Review

Phytotherapy in the Management of Diabetes: A Review

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Abstract: Phytotherapy has long been a source of medicinal products and many attempts to use herbal medicine for the treatment of diabetes has been done over the years. Several medicinal plants and their preparations demonstrated to act in key points of glucidic metabolism. The most common mechanisms of action found include the inhibition of α-glucosidase and of AGE formation, the increase of GLUT-4 and PPARs expression and the antioxidant activity.
Despite the large amount of literature available, the actual clinical effectiveness of medicinal plants in controlling diabetes related symptoms is still controversial and there is a crucial need for stronger evidence-based data.
In this review, an overview of the medicinal plants, which use in the management of diabetes is supported by authoritative monograph, is provided. References to some species which are currently under growing clinical investigation are also reported.

Keywords: phytotherapy; hyperglycemia; diabetes; medicinal plants

1. Introduction

In the last decade, the concept of metabolic syndrome (MS) has been extensively debated by the scientific community [1–3]. Although the difficulty in establishing an exhaustive definition [4], MS is nowadays recognized as a major cardiovascular disease risk factor by the World Health Organization (WHO) and other institutions such as the International Diabetes Federation (IDF)[5–7]. MS can be defined as a concurrence of conditions, including obesity, hypertension, dyslipidemia and altered glycaemia [8]. MS is associated with a higher risk of type 2 diabetes and cardiovascular diseases onset [9] and involves about 25% of the world's adult population [10], with women having a higher risk of developing MS [11].

Phytotherapy has long been a source of medicinal products and many attempts to use herbal medicine for the treatment of diabetes has been done over the years [12,13]. Furthermore, the number of scientific publications regarding herbal medicine and type 2 diabetes is continuously increasing [14].

Among the possible mechanisms of action of natural products in diabetes, the inhibition of α-glucosidase and α-amylase, the effects on glucose uptake and glucose transporters, the enhancement of insulin secretion and of pancreatic β-cell proliferation, the inhibition of protein tyrosine phosphatase 1B activity and the antioxidant activity have been deeply studied [15].

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Despite the large amount of literature available, the real clinical effectiveness of medicinal plants in the management of diabetes is still controversial and there is a crucial need for stronger evidence-based data [16].

The aim of this review is to provide an overview of the use of medicinal plants in the management of diabetes, focusing on the species which use is supported by authoritative documents such as the monographs drafted by the World Health Organization (WHO). Furthermore, a deepening on some of the most promising species, which are attracting the interest of the scientific community, is also provided.

2. Medicinal plants used for the management of diabetes

Medicinal plants possessing therapeutic uses in diabetes and supported by clinical data or described in pharmacopoeias and well established documents are enlisted in WHO monographs and they are reported in table 1.

Table 1. Species enlisted in WHO monographs with indication of use for diabetes.

Use supported by clinical data	Use described in pharmacopoeias and in traditional systems of medicine
Ocimum tenuiflorum L., folium *Trigonella foenum-graecum* L., semen	*Allium cepa* L., bulbus *Azadirachta indica* A. Juss., folium *Momordica charantia* L., fructus *Ocimum tenuiflorum* L., folium *Panax ginseng* C.A. Meyer, radix *Panax quinquefolius* L., radix *Rehmannia glutinosa* (Gaertn.) DC., radix

2.1 Allium cepa L., bulbus

Allium cepa L. is a perennial herb belonging to the family of Amaryllidaceae. The herbal substance is represented by the fresh or dried bulbs, commonly known as onion, which are commercially cultivated worldwide [17]. The main chemical constituents are sulfur-containing compounds, such as L-cysteine sulfoxides, and flavonoids, such as quercetin and its glycosides [18].

A. cepa seems to exert its antidiabetic activity regardless of the form in which it is administered [19].

A preliminary study evaluated the hypoglycemic effects of the oral administration of small slices of *A. cepa* (100 g/day) in type 1 and type 2 diabetic patients. Onion exhibited significant antidiabetic effects, reducing fasting blood glucose by about 89 mg/dl in type 1 diabetes patients and by 40 mg/dl in type 2 diabetes patients. A reduction of the induced hyperglycemia by 120 mg/dl in the diabetes 1 group and by 159 mg/dl in the type 2 diabetes was also observed [20].

