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The role of medicinal plants in the treatment of diabetes: a systematic review

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Abstract

Introduction: Diabetes is a serious metabolic disorder and plenty of medical plants are used in traditional medicines to treat diabetes. These plants have no side effects and many existing medicines are derived from the plants. The purpose of this systematic review is to study diabetes and to summarize the available treatments for this disease, focusing especially on herbal medicine.

Methods: Required papers about diabetes and effective plants were searched from the databases, including Science direct, PubMed, Wiley, Scopus, and Springer. Keywords in this study are ”medicinal plants”, “diabetes”, “symptom”, “herbal”, and “treatment”. Out of the 490 collected articles (published in the period between 1995 and 2015), 450 were excluded due to non-relevance or lack of access to the original article.

Results: Diabetes is mainly due to oxidative stress and an increase in reactive oxygen species that can have major effects. Many plants contain different natural antioxidants, in particular tannins, flavonoids, C and E vitamins that have the ability to maintain β-cells performance and decrease glucose levels in the blood.

Conclusion: According to published results, it can be said that medical plants are more affordable and have less side effects compared synthetic drugs, and are more effective in treatment of diabetes mellitus.

Keywords: medicinal plants, diabetes, symptom, herbal, treatment

1. Introduction

Diabetes is a chronic disorder in the metabolism of proteins, fats, and carbohydrates (1, 2). It is described as an increase in blood glucose after any type of meal. Diabetes results from either insulin deficiency or malfunction (2). According to statistics, 2.8% of the world’s population suffer from this disease and it is expected to increase to more than 5.4% by 2025 (3). Diabetes requires early diagnosis, treatment, and lifestyle changes. Diabetes is a disease that affects many people in the 21st century and is known as the fifth leading cause to death (4). High prevalence, variable pathogenesis, progressive process, and complications of diabetes all highlight the urgent need for effective treatments. Nowadays, different treatments, such as insulin therapy, pharmacotherapy, and diet therapy, are available to control diabetes. There are several types of glucose-lowering drugs that exert anti-diabetic effects through different mechanisms. These mechanisms include stimulation of insulin secretion by sulfonylurea and meglitinides drugs, increasing of peripheral absorption of glucose by biguanides and thiazolidinediones (5), delay in the absorption of carbohydrates from the intestine by alpha-glucosidase, and reduction of hepatic gluconeogenesis by biguanides (6). In the past three decades, despite the significant progress made in the treatment of diabetes, the results of treatment in patients is still far from perfect. These treatments have some disadvantages, including drug resistance (reduction of efficiency), side effects, and even toxicity. For example, sulfonylureas lose their effectiveness after 6 years of treatment in 44% of patients. It is also said that the glucose-lowering drugs are not able to control hyperlipidemia (8). In addition, the side effects of medicines and their interactions with each other in vitro

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must be considered by medical staff. Today, many treatments that involve the use of medicinal plants are recommended (9). Most plants contain carotenoids, flavonoids, terpenoids, alkaloids, glycosides and can often have anti-diabetic effects (10). The anti-hyperglycemic effects that results from treatment with plants are often due to their ability to improve the performance of pancreatic tissue, which is done by increasing insulin secretions or reducing the intestinal absorption of glucose. The number of people with diabetes today has been growing and causing increasing concerns in medical community and the public. The main purpose of this article is to introduce a number of effective medicinal plants used for treating diabetes and other mechanisms of plant compounds used to reduce glucose levels and increase insulin secretion.

2. Material and Methods

2.1. Materials

Publication regarding diabetes and effective plants were found in databases such as Science Direct, PubMed, Wiley, Scopus, and Springer. Keywords used in this study included ”medicinal plants”, “diabetes”, “symptom”, “herbal”, and “treatment”. Out of the 490 collected articles (published in the period between 1995 and 2015), 450 were excluded due to non-relevance or lack of access to the original article.

