2 diabetes patients suffering from different symptoms [17, 18]. New drugs in development based on natural substances could help in the management of both types of diabetes [19].

Approximately 20% of the population is using herbal medicine today [20]. Large fractions of the population in developing countries rely on herbal medicines, medicinal plants, and traditional practitioners, even though modern medicine is now available in most parts of the world. In past decades, public interest in natural therapies and the use of herbal medicines has also increased in industrialized countries; with 40% of adults in the U.S. have been reported to use them [21].

Herbal products are comprised of a complex mix of compounds. Organic chemicals can be developed from any raw or processed part of a plant including leaves, flowers, roots, and seeds. Manufacturers can produce and market herbals without demonstrating safety and efficacy, since unlike pharmaceutical drugs under current law, herbs are defined as dietary supplements. However, people have reported many varied side effects, which may be due to contaminants, interactions with other drugs, or their active ingredients, even though they are perceived as "natural" [22].

Currently, there is growing interest in herbal agents because of the side effects associated with oral hypoglycemic agents (therapeutic agents) in the treatment of diabetes. The traditional herbal medicines, which are primarily obtained from plants, may thus play an important role in managing diabetes. In recent years, herbal medicines have gained importance as a source of hypoglycemic agents [23, 24]. In 1990, more than 20,000 plants have been listed for the use of medicinal purposes [25], and even the number of 70,000 plant species has been cited [26].

The aim of the present review is to focus on the role of traditional therapeutics and natural medicines from the traditional medicinal system in the treatment of diabetes, and to highlight their benefits and limitations. Additionally, the article reviews the molecular mechanisms, including abnormalities in growth factors, cytokines, and metabolic derangements, highlights clinical implications, and illustrates therapeutic options based on natural medicine.

2. Angiogenesis in diabetes

2.1 Angiogenesis-stimulating conditions

Angiogenesis is the formation of a new capillary network (microvascular) in response to hypoxia or other stimuli. The process of angiogenesis involves the local secretion of angiogenic factors from both hypoxic endothelium and supporting pericytes that induce endothelial proliferation and neovessel sprouting [27]. This process is different from arteriogenesis, which is the growth and expansion of existing arteriole networks in response to acute arterial occlusion or physical forces (e.g., exercise-induced shear stress). Earlier, patients with long-term type 1 diabetes were described exhibiting abnormal blood vessels in glomeruli [28], and these findings were later shown to occur in patients with type 2 diabetes as well [29].

The concept of angiogenesis was first referred to as the sprouting of endothelial cells (ECs) from pre-existing vessels into previous vascular tissue. Recently, this concept was extended by the growth and remodeling process that modifies an initial

vascular system to form a complex branching network, characteristic of the mature vasculature [30]. Angiogenesis is, therefore, a complex multistage process involving extracellular matrix (ECM) degradation, proliferation, survival, migration, and morphological changes of ECs and their anastomosis to assemble into a vascular structure [31]. During angiogenesis, the perivascular ECM plays a critical role in determining proliferative, invasive, and survival responses of the local vascular cells.

The dynamic changes in both the ECM and the local vascular cells act in concert to regulate new blood vessel growth [32]. To enable this complex angiogenic process, a large number of pro- and anti-angiogenic factors need to act in a coordinated and synergistic manner to assemble functional blood vessels. The pathophysiological mechanisms characterizing diabetes encompass high glycemia, nonenzymatic glycation and lipoxidation end products, chronic inflammation, enhanced reactive oxygen species (ROS), and hyperinsulinemia [33]. Therefore, vascular cells are exposed to abnormally high concentrations of ROS signaling molecules in patients with diabetes; this scenario results in imbalanced signaling pathways. A specific characteristic of the pathogenesis of diabetes seems to be the paradox that vascular impairment and excessive angiogenesis co-exist in different organs [34].