In 2009, an *in vivo* study demonstrated that *A. cepa* (7% freeze-dried onion powder added into control diet) may represent an interesting anti-hyperglycaemic dietary adjunct for diabetic

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therapy, since it decreases serum cholesterol, triacylglycerol and LDL-cholesterol in streptozocin-induced diabetics rats, without alterations in the cholesterol and HDL-cholesterol concentrations [21]. Hyperglycemia causes glucose autoxidation, impaired mitochondrial bioenergetics and induce reactive oxygen species (ROS) production, leading to an impairment of intracellular pathways (i.e. JAK/STAT, JNK, p38, ERK/MAPK) and to insulin resistance [22]. Onion (400 mg/day) possesses a significant free radical-scavenging property and exerts a regulation on lipid metabolism, decreasing superoxide dismutase activity and lowering lipid hydroperoxide and lipoperoxide concentrations in diabetic rats [23].

A. cepa exerts its antidiabetic activity through multiple pharmacologic actions attributed to the presence of many active constituents: for example, quercetin is responsible for α-glucosidase inhibition [24] and, along with rutin, for the increase of GLUT-4 translocation, glucose uptake and insulin action [25]. Differently, L-cysteine sulfoxides and allyl propyl disulphide can act directly as free radicals scavengers. In fact, they take part in the redox process of glutathione and cysteine, and can also increase the activity of superoxide dismutase and catalase, independently or through the stimulation of insulin secretion [26,27].

2.2. *Azadirachta indica* A. Juss., folium

Azadirachta indica A. Juss., also known as neem, is a deciduous tree belonging to the family of Meliaceae. The herbal substance is represented by the dried leaves [28]. It contains characteristic compounds, such as oxidized tetranotriterpenes, known as azadirachtins [29].

An ethanolic extracts (400 mg/kg) obtained from neem leaves demonstrated several effects, such as anti-lipid peroxidation, anti-hyperglycaemic and anti-hypercholesterolaemic activities as well as a reduction in serum triglyceride levels in alloxan-induced diabetic rats [30].

Two water extracts were also tested in high-fat diet-induced diabetic rats (400 mg/kg) and in normal and alloxan-induced diabetic rabbits (500 mg/kg), showing a partial prevention of the rise in blood glucose levels and a normalization of the altered levels of serum insulin, lipid profile and insulin signaling molecules as well as GLUT-4 proteins [31,32].

Chloroform extracts activities were studied *in vitro* and *in vivo* in streptozocin-induced diabetic rats (200-300 mg/kg) produced an attenuation of non-enzimatic glycation, inhibiting advanced glycation end product (AGE) formation, and alleviated oxidative stress, increasing level antioxidant enzymes, glucose-6-phosphatase, hepatic glycogen content and insulin plasma levels, and decreasing glucokinase and lipid peroxidation [33,34].

The main mechanism of action of azadirachtins (*e.g.* azadirachtolide, azadiradione, gedunin and meliacinolin) is the inhibition of α-amylase and α-glucosidase [35–37].

2.3. *Momordica charantia* L., fructus

Momordica charantia L. is a monoecious annual climbing vine belonging to the family of Cucurbitaceae. The herbal substance is represented by the fresh or dried fruits, known as bitter melons [38]. The main chemical constituents are sterols, triterpenes and bioactive proteins [39].

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The clinical potential of bitter melon has been examined administering capsules or tablets containing preparations from bitter melon fruits or leaves, in diabetic patients. No statistically significant improvement of blood glucose control, in terms of normalization or reduction of fasting blood glucose, reduction of glycosylated haemoglobin A1c or fructosamine, compared to placebo have been observed [40–42]. More recently, *M. charantia* capsules (500 mg of dried powder of the fruit pulp, containing 0.04-0.05% of charantin), administered in type 2 diabetes patients (2000 mg/day), demonstrated a significant decrease in fructosamine levels after 4 week of treatment and no side effects were observed [43].

The whole plant and/or different plant parts such as fruit pulp, seeds, and leaves have been reported to possess hypoglycemic and anti-hyperglycemic activities in several animal models: in particular, bitter melon reduced blood glucose levels and increased plasma insulin [44].