2.2. Inclusion and exclusion criteria

The search was restricted to English and Persian language articles. All studies found during the search were independently evaluated for competence and inclusion by two different authors. After compliance with inclusion criteria, experimental research and clinical trials that evaluate the effect of medicinal herbs or plant component in diabetic animals or patients were included in the current research. Irrelevant studies or original article that evaluated mixed plant extract, algae, or mushroom extracts were also excluded.

3. Results and discussion

3.1. Acacia arabica

In a study that was done to evaluate the anti-diabetic activity of the acacia plant, oral administration of 200 mg/kg and 100 mg/kg of *Acacia arabica* bark extract to streptozotocin (STZ)-induced diabetic rats over a 21 days period increased serum insulin. In addition, high serum glucose and insulin resistance decreased, and the lipid profile improved. This plant contains polyphenols, tannins, and flavonoids (for example, quercetin). The presence of these substances with antioxidant properties is an explanation for anti-diabetic effects of this plant. The *Acacia arabica* extract improves plasma glucose levels, metabolic disorders in lipid metabolism, and oxidative stress in STZ-induced diabetic rats (11). Also, the chloroform extract of *Acacia arabica* bark was used for 2 weeks in diabetic rats, significantly reduced the blood glucose level and improved the cholesterol, triglyceride, HDL, and LDL levels (12).

3.2. Achyranthes aspera

The ethanolic extract of *Achyranthes aspera* leaves (1000 mg/kg) used in STZ-induced diabetic rats significantly reduced their blood glucose level. This is probably due to the inhibition of glucose absorption from the intestine or because of an increase in glucose transport from the blood (13).

3.3. Acosmium panamense

Oral administration of doses of 200 and 20 mg/kg of aqueous *Acosmium panamense* extract and 100 and 20 mg/kg doses of butanolic extract of the mentioned herb reduced the plasmas glucose level in STZ-induced diabetic rats within 3 hours. The effects on hypoglycemic for the extract of this plant and glibenclamide (the main drug used to treat diabetes) are similar (14).

3.4. Aegle marmelose

Oral administration of the aqueous extract dervied from *Aegle marmelose* fruit (125 and 250 mg/kg) in streptozotocin diabetic Wistar rats twice daily for approximately 4 weeks caused a significant decrease in blood glucose, plasma thiobarbituric acid reactive substances, hydroperoxides, ceruloplasmin, alpha-tocopherol, and a considerable increase in plasma reduced glutathione, and vitamin C. The use of a 250 mg/kg dose of the extract was more effective than glibenclamide in the improvement of these parameters. In this research, results clearly show the hypoglycecmic activities of *Aegle marmelose* extract (15).

3.5. Allium sativum (garlic)

Anti-diabetic effects of ethanolic extracts derived from *Allium sativum* were measured in normal and streptozotocin induced diabetic rats. Oral administration of the ethanolic extract of this plant for 14 days showed a reduction in the

level of serum glucose, total cholesterol triglycerides, urea, uric acid, creatinine, AST (aspirate aminotransferase), and ALT (aspirate aminotransferase). However, this extract increased the serum insulin in diabetic rats, but not in normal ones. Comparing the performance of the garlic extract and 600 mg/kg of glibenclamide demonstrated that the anti-diabetic activity of the extract is more effective than glibenclamide (16). In another study, it revealed that oral administration of ethanolic extract, juice, and oil of ripe bulb of *Allium sativum* reduces the blood glucose in STZ-induced diabetic rats by stimulating insulin secretion from pancreas cells. Daily oral administration of 100mg/kg of garlic extract significantly decreased plasma glucose levels by increasing plasma insulin levels (4).

3.6. Aloe barbadensis Miller

The *Aloe barbadensis Miller* plant, which is also known as *Aloe vera*, is used in traditional medicine by many people. Treatment with the ethanolic extract of the fresh leaf gel from this plant (300 and 500 mg/kg) in STZ-induced diabetic rats for 42 days resulted in a significant decrease in the fast blood glucose levels. The hypoglycemic effect of this extract can be compared to standard anti-diabetic drugs (glibenclamide and metformin) (17).