2.2 Mechanisms of angiogenesis in diabetes

Angiogenesis requires the activation of many receptors by specific ligands, such as placental growth factor (PlGF), acidic and basic fibroblast growth factors (aFGF and bFGF, respectively), angiopoietins, hepatocyte growth factor (HGF), platelet derived growth factor (PDGF), and platelet derived-endothelial cell growth factor (PD-ECGF) [35]. For more than a decade, the role of vascular endothelial growth factor (VEGF) in the regulation of angiogenesis was the focus of intense investigation. Recent evidence indicated that new vessel growth and maturation are highly complex and coordinated processes, requiring the sequential activation of a series of receptors by numerous ligands. However, VEGF signaling often represents a critical rate-limiting step in physiological angiogenesis [36]. VEGF engages and activates its tyrosine kinase receptors VEGFR-1 and VEGFR-2 on ECs.

Despite VEGF binding to both receptors, the majority of its biological functions is mediated by VEGFR-2 signaling, which is involved in several steps of the angiogenic process [37]. Moreover, VEGF is the major factor involved in the endothelial progenitor cell (EPC) mobilization from the bone marrow to the peripheral circulation and the angiogenic sites, where they differentiate and integrate the neovasculature [38]. The majority of these receptors present in vascular wall cells act by triggering signaling cascades of phosphorylating kinases. Nonetheless, for these cellular transduction pathways to function properly, a balance between phosphorylating kinases and dephosphorylating phosphatases must exist. Protein tyrosine phosphatases (PTP) comprise a very large family of enzymes that catalyze dephosphorylation of tyrosine residues [39].

Diabetes-related insults including hyperglycemia, oxidative stress, and insulin resistance act frequently in concert with vascular cells impairing phosphorylation/dephosphorylation reactions, which may result in the enhancement of protein phosphorylation. Vessel remodeling is a consequence of PTP phosphorylation. Vascular cell adhesion protein VCAM-1-dependent lymphocyte extravasations through the endothelial layer require protein tyrosine phosphatase 1 B (PTP1B) phosphorylation, a highly expressed non-receptor PTP that possesses a variety of regulating properties [40].

Interestingly, the inhibition of PTP1B enhances epidermal growth factor receptor (EGFR) phosphorylation and activity, which result in proliferation in the corneal EC. Therefore, diabetes increases PTP1B activity in the retina, thereby preventing autophosphorylation of the retinal insulin receptor [41]. Altogether, these findings emphasize the relevance of this family of phosphatases in diabetes-derived vascular complications by their direct actions within the angiogenic phosphorylating signaling pathways. Targeting PTP may be a putative strategy for improving insulin sensitivity in diabetic patients [42].

2.3 VEGF-A and angiogenesis

Extensive evidence indicates that the pathologic ocular angiogenesis in diabetic retinopathy is regulated by vascular endothelial growth factor-A (VEGF-A). In the retina, the primary sources of VEGF-A are ganglion cells, Muller cells, and retinal pigment epithelium cells. High-affinity VEGF receptors have been identified in the retinal endothelial cells and pericytes. The ocular vasculature can be activated to produce new capillaries, a morphogenic process that is controlled by the angiogenic switch mechanism. The VEGF-A level in the ocular tissues correlates with new vessel for-

mation. On the other hand, VEGF-A plays a role in increasing vascular permeability and the development of macular edema in diabetic retinopathy. VEGF-induced leakage is likely mediated by various factors, including leukocyte-mediated endothelial injury, fenestrae formation, dissolution of tight junctions, and transcellular bulk flow. The amount and duration of VEGF exposure required for blood-retina barrier breakdown may be less than that required for neovascularization [43, 44]. Neovascularization may be necessarily preceded by an increase in vascular permeability [45].

2.4 Anti-angiogenic effects of natural herbs

It is helpful in the treatment of microvascular diabetic complications to suppress high VEGF exposure to vascular endothelial cells. Herbal extracts have shown VEGF-inhibitory effects. Anthocyanidins, which are constituents of bilberry anthocyanosides, are able to inhibit VEGF-induced tube formation [46]. They could thus be applied to prevent VEGF-induced endothelial injury.

Some herbs exert their anti-angiogenic properties by suppressing inflammation such as Ficus carica Linn., also called figs. A recent *in vivo* study showed that leukocyte accumulation and the production of TNFα, PGE2, and VEGF were significantly decreased. Angiogenesis was significantly inhibited by all administered doses of fig extract [47]. Interestingly, the angiogenesis and inflammation parameters exerted by the extract were similar to those of diclofenac. This biological activity may contribute to the prevention of vascular complications in diabetes.