The activation of the AMP-activated protein kinase (AMPK) system and a role of the α- and γ-peroxisome proliferator-activated receptors (PPARα and PPARγ) have been hypothesized as possible mechanisms of action for *M. charantia* in diabetes treatment [45–47].

Cucurbitane triterpenoids from *M. charantia* displayed hypoglycemic effect, reducing blood glucose levels, moderating insulin secretion activity, increasing glucose uptake through stimulation of GLUT-4 translocation and increasing the phosphorylation of AMPK and insulin receptor substrate-1 [48–52].

Among bitter melon triterpenoids, 5β,19-epoxy-25-methoxy-cucurbita-6,23-diene-3β,19-diol (EMCD) and momordin have been studied in detail: it has been observed that EMCD (20 μM) can suppress the TNF-α induced expression of iNOS and nuclear translocation of NF-κB in FL83B mouse liver cells [53], while momordin is responsible for the increase of PPARδ mRNA expression at nanomolar concentrations in HepG2 human liver cells [54].

Despite the copious data from *in vitro* and *in vivo* studies, the available clinical data are often flawed by small sample size, lack of control and poor study designs. Better-designed clinical trials with sufficient sample size and statistical power will be indispensable to further confirm the efficacy of *M. charantia* as a natural treatment for diabetes mellitus [55].

2.4. Ocimum tenuiflorum L., folium

Ocimum tenuiflorum L., commonly referred to as tulsi, is a up to 1 meter high herb or shrub belonging to the family of Lamiaceae. It is indigenous to India and parts of north and eastern Africa, Hainan Island and Taiwan, China and the herbal substance is represented by the fresh or dried leaves [56]. The main chemical components are tannins and essential oil (mainly composed of eugenol, methyleugenol, and α- and β-caryophyllene) [57].

In 1996, a randomized, placebo-controlled, crossover single blind trial analyzed the effects of *O. tenuiflorum* and *O. album* leaves on fasting and postprandial blood glucose and serum cholesterol levels in patients with noninsulin-dependent diabetes mellitus. A significant decrease in fasting and postprandial blood glucose levels, a similar trend in urine glucose, and a mild reduction of mean total cholesterol levels during treatment period were observed [58].

More recently, a randomized, parallel group, open label pilot study investigated the effect of tulsi extract on metabolic and biochemical parameters in 30 young overweight/obese subjects.

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The supplementation with *O. tenuiflorum* capsules (250 mg twice daily for 8 weeks) decreased plasma insulin and insulin resistance by 28.49% and 24.79% respectively, caused the normalization of serum lipid profile, and reduced body weight and BMI, compared to the control group (no intervention) [59].

Animal studies enlightened that the oral administration of *O. tenuiflorum* aqueous extracts (200 mg/kg) could delay the development of insulin resistance. Indeed, tulsi determined a considerable improvement in fasting blood glucose and in glucose tolerance and a correction of the abnormal lipid profile, through the reduction of serum total and LDL cholesterol levels. A decrease of the levels of lipid peroxidation, increasing not only the level of antioxidant compound reduced glutathione, but also the activity of antioxidant enzymes (*i.e.* glutathione peroxidase, glutathione S-transferase, superoxide dismutase and catalase) have also been observed [60–62].

Ethanol (80% w/w) extracts obtained from *O. tenuiflorum* leaves were effective in lowering of blood glucose levels in normal, glucose fed hyperglycemic and streptozocin-induced diabetic rats, also potentiating the action of exogenous insulin in normal rats [63]. The glucose lowering effects was found to be mediated through its insulin secretagogue effects on *ex vivo* rat pancreas and in BRIN-BD11 rat clonal β-cells [64].

A reduction in the level of hepatic lipids and the reversion of the diminution of lipoprotein lipase, plasma postheparin lipolytic and lecithin cholesterol acyl transferase activities was obtained by administering 500 mg/kg of a different *O. tenuiflorum* ethanolic (95% w/w) leaves extract for 15 days in streptozocin-induced diabetic rats [65].

It has been proposed that fixed oil extracted from *O. tenuiflorum* leaves (46.54 mg/kg/day for three weeks) may be responsible for the free radical scavenging activity, for the decrease in plasma glucose and for the increase in insulin release observed in streptozocin-induced diabetic rats, and this has been related to the content in α-linolenic acid [66].