3.7. Andrographis paniculata

Oral administration of ethanolic extract derived from the aerial parts of *Andrographis paniculata* (different doses of 0.1, 0.2 and 0.4 g/BW) caused a significant reduction in levels of the serum glucose in STZ diabetic rats. However, the effect was not seen in normal rats. This extract and anti-diabetic drugs dramatically reduced the activity of liver glucose-6-phosphatase. Further research has shown that the extract reduces the level of fasting serum triglyceride by 49.8%, while metformin drugs reduces levels by 27.7%, but neither the extract or metformin affect cholesterol levels. In addition, further studies concluded that the ethanolic extract of this plant has anti-diabetic activity that is involved in the increase of glucose metabolism (18).

3.8. Annona squamosa

The aqueous extract of this plant leaf have many antioxidant effects. The blood glucose, haemoglobin, glycosylated haemoglobin, plasma insulin, antioxidant enzymes, lipid peroxidation in liver and kidneys were examined in STZ-induced diabetic rats. Oral administration of *Annona squamosa* aqueous extract for 30 days caused a significant reduction in the blood glucose, lipids, and lipid peroxidation, but the activity of the plasma insulin and antioxidant enzymes, like catalase and superoxide dismutase, increased. On the other hand, the activity of glutathione and glutathione peroxidase decreased.Generally, the aqueous extract of this plant is useful for controlling blood glucose levels and improving 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 (19).

3.9. Argyreia nervosa

Oral administration of ethanolic extract of *Argyreia nervosa* root (500 mg/kg/BW) decreased blood glucose levels in normoglycaemic rats. While loading rats with oral glucose for 2 hours, the glucose levels decreased from 118.45.4 to 96.44.2 mg/dl. After the consumption of the extract for 7 days in STZ diabetic rats, a significant anti-hyperglycemic effect occurred (20).

3.10. Artemisia herba

Oral administration of aqueous extract derived from theaerial parts of this plant (0.39 g/kg/BW) for 2-4 weeks in diabetic rats and rabbits caused a significant reduction in glucose levels and prevented an increase in the levels of glycosylated haemoglobin. Furthermore, this plant has hypoliposis effects and can prevent weight loss in diabetic animals (21).

3.11. Averrhova bilimbi

The hypolipidemic and hypoglycemic activity of ethanolic extract of *Averrhova bilimbi* leaves (ABE) was investigated using STZ-induced diabetic rats. Diabetic rats were treated with distilled water, ABE (125mg/kg), or metformin (500mg/kg) twice a day for two weeks. Like metformin, ABE, in comparison with distilled water, significantly reduced the blood glucose level by 50% and the triglyceride level by 130%. In addition, ABE, in comparison with distilled water, increased the concentration of HDL-cholesterol by 60%. It is important to note that the extracts, like metformin, had no effects on the concentration of cholesterol and LDL-cholesterol, but significantly decreased levels of lipid peroxidation. Research has revealed that ABE has hypoglycemic, hypotriglyceridemic, anti-lipid per oxidative, and anti-atherogenic activities in STZ-induced diabetic rats (22).

3.12. Azadirachta indica

Administration of the leaf extract and seed oil for 4 weeks reduced the blood glucose levels in alloxan diabetic rabbits. This extract had similar effects as the anti-diabetic drug glibenclamide. The neem extract can control blood glucose and appears to be helpful in preventing or delaying the onset of diabetes (23). In another study, the anti-diabetic effects of the neem was evaluated and it was found that the administration of a single dose of aqueous extract of the bark and root (250 mg/kg) can decrease urea (13%), triglycerides (32%), cholesterol (15%), glucose (18%), lipids (15%), and creatinine (23%) in diabetic rats (24) for 24 hours after treatment.

3.13. Barleria prionitis

Anti-diabetic activities of *Barleria* prionitis were studied in normal and alloxan induced diabetic rats. The use of the alcoholic extract of this leaf (200 mg/kg) for 14 days created a significant reduction in blood glucose and glycosylated hemoglobin levels, while a substainal increase occurred in the levels of insulin and liver glycogen. This extract prevented weight loss in the experimental subjects (25). In another study, the extract of the plant leaves and roots lead to a significant decrease in blood glucose level in diabetic rats (26).