3. Chronic inflammation in diabetes

Diabetes is characterized by inflammatory mediators, such as cytokines, growth factors, and free radicals that may be cytotoxic to β-cells and that may accelerate the development of diabetes. Among the free radicals, nitric oxide (NO) has attracted special attention [48]. The expression of the inducible form of nitric oxide synthase (iNOS) has been observed in different autoimmune diseases. iNOS is expressed by islet cells and invading macrophages in the insulitis present in diabetes-prone biobreeding rats and NOD mice [49]. Thus, inflammatory and oxidative events seem to act in concert in the development of chronic pancreatic inflammation leading to type 1 diabetes.

Moreover, iNOS mRNA expression is detected in both rodent and human pancreatic islets exposed to cytokines *in vitro* [50]. Transgenic expression of iNOS in cells induces cell destruction and diabetes, whereas the lack of iNOS expression prevents diabetes induced by multiple subdiabetogenic doses of streptozotocin and the *in vitro* inhibitory effects of interleukin (IL) 1 on mouse cell function. On the other hand, there are conflicting data on whether blocking iNOS activity by pharmacological agents prevents cytokine-induced cell dysfunction and death in both rodent and human islets [51, 52]. It is unclear whether radical NO contributes to cytokine-induced cell necrosis and apoptosis [53]. A possible reason for these conflicting observations is the use of non-specific pharmacological blockers of iNOS [54].

Pancreatic β-cells express another constitutive isoform of NOS, namely neuronal NOS (nNOS), which is assumed to participate in cell physiology. It is conceivable that pharmacological NO synthase inhibitors affect both isoforms of the enzyme [55]. Moreover, several analogs used to inhibit iNOS activity, such as aminoguanidine, may directly interfere with cell function, making it difficult to evaluate their potential impact on cytokine-induced β-cell dysfunction [56]. When pancreatic cells are exposed to cytokines, they express several genes and proteins that may contribute to cell dysfunction, death, or cell repair [57]. Among these genes are the putative protective agents, heat shock protein (hsp) 70 [58], manganese superoxide dismutase (MnSOD) [59, 60], and the pro-apoptotic gene Fas [61-63].

Different medical herbs have anti-oxidative and anti-inflammatory potential. Cinnamon polyphenols have been shown to inhibit iNOS expression and activation in diabetic mice [64]. Another effective herbal medicine is made from Ficus carica Linn. (Moraceae), commonly known as edible fig. Extracts from the leaves, roots, and fruits of the plant are medicinally used in several diseases. Recently Ali *et al*. reported about the anti-inflammatory and free radical scavenging activity of F. carica leaves [65]. Despite the fact that human studies are outstanding, it would be interesting to consider extracts from these herbs as concomitant treatment in a diabetes combination therapy.

4. Oxidative stress in diabetes

Another pathophysiological condition in diabetes is the presence of oxidative and nitrosative stress. Several lines of evidence indicate that ROS production activates signaling pathways that promote angiogenesis [66, 67]. ROS can be formed in many distinct ways in the human organism.

NAD(P)H oxidases (Nox) are present in vascular endothelial cells (ECs) and smooth muscle cells (SMCs), and are a relevant source of ROS formation from molecular oxygen. Moreover, a wide variety of angiogenic stimulators can be upregulated by Nox [68].

ECs present the endothelial isoform of nitric oxide synthase (eNOS), which contributes to ROS generation [69]. eNOS catalyzes the synthesis of nitric oxide (NO), an established scavenger of superoxide anion (O_2^-), but also a potent vasodilator and angiogenic stimulator. Recently, NO has been reported to promote ROS production [70]. Accordingly, NO may be reduced by the cytochrome c oxidase enzyme complex at the mitochondrial electron transport chain (ETC) in specific redox conditions, preventing oxygen reduction in water, which in turn leads to ROS accumulation [71]. In diabetes, ROS is extensively produced because of either the chronic inflammatory status or metabolic changes associated with this disorder (e.g., glucose and fatty acid elevation in plasma). ROS activates the stress-sensitive signaling pathways, which might cause insulin resistance and cell dysfunction, which are two mandatory conditions of diabetes [72].