16-hydroxy-4,4,10,13-tetramethyl-17-(4-methyl-pentl)-hexadecahydro-cyclopenta[a]phenanthren-3-one, a tetracyclic triterpenoid isolated from the aerial part of *O. tenuiflorum*, was able to decrease serum glucose levels, total cholesterol, triglycerides and HDL cholesterol and to increase serum LDL cholesterol level in alloxan-induced diabetic rats [67].

2.5. Panax ginseng C.A. Meyer, radix and *Panax quinquefolius* L., radix

Ginseng has been used in traditional Chinese medicine for more than 5000 years [68]. Thanks to its restorative, tonic, nootropic, and anti-aging properties [69], in fact, ginseng preparations have been applied to several pathological conditions such as hypodynamia, anorexia, shortness of breath, palpitation, insomnia, impotence, hemorrhage and diabetes [70].

Confirming the clinical strength of many of the traditional uses of ginseng, in 2014 the European Medicines Agency released a monograph which validated the use of ginseng as a traditional medicine for treating asthenia in western countries too [71].

In medicine, the term ginseng may usually refers to several *Panax* species, which are often used indiscriminately. Nevertheless, the most common used are *Panax ginseng* C.A. Meyer and *Panax quinquefolius* L. In this review, the antidiabetic properties of *P. ginseng*, *P. quinquefolius* and their main constituents will be discussed together.

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188 *Panax ginseng* C.A. Meyer is a perennial herb, native to Korea, Cina and Japan, with
189 characteristic branched roots belonging to the family of Araliaceae. The herbal substance is
190 represented by the dried roots, which main constituent are triterpenes saponins, known as
191 ginsenosedes [17].
192 *Panax quinquefolius* L. is a perennial herb belonging to the family of Araliaceae. Differently
193 to *P. ginseng* it is native to North America. The herbal substance is represented by the dried roots,
194 containing ginsenosedes, with a higher concentration of protopanaxadiols compared to *P. ginseng*
195 [72].
196 Several systematic reviews described the potential of ginseng in the management of
197 diabetes. In 2011, Kim and coworkers analyzed data deriving from four different randomized
198 clinical trials in which ginseng (0.78-6 g/day for a maximum of 12 weeks) demonstrated no
199 significant effects in controlling blood glucose in type two diabetes patients [73]. Nevertheless,
200 promising results in improving glucose metabolism were found by Shergis and colleagues in 2013,
201 by analyzing 6 clinical trials [74]. More recently, Shishtar and colleagues evaluated sixteen trials in
202 which 0.1-20 g/day of different ginseng preparations were administered for 4-24 weeks to patients
203 with and without diabetes. A modest yet significant reduction of fasting blood glucose was
204 observed in both groups [75]. Finally, in 2016, a meta-analysis from Gui and coworkers failed to
205 attributed significant improvement in hemoglobin A1c levels for ginseng treated patients (0.96-13.6
206 g/day for 4-20 weeks) alone and in combination with conventional therapies, compared to control
207 group. However, improved fasting glucose and post prandial insulin levels were observed when
208 ginseng was administered alone [76].
209 The effects of ginseng extracts and its main constituents have been extensively studied *in*
210 *vivo*. Ginseng total saponins (150-300 mg/kg) significantly reduced hyperglycemia by increasing
211 glucagone-like peptide-1 in high fat and low streptozocin-induced diabetic rats [77]. A fractionated
212 extract containing water soluble ginseng polysaccharides, administered 1 g/kg/day for 2 weeks to
213 streptozocin-induced diabetic rats, caused significant effects on purine, tryptophan, fatty acids and
214 energy metabolism [78]. Protopanaxadiol and protopanaxatriol-type saponins (50-150 mg/day)
215 reduced fasting blood glucose, glucose tolerance and insulin resistance in high fat and low
216 streptozocin-induced diabetic rats. Among the mechanism of action analyzed, a suppression of
217 TNF-α and IL-6 release, an increase in superoxide dismutase and a decrease in malondialdehyde
218 levels, together with the downregulation of PPAR-γ coactivator 1α, phosphoenolpyruvate
219 carboxykinase and glucose-6-phosphatase were observed [79]. In the same animal model,
220 compound K, a metabolite of panaxadiol, (30-100-300 mg/kg) caused a dose dependent reduction of
221 fasting blood glucose and an enhancement of fasting serum insulin and insulin sensitivity, by
222 promoting the expression of insulin receptor, insulin receptor substrate-1, PI3Kp85, pAkt and
223 GLUT-4 [80]. Ginsenoside-Rg1 was administered 10 mg/kg to streptozocin-induced diabetic mice,
224 improving angiogenesis by increasing eNOS activation, VEGF expression and inhibiting apoptosis
225 [81]. Two *in vivo* studies described the effects of 20(S)-ginsenoside-Rg3 (20 mg/kg) in