3.14. Biophytum sensitivum

The *Biophytum* genus from the Oxalidaceae family is also known as a life plant. The extract of this plant has amino acids, steroids, terpenes, tannins, saponins, flavonoids, polysaccharides, oil essential, and pectin. Studies assessing the hypoglycemic activity of *Biophytum sensitivum* showed that oral administration of this plant (200 mg/kg) for approximatly 28 days can lead to a significant decrease in blood glucose and glycosylated haemoglobin levels in normal and steptozotonic-nicotinamide-induced diabetic rats. Also, it can cause a significant increase in the total hemoglobin, plasma insulin, and liver glycogen in diabetic rats. Due to the extract effects, the activity of glucose 6-phosphatase increased, and fructose- 1-6 bisphosphatase activity was reduced in diabetic rats (27). According to published observations, it is most likely that the hypoglycemic responses to *Biophytum sensitivum* is because of the synthesis or secretion of insulin from Beta-cells (28).

3.15. Brassica nigra

In a recent study, the anti-diabetic activity of this plant was obvious. Treatment of STZ-induced diabetic rats with aqueous extract of the seed (200mg/kg/BW) once a day for 30 days decreased the fasting blood glucose level. In addition, there was a poor increase in the glycosylated hemoglobin and serum lipids levels for the treated group (29).

3.16. Bryonia alba

Laboratory studies state that oral administration of ethanolic extract of *Bryonia alba* root (200mg/kg) for 7 days causes a significant decrease in glucose level in alloxan-induced diabetic rats. Also, these studies confirmed the historic claims about the anti-diabetic activity of the plant (30).

3.17. Caesalpinia bonducella

This plant has anti-nociceptive, anxiolytic, anti-filarial, and anti-diarrhoeal activities. Phytochemical analysis determined the presence of alkaloids, flavonoids, glycosides, saponins, tannins, and triterpenoids in this plant (31).
Oral administration of the plant seed extract (300mg/kg) caused a tangible anti-hyperglycemic effect in alloxan-induced hyperlipidemia and decreased the BUN level. This extract caused a significant reduction in cholesterol levels and increased LDL levels in diabetes induced hyperlipidemia. The anti-diabetic actions of the extract is thought to be due to glucose absorption blockage (32). In another study, hypoglycemic activities of aqueous extract was examined in normal and STZ diabetic rats. Administration of 100 mg/kg doses showed hypoglycemic activity and the effects of aqueous extract was longer than ethanolic extracts. After the fifth day, both extracts caused a remarkable hypoglycemic activity in diabetic rats (33).

3.18. Cajanus cajan

This plant is used in Panamanian culture as a medicinal plant for treating diabetes. Different parts of the plants are used in Africa, Asia, and South America to control disorders, including ulcer, diarrhea, pain, diabetes, cough, and sores. Among the four tested extracts of this plant, viz petroleum ether, choloroform, ethyl aceate, and methanol extract, only ethyl acetate and methanolic extracts decreased glucose levels, and reached 27.09% and 37.68% by oral administration of 250mg/kg for 10 days in diabetic mice. Also, insulin decreased blood glucose levels by 32.66%. These two extracts increased insulin activity and the simultaneous use of ethyl acetate and methanolic extracts caused a reduction in blood glucose levels, by 43.07% and 48.14%, respectively. It was concluded that these two extracts of the *Cajanus cajan* plant are more likely to have anti-diabetic bioactive components (34). Another

study found that aqueous extracts of leaves and stems of this plant do not reduce the blood glucose level in normoglycemic mice and the doses of 1000 and 500 mg/kg have hyperglycemia effects. The only dose that caused a significant reduction in the blood glucose level in a short time was 300 mg/kg (35).