Herbal extracts from several plants such as bilberry, cinnamon, and allium have been shown to possess antioxidant properties. They are able to inhibit ROS production and thus protect endothelial cells and even pancreatic islets from oxidative injury [46, 64, 73, 74]. Li *et al*. showed that streptozotocin-induced diabetic mice treated with cinnamon polyphenols showed significantly downregulated blood glucose and insulin levels in serum. The levels of oxidative stress markers were markedly lowered, shown by reductions in iNOS and NF-κB expression levels. Simultaneously, the pathological damage in pancreatic islet was significantly reduced [64].

5. Antidiabetic agents and their mechanisms of action

Type 2 diabetes (T2D) is a disorder characterized by insulin resistance and a progressive decline in pancreatic beta-cell function associated with increasing glucose levels. Defective beta-cell function occurs early, and can be detected in individuals with impaired fasting and/or postprandial glucose levels (prediabetes) [75].

The targets for glycemic control, as set by the American Diabetes Association (HbA1c < 7%) [76], and the American Association of Clinical Endocrinologists (HbA1c < 6.5%) [77], appear unattainable for many diabetics. As patients react differently to anti-diabetic drug therapy, the therapy needs to be tailored to the individual patient.

5.1 Insulin secretagogues

Suphonylureas (e.g. glibenclamide, gliclazide, glipizide, glimepiride) act to enhance the sensitivity of beta-cells to glucose. They are bound to the transmembrane sulphonylurea receptor (SUR-1) which mediates the potassium sensitive ATP channels on the cell membrane [78]. Even if glucose concentrations may be below the normal brink for glucose-stimulated insulin release, hypoglycemia can occur because the drugs are potentiating [79].

Non-obese type 2 diabetes patients who failed to improve on non-pharmacological measures are still a popular choice for sulphonylureas, even though metformin is now being recommended as the first-line therapy for all patients with type 2 diabetes [80]. Sulphonylureas can be used at the same time as other classes of anti-diabetic drugs except for secretagogues and that includes meglitinides, which can be used with long-acting insulin as part of a daytime / sulphonylurea night time regimen as well [81]. To achieve optimal glycemic control, it is recommended to start with a low oral dose. The dosage can be increased at intervals of 2 to 4 weeks.

The use of sulphonylureas is contraindicated in type 1 diabetes, pregnancy (class C indication for use), and renal and liver disease. The last two conditions drastically alter the half-life of these drugs, and can increase the plasma concentrations up to 3 times, which contributes greatly to increased risk of hypoglycemic events. It is not advisable to use these drugs once the glomerular filtration rate (GFR) falls to below 40 ml/min [82, 83].

Side effects that have been described include hypoglycemia, weight gain (1-4 kg over 6 months), skin reactions, acute porphyria, and hyponatremia [84]. There have also been reports indicating glimepiride-induced acute cholestatic hepatitis [85].

Non-sulfonylurea insulin secretagogues such as repaglinide are a new chemical entity, a carbamoymethyl benzoic acid derivative that differs structurally from sulphonylureas and belongs to the meglinitide group of drugs [86]. The inhibition of ATP that is dependent on potassium ion channels in the pancreatic beta-cell membrane results in the depolarization of the cell membrane and a higher amount of calcium ion transport through calcium channels that are voltage gated. Insulin

secretion along with intracellular calcium concentration is increased by repaglinide intake. Repaglinide is bound with a high likeness to a receptor that is different from sulphonylurea receptors. It also binds with low affinity to classic suphonylurea receptors. Because of the different binding, it results in more stimulation of insulin release. This is taken from the gastrointestinal (GI) tract that has a half-life of less than an hour. The liver primarily metabolizes it, and then it is mostly excreted in the bile, indicating this safer for use in renal failure patients and the elderly. It is a useful after-meal glucose regulator. The reduction can be pushed up by 1.5% when monotherapy causes a reduction in HbA1c of 1-2% [87]. These drugs can also be combined with other oral hypoglycemic agents (excluding SUs) with the added benefit [88]. Adverse effects include GI intolerance and hypoglycemia.