streptozocin-induced diabetic rats. The first one reported a decrease in water intake and urine volume, together with a reduction in serum glucose, glycosylated protein and thiobarbituric acid-reactive substances production, leading to an improvement in renal dysfunction compared to control, which was related by the authors to the inhibition of NMDA receptor-mediated nitrosative stress [82]. The second further describes its positive effects on the metabolism of nucleic acid, energy and gut flora [83]. Finally, ginsenoside-Rh2 (1 mg/kg) lowered plasma glucose in streptozocin-induced diabetic rats, by increasing β-endorphin secretion, which is responsible for opioid μ-receptor activation, resulting in an increase of GLUT-4 expression [84].

It is then worth to be mentioned that several innovative extraction methods are currently under investigation in order to improve ginseng pharmaceutical applications. A heat-processed Korean ginseng extract was administered 100 mg/kg to streptozocin-induced diabetic rats, causing a reduction of blood glucose levels and an improvement of renal dysfunction without altering the expression of proteins involved in oxidative process, in a more potent manner compared to standard Korean ginseng extract [85]. Black ginseng, obtained as a consequence of nine cycles of steaming and drying of ginseng, was administered 200 mg/kg to streptozocin-induced diabetic rats in two different studies. A modulation of glucose metabolism [86] as well as a more effective reduction of hyperglycemia, increase in insulin/glucose ratio and improvement of islet architecture and β-cells function was observed compared to standard red ginseng [87]. The inhibition of β-cells apoptosis was related by the authors to the suppression of cytokine-induced NF-κB translocation. In the same animal model, a pectin lyase-modified ginseng extract (20-50-100 mg/kg) decreased the serum levels of AGE and their cross-linking with protein [88]. Finally, a tissue culture raised mountain ginseng adventitious root extract enriched with ginsenosides, administered 250-500 mg/kg, was more effective than field cultivated Korean ginseng in lowering blood glucose, total cholesterol and triglycerides in streptozocin-induced diabetic rats [89].

2.6. Rehmannia glutinosa (Gaertn.) DC., radix

Rehmannia glutinosa (Gaertn.) DC. is a perennial herb belonging to the family of Plantaginaceae. The herbal substance is represented by the dried roots and rhizomas [28]. The main constituents are iridoid glycosides and monoterpenes [90].

Within the various *R. glutinosa* preparations, the aqueous extract is preferred since it contains the largest amount of characteristic constituents [91]. The whole extract, the polysaccharides fraction and some isolated compounds exhibited beneficial activities in improving glucolipid metabolism and redox homeostasis in both *in vitro* and *in vivo* models. In particular, a water extract obtained from fresh rhizome exerted a high free radical scavenging activity and, in addition, was able to reduce ROS production, to suppress NF-κB activity and to down-regulate the expression of pro-inflammatory genes, such as TNF-α, COX-2, monocyte chemotactic protein-1 (MCP-1) and inducible protein-10 [92]. Furthermore, two different polysaccharides fraction exerted a significant hypoglycemic effect in normal, glucose- and alloxan-induced diabetic rats at 100 mg/kg

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(reducing hepatic glucose-6-phosphatase activity, increasing hepatic glycogen content and raising plasma insulin levels) [93], and in streptozocin-induced diabetic mice at 20, 40 and 80 mg/kg (increasing the mRNA expression of phosphoenolpyruvate and the hepatic glycogen content) [94].

A water extract fraction containing about 60.51% of stachyose was administered 200 mg/kg/day for 15 days to normal, glucose-, adrenaline- and alloxan-induced diabetic rats, resulting in a significant hypoglycemic effect, even if the mechanism of action was not investigated [95].

Catalpol at micromolar concentrations reduced AGE-induced inflammatory responses, inhibited the formation of intracellular ROS production and had a suppressive effect on NADPH-oxidase activity in THP-1 cells [96]. The protective effects of catalpol (20-120 mg/kg/day) through suppression of AGE-mediated inflammation have been extensively confirmed in animal models [97–100].

2.7. Trigonella foenum-graecum L., semen

Trigonella foenum-graecum L., fenugreek, is an annual aromatic herb belonging to the family of Fabaceae. The herbal material is substance by the dried ripe seeds, which contains mucilage and a variety of other secondary metabolites such as trigonelline [28].

A broad range of therapeutic uses, such as to ease childbirth, to increase milk flow, to alleviate menstrual pains and to treat body weakness, have been described in the traditional medicine of eastern Mediterranean areas [101].

Although results from clinical trials are substantially heterogeneous and there is still very limited evidence about the impact of dietary consumption or supplementation with *T. foenum-graecum* for the management of diabetes, recent systematic reviews and meta-analysis conclude that fenugreek seeds (5-100 g/day) may be a promising complementary option for the clinical management of diabetes. This drug, indeed, contributes to a better glycemic control in type 2 diabetes mellitus patients, reducing fasting blood glucose, 2 h post load blood glucose and glycated haemoglobin [102–105].

In vivo studies agree on fenugreek hypoglycemic and hypolipemic activities: the seeds powder (5% in the diet for 21 days) decreased the level of lipid peroxidation in alloxan-induced diabetic rats [106], and significantly restored to control values the elevated fasting blood glucose levels in the same animal model (2 g/kg for 7 days) [107].

The mechanisms underlying fenugreek antidiabetic action include the lowering of blood glucose through an insulin signal pathway and the stimulation of glucose uptake in peripheral tissues [108].

The bioactive compounds which has been more deeply studied for the hypoglycemic actions are trigonelline, diosgenin, 4-hydroxyisoleucine and the soluble dietary fiber fraction of fenugreek seeds [109]. Other than possessing antioxidant activity, trigonelline affects the activity of enzyme related to glucose metabolism, β-cell regeneration and insulin secretion [110]. Diosgenin is implicated in the renewal of pancreatic β-cells and in the stimulation of insulin secretion, has antioxidant effects and promotes adipocyte differentiation and enhancement of insulin-dependent glucose uptake [111–113]. 4-Hydroxyisoleucine stimulates glucose-dependent insulin secretion, reduces insulin resistance and inhibits sucrose α-D-glucosidase and α-amylase [114–117]. The

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soluble dietary fiber fraction of fenugreek (*i.e.* galactomannan) enhances glycemic control inhibiting lipid-hydrolyzing and carbohydrate-hydrolyzing enzymes in the digestive system and reducing the rate of glucose uptake [118–120].

3. Other species with promising data for the management of diabetes

Several other species have been used in the ethnobotanical traditions of many countries around the world to treat diabetes [121–123], and most of them are under investigation for their potential role in the management of diabetes and related diseases [124–126]. To name one, *Gymnema sylvestre* (Retz.) R.Br. ex Sm., commonly known as gurmar, has been used since ancient times, particularly in the Ayurvedic medicine, and its anti-obesity and anti-diabetic efficacy has been demonstrated in animal models [127]. The anti-diabetic activity of gurmar has been attributed mainly to gymnemic acids, gymnemasaponins and gurmarin contained in the leaves [128]. The proposed mechanisms of action include the increase of insulin secretion and the promotion of islet cell regeneration, togheter with the reduction of intestinal and blood glucose adsorption [13]. Clinical trial are arising, reporting the effectiveness of *G. sylvestre* on metabolic syndrome and diabetes [129], nevertheless, more studies are needed in order to support its use in the treatment of diabetic patients [130].