5.2 Insulin sensetizers

Biguanides were introduced in 1958. Following the UGDP study, they were out of favor because of fear of lactic acidosis, but have bounced back as they are known to significantly counteract insulin resistance. Metformin is preferred to phenformin, it does not inhibit mitochondrial oxidation of lactate, and lactic acidosis with this drug is a rarity. There are significant improvements in glycemic control, lipid profile, and no notable increase in plasma lactate, serum insulin, weight gain, and frequency of hypoglycemia has been observed with this group of drugs [89]. Its major modes of action include 1) inhibition of gluconeogensis, 2) reduction of hepatic glucose output, and 3) reduction of weight [90]. The improvement in insulin sensitivity is a byproduct of these alterations.

Contraindications include conditions predisposing the patient to hypoxia, impairment of renal function, shortened perfusion due to increased risk of lactic acidosis, history of lactic acidosis, and liver disease. There is a decrease in glucose levels estimated at 2-4 mmol/l, which causes a drop in HbA1c levels of 1-2% when used at the most favorable dosages. It was shown that overweight patients started therapy according to the UKPDS study. Biguanides have lower risks of myocardial infarction of about 39 percent more than patients on normal therapies [91]. Lactic acidosis is a known side effect. A reduction in the activity of pyrovate dehydrogenase enzyme, through shifting metabolism to the anaerobic spectrum, is because metformin increases lactate production in the portal venous system and in the splanchnic bed. However, cases of metformin-induced lactic acidosis are rare. Only 0.03 cases per 1,000 patient years are reported. Diarrhea and abdominal pain are side effects that are most common with these drugs. Also, vitamin B12 deficiency owing to decreased GI absorption rates can occur [92].

Pioglitazone and rosiglitazone are another group of insulin sensitizers called thiazolidinediones. They act by enhancing insulin sensitivity. They are used as adjuncts to diet and exercise in patients with type 2 diabetes. Although periodically used as monotherapy, thiazolidinediones are more frequently used in combination with other oral anti-diabetic agents and/or insulin in patients who do not reach glycemic goals. Clinical data suggest that patients taking thiazolidinediones may impair heart failure [93]. Therefore, they should be used with caution in patients with a history of cardiovascular disease. Their action depends on increasing insulin sensitivity by affecting the peroxisome proliferator-activated receptor γ (PPARγ). Acting as an agonist to PPARγ, thiazolidinediones decrease insulin resistance in adipose tissue, skeletal muscle, and liver. Adverse reactions are weight gain, edema, and hypoglycemia (when coupled with insulin or other hypoglycemic drugs) [94].

5.3 Glucosidase inhibitors (acarbose)

Glucosidase inhibitors (acarbose) are being widely used for postprandial glucose regulation. They are usually applied in T2D patients in conjunction with SUs or biguanides, or as monotherapy. In diet-treated T2D patients, the average decrease in postprandial blood glucose during acarbose treatments was 3 mmol/l; the maximum decrease in HbA1c was about one percent. It is recommended that acarbose doses of 50 to 200 milligrams be taken with the first bite of major meals three times a day. The way the dosages are titrated is important. The titration of doses is necessary to achieve the optimal benefits, and the least side effects, which include cramping, diarrhea, and flatulence [95].

5.4 New drug modalities mimicking incretins (exendin-4, liraglutide, vildagliptin, sitagliptin)

New drugs based on the incretin effect, slowed gastric emptying, or GI absorption are designed to improve therapy and to reduce side effects and hypoglycemia.