Within the most studied hypoglycemic herbal products, cinnamon is undoubtedly attracting a great interest by the scientific community. For this reason, although there is a lack in authoritative documents reporting specific indications in diabetes, a section of this review is dedicated to a critical analysis of the available literature on cinnamon and its role in diabetes.

3.1. Cinnamon

Botanical preparation of cinnamon may results from the dried inner bark of the shoots grown on cut stock of *Cinnamomum verum* J. Presl. as well as from the trunk bark, freed or cork of *Cinnamomum cassia* (L.) J.Presl., both species belonging to the family of Lauraceae [17]. The herbal substance is represented by the dried bark, free from the outer cork, which contains mainly cinnamaldehyde, eugenol and coumarin in concentrations that can vary abundantly between the two species [131].

Many systematic reviews evaluating cinnamon effectiveness on diabetic patients has been published in the last five years. The oral consumption or supplementation with cinnamon, usually in combination with standard hypoglycemic medications or other lifestyle therapies, has been associated to modest effects on fasting plasma glucose and hemoglobin A1c [132], and to a decrease in levels of triglycerides, total and LDL cholesterol and to an increase in HDL cholesterol [133]. Although being judged as promising by Akilen and colleagues [134], the use of cinnamon on glycemic control need to be investigated in better conduced clinical trials [135–137].

In vitro and *in vivo* evidences indicate that cinnamon may have benefits in improving insulin sensitivity and glycaemic control. Its hypoglycaemic activity may be attributed to multiple mechanisms of action, including the stimulation of insulin release and insulin receptor signalling, the activation and regulation of enzymes involved in carbohydrate metabolism, glycolysis and gluconeogenesis (*i.e.* inhibition of pancreatic and intestinal amylase and glucosidase and increased

of glycogen synthesis in the liver), stimulation of cellular glucose uptake and glycogen content (*i.e.* increased glucose transporter-4 receptor synthesis) and increased expression of PPARs [138–147].

It has been suggested that cinnamon effects on blood glucose can be attributed to its active constituent cinnamaldehyde. The insulinotropic effects of cinnamaldehyde have been preliminarily investigated and are thought indeed to be responsible for promoting insulin release, enhancing insulin sensitivity, increasing insulin disposal, and exerting activity in the regulation of protein-tyrosine phosphatase 1B and insulin receptor kinase [141,143,148]. It is important to consider that the quantity of active cinnamaldehyde may vary among species and formulations [149].

4. Conclusions

Traditional medicine and ethnobotany are an enormous source of information on safety and biological effects of herbal products and many of the medicinal plants currently used to treat hyperglycemia, indeed, derive from traditional use. Medicinal plants possessing anti-diabetes activities, which use has been officially recognized in one or more World regions and is supported by clinical evidence, are considered by WHO and enlisted in WHO monographs on medicinal plants.

This review highlights how many interesting actions are attributable to edible plants such as onion, suggesting that, once again, simple food preferences could actually help in preventing metabolic diseases.

Among all the medicinal plants reviewed, ginseng and fenugreek possess stronger clinical evidence, and their use is supported not only by WHO monographs, but also by the EMA, that summarized scientific data on these species, their preparations and chemical constituents in officially published assessment reports [150,151]

Cinnamon anti-diabetic activity lacks of authoritative support, but many clinical trials have been conducted in the last five years, suggesting an increasing interest concerning its application in the management of diabetes.

The most common hypoglycemic mechanisms of action found for the reviewed medicinal plants and their constituents include the inhibition of α-glucosidase and of AGE formation, the increase of GLUT-4 and PPARs expression and the antioxidant activity. Moreover, the use of herbal products often relie on the synergistic and multitarget effects of the phytocomplex, which may lead to a clinical effectiveness togheter with a lower incidence of adverse events [152].

The comprehensive overview of the dataset suggests that dietary natural products and phytotherapy have today an interesting role in controlling the normal to border-line glucidic levels and as an integrative therapy, but they could not be considered as alternative drugs to mono-molecular ones for type I and type II diabetic patients. Well conducted clinical trials using modern standardized extracts are mandatory and it is necessary to better investigate correlations between hypoglycemic activity and chemical composition of herbal preparations with the aim of optimizing extracts to better trigger specific pathways and, finally, to propose correct dosages to exert safety and effectiveness.

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