With food intake, the small intestine secretes glucose-dependent insulinotropic polypeptide (GIP, previously called a gastric-inhibitory peptide) and secretes glucagon-like peptide-1 (GLP-1). These types of hormones stimulate insulin gene expression, pancreatic beta-cell growth, and insulin secretion. Following oral administration of glucose, they mediate the incretin effect which augments insulin secretion. The DPP-IV (dipeptidyl peptidase) enzyme causes a rapid degradation in the GLP-1 molecule. Decreased levels of GLP-1 which lead to a drop in glucose-dependent secretion of insulin by the pancreatic beta-cells cause patients with type 2 diabetes to have a higher impaired or absent incretin-mediated insulin secretion [96, 97]. There are several ongoing clinical trials aimed at evaluating the long-term effects and possible side effects of the drugs, which include:

- Enzyme-resistant GLP-1 analogues (exendin-4)
- Albumin-bound GLP-1 derivatives (liraglutide)
- DPP-IV enzyme inhibitors (vildagliptin, sitagliptin)

5.5 Amylin analogues (pramlintide)

Human amylin is a 37-amino acid glucoregulatory peptide that is secreted by pancreatic beta-cells in combination with insulin. The effects caused by pramlintide, a synthetic analogue, include increased satiety and slowed gastric emptying. Application results in decreased postprandial glucose levels and reduced introductions of glucose into the circulation. Usually, pramlintide is administered through a subcutaneous injection before a meal. The peptide will then undergo renal clearance and has a t½ of 50 minutes. It is well tolerated and there is no risk of hypoglycemia [98, 99].

6. Herbal medicines and treatment of diabetes

Herbal medicines have gained attention in the last decades. The demand for natural products to treat diabetes is increasing worldwide. More than 1,000 plant species are used as folk medicine for diabetes [100, 101]. The chemical composition-based biological actions of plant products used as alternative medicines for treating diabetes are related to each other. Several plant and herbal products are rich in constituents that cause reductions in blood glucose levels. Among these constituents are coumarins, flavonoids, phenolic compounds, terpenoids, and many more [102, 103]. Also, several species of herbal medicines have been described in the scientific and popular literature as having anti-diabetic activity [104]. Plants have been used as a dietary adjuvant for treating numerous other diseases until today, even though their chemical constituents and biological mechanisms are not fully understood. This practice may be attributed to the uncompromised cost and side effects of synthetic hypoglycemic agents [105, 106].

In this regard, the use of plants and plant extracts for treating a disease or disease symptoms have played a role in medical care for thousands of years. Although the use of plant extract is no longer a major aspect of medical care practiced in Western countries, it is still popular in large parts of the world's population, particularly in Asia and Europe [107]. However, many pharmaceutical agents currently being prescribed have been derived from natural compounds found in traditional medicinal plants; a fact that seems to be disregarded by medical practitioners in the western world [108]. A specific example is biguanide metformin, which is considered to be one of the first-line agents used for treating type 2 diabetes. Its use can be traced back to the traditional use of Galega officinalis, which was applied to treat diabetes, and the subsequent search to identify active compounds with reduced toxicity [109]. It has been reported that more than 1,200 traditional plants have been used for actual or perceived benefits in the treatment of diabetes [110]. Many spices and herbs have a long history of traditional use in treating elevated blood sugar levels [111].

6.1 Crude cinnamon

Cinnamon is one of the compounds which have recently been the subject of intense research; it is generally regarded as safe (GRAS) when ingested, as approved by the US Food and Drug Administration (FDA). Cinnamon has many pharmacological properties, such as anti-oxidant activity and antibacterial effects [112, 113]. It has been demonstrated that cinnamon increases insulin-dependent *in vitro* glucose metabolism and decreases fasting blood glucose [114-116]. Recently, cinnamic acid extract was shown to improve glucose tolerance *in vivo* and stimulating insulin secretion *in vitro* [117]. The herb could thus be beneficial in the control of glucose intolerance and type 2 diabetes.

6.2 Bilberry (Vaccinium myrtillus)

Bilberry anthocyanoside extract is recognized as highly effective in preventing diabetic retinopa-

thy, with several clinical studies supporting its efficacy [118]. Although bilberry constituents have multiple pharmacological actions, most of the research has focused on anthocyanosides, which belong to a family of molecules called flavonoids. Constituents from anthocyanosides, in particular anthocyanidins, possess strong antioxidant properties. They were able to scavenge 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals in human umbilical vein endothelial cells [46], and to reduce ROS levels and oxidative DNA damage in human colon cells [72].

Further beneficial effects comprise the stabilization of collagen fibers, promotion of collagen biosynthesis [119], decrease of capillary permeability and fragility by inhibiting VEGF-induced injury [46, 120], and inhibition of platelet aggregation [121]. Moreover, anthocyanosides and bilberry leaf constituents prevent the release and synthesis of pro-inflammatory compounds, such as histamine, prostaglandins, and leukotrienes [122]. Finally, bilberry extracts administered orally have been shown to lower blood glucose levels [123, 124] and improve the lipid profile by counteracting hypercholesterolemia [125]. Thus, a healthy diet with a high content of flavonoids indicates preventive properties in diabetes and its vascular complications. In particular, bilberry anthocyanosides have shown the highest efficacy compared with other flavonoids in most of the studies cited here.

7. Further herbal products used as traditional antidiabetic medicine

For many years, the use of herbal extracts as medicinal products has been an important part of nearly every culture on earth. In the areas in which the plants grow, herb and plant derivatives listed below are applied traditionally in the treatment of diabetes.

7.1 Allium

Allium cepa (onion) and Allium sativum (garlic) belong to the Liliaceae family. The plants probably originate from southwest Asia, but are widely cultivated throughout the world today. Allium cepa has a bulb that lies underground as part of the stem, and is often used as household vegetable. For hundreds of years, Allium has been used medicinally. Its most popular application is to lower blood pressure [126, 127]; besides it acts antiseptic [128], hypoglycemic, hypocholesterolemic [129], and inhibits oxidative stress [74, 130]. Allium cepa's active ingredient is allyl propyl disulfide (APDS); it also has active sulfurous compounds, such as S-methyl cysteine sulphoxide (SMCS), which act in an antidiabetic and hypolipidemic manner [130].

7.2 Bauhinia candicans (Pata de vaca)

The hypoglycemic activity found in Bauhinia candicans or Pata de vaca's was reported first by a Brazilian researcher in an *in vivo* clinical study conducted in 1929, which was then followed up by another *in vivo* study in 1931 using dogs [131, 132]. In 1941, the same Brazilian researcher published another study showing the antihyperglycemic effects of pata de vaca in rabbits, dogs, and humans [133]. In 1945, a study was started to determine the active constituents that are responsible for the antihyperglycemic activity [134]. It quickly became a popular natural remedy because it was a simple tea leaf that could help to balance sugar levels. However, no studies were started or completed for many years because of a lack of funding for nonproprietary drugs and remedies.

Two further Brazilian studies were performed in the mid-1980s, when herbal remedies became popular once again. Pata de vaca's continued use as a natural insulin substitute was backed up by these studies. Both studies showed *in vivo* hypoglycemic actions in different human and animals [135, 136]. In 1999, a Chilean study discovered the actions of pata de vaca in alloxan-induced diabetic rats. The study showed that pata de vaca exerted exceptional hypoglycemic effects, and generated a decrease of glycemia in alloxan diabetic rats by thirty nine percent [137].

In 2002, two more *in vivo* studies by two independent research groups from Brazil confirmed the blood-sugar-lowering effects of pata de vaca. In the first study, a significant blood glucose-lowering effect was seen at dosages of 500 mg/kg (in normal rats) and 800 mg/kg (in diabetic rats) [138]. In the second study, 150 g of the leaf per liter of water was given to streptozotocin-diabetic rats in drinking water. For more than a month, those animals receiving pata de vaca showed a noticeably high reduction in serum and urinary glucose and urinary urea compared with the control group [139]. Pata de vaca is still a popular natural medicine for patients with diabetes in South America; the clinical research conducted so far supports its continued use. The usual way to consume it is to brew it like tea and take it after meal. Pata de vaca is frequently combined with pedra hume caá which is another South American plant also used as tea af-

ter meal. North American practitioners and herbalists are now applying it to treat diabetes, hyperglycemia, and polyuria [140].

7.3 Coccinia indica

Coccinia indica, also known as Coccinia grandis, Coccinia cordifolia, ivy gourd, or little gourd, is part of the Cucurbitaceae family known as Kandutikibel in Hindi, Bimba in Sanskrit, and Rantondli in Marathi. Ayurvidic and Unani practitioners in the Indian subcontinent use the plant extensively [141]. It is a smooth green fruit with long fleshy roots.

The juice of the roots is used to treat diabetes. The plant has other therapeutic uses. Gonorrhea is treated from the tincture of the leaves; a paste made from the leaves is used to treat skin diseases. A good cathartic is used from dried bark. Antispasmodic and expectorant are made from the leaves and stems. The green fruit is very bitter to the taste, but is used to cure sores on the tongue when chewed [142].

7.4 Figs

Figs (Ficus carica Linn.) are a widespread species commonly grown, especially in warm, dry climates. For centuries figs have been cultivated; so long in fact that it is the most frequently fruit talked about in the Bible [143]. The synonym for fig is sycomorous from the family of Moraceae. Native systems of medicine use the fruit, roots and leaves for the treatment of different respiratory disorders such as sore throat, bronchial problems, and cough. They are also used for gastrointestinal disorders such as loss of appetite, colic, diarrhea, and indigestion. Cardiovascular disorders are treated with figs as well [144]. The fruit extracts possess antianaemia and anticarcinogenic activity. Traditionally, the plant is used as purgative, aphrodisiac, anti-inflammatory, expectorant, diuretic, and anti-anxiety (mild sedative). Due to its antioxidant, anti-inflammatory, and antispasmodic purposes [65], fig is used as a cardiovascular, metabolic, respiratory, and antispasmodic drug [145].

7.5 Ginseng

The hypoglycemic ability of ginseng root extract has been known for a few decades. Our laboratory has recently demonstrated similar biological activities of berry and leaf extracts of Asian and American ginseng in diabetic and obese transgenic mouse models [146, 147]. Others have found antidiabetic effects in streptocytocin-induced diabetic rats [148]. The total ginsenoside concentration and the proportion of specific ginsenosides in the root, berry, and leaf of ginseng plants are different and could account for differences in their antidiabetic effects.

On the other hand, the known adverse effects of ginseng are substantial and include insomnia, diarrhea, vaginal bleeding, breast pain, headache, schizophrenia, and fatal Stevens-Johnson syndrome [149]. The recommended dosage of ginseng application is 1-3 g of root or 200-600 mg of extract [150]. Ginseng can extend bleeding time; it should therefore not be used in combination with warfarin. It may also cause headache, tremulousness, and manic episodes in patients treated with phenelzine sulfate [151].

8. Conclusions

More than 300 million people worldwide are treated for diabetes; it is the most common endocrine disorder. Therapies developed based on western medicine principles sometimes lack efficiency or have serious adverse effects, and they are costly, especially for developing countries. Treating diabetes with plant-derived compounds may be an alternative and has some benefits such as accessibility, non-requirement of pharmaceutical synthesis, cost-effectiveness, and convenience of usage.

The use of plants for medicinal purposes, and the study of such use, may be promising for the development of alternative, safe, and cost-effective medication in the treatment for diabetes and its vascular complications. Despite the availability of effective pharmacological agents, traditional medicine is still widely practiced today. On the other hand, modern medicine recognizes herbalism as a form of alternative medicine, as the practice of herbalism is not strictly based on evidence gathered by scientific methods. However, plants have been the basis for medical treatments ever since. Modern medicine makes use of plant-derived compounds as basis for evidence-tested pharmaceutical drugs and phytotherapy works to apply modern standards of effectiveness to testing of herbs and medicines that are derived from natural sources.

Herbal medicines are still in their infancy and warrant additional examination and confirmation. Research has been lagging in preparing antidiabetic herbal formulations using novel medication delivery systems to achieve effective diabetes treatment. The herbal substances reviewed in this article provide beneficial antidiabetic, antioxidant,

antiangiogenic, and anti-inflammatory effects. Given the high medicinal potential of natural and herbal drugs, the safety and effectiveness of these compounds needs to be explored more intensively and expeditiously in order to develop new medications for the treatment of diabetes, vascular complications, and inflammation. Medication based on herbal products can be produced in several ways: using methodologies similar to the traditional medicine, preparing extracts developed for phytotherapy, or pharmacologically isolating the active compounds. Probably, it is even recommendable to use the entire herbal product or extract and avoid isolation as the plants contain further compounds, such as flavonoids, cyanins, polyphenols, and other substances in combinations not yet determined by pharmacology.

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