3.19. Carum carvi

The hypoglycemic effects of aqueous extracts of *Carum carvi* fruit and *Capparis spinosa* were determined in normal and streptozotocin (STZ) diabetic rats. Oral administration of a single dose or the consumption daily of 14 doses of aqueous extracts of these plants cause a significant reduction in blood glucose levels in STZ diabetic rats. Blood glucose levels were normal approximately 2 weeks after the use of both extracts. In addition, no changes in plasma insulin concentrations were observed after the treatment in normal or STZ diabetic rets. It seems that the mechanisms of action for these plants are independent on insulin secretions. In fact, the anti-hyperglycemic activities of aqueous extracts from *Carum carvi* and *Capparis spinosa* in diabetic rats STZ occur without affecting the basal plasma insulin concentration (36).

3.20. Casearia esculenta

Casearia esculenta is a native anti-diabetic plant used in southern India. The extract reduces blood glucose levels in normal and STZ-induced diabetic rats. Oral administration of aqueous extract from the plant root (300 mg/kg/BW) shows high antioxidant activity, and therefore provides anti-oxidant protection in STZ-induced diabetic rats (37). Another study done to evaluate the anti-diabetic activities of extract in normal and streptozonic induced diabetic rats found that oral administration of aqueous extract of *Casearia sculenta* (300 mg/kg/BW) for 45 days significantly reduced blood glucose levels. Also, treatment with this plant can lead to a reduction in glucose 6-phosphatase, fructose-1,6 bis phosphatase activity, and increases liver hexokinase activity (38).

3.21. Chamaemelum nobile

The study of anti-diabetic activities of *Chamaemelum nobile* demonstrated that oral administration of a single dose of 20 mg/kg aqueous extract of this plant for 15 days caused a significant decrease in blood glucose levels in normal and STZ diabetic rats (39).

3.22. Cichorium intybus

In India, the ethanolic extract of *Cichorium intybus* (CIE) is a traditional treatment for diabetes. A 125mg/kg/BW dose of CIE showed the most effective hypoglycemic activity. Daily administration of this dose for 14 days caused a reduction in triglycerides levels by 91%, serum glucose by 20%, and total cholesterol by 16%. However, there weren't any changes in the density of plasma insulin. Extract of CIE, in comparison with the control group, decreased glucose-6-phosphatase activity and led to a reduction in the production of hepatic glucose. Also, it decreased the blood glucose levels in diabetic rats treated with this extract (40). In other research, it was determined that aqueous extract of the CIE seed (125mg/kg/BW) used for 28 days prevented weight loss in STZ diabetic rats and caused the reduction of fasting blood glucose. In the treated group with CIE, the activity of sera for ALT and the level of triglyceride, TC, and HbA1c decreased. However, there was an increase in the density of nitric oxide (41).

3.23. Citrulus colocynthis

In a recent study evaluating the effects of a 200 mg/kg dose of *Citrulus colocynthis* extract on the glucose, insulin, and the insulin resistance index (FIRI), it was observed that the aqueous extract of the seed of this fruit reduced the glucose level and increases serum insulin, while the hydro-alcoholic extract of the peel increases the glucose level and decreases serum insulin. The most effective part of this fruit in treating type 2 diabetes is the seed, while the peel is harmful for diabetes treatment (42).

3.24. Coriandrum sativum

Anti-diabetic activity of the aqueous extract of this plant was examined in STZ-induced diabetic rats. Doses of 500 and 250 mg/kg of extract caused 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 (43).

3.25. Dorema aucheri

In a study on the anti-diabetic and hypoglycemic effects of hydro-alcoholic extract of *Dorema aucheri* leaves (100,200 and 400 mg/kg/BW) in nicotinamide streptozotocin induced type 2 diabetic rats, it was found that the

administration of the extract in the diabetic group had anti-hyperglycemic effects and salutory effects on the lipid profile and on the livers enzyme activities. A dose of 200 mg/kg was more effective than other tested doses. Flavonoids are often considered to be an important component of this plant and this is demonstrated by the extracts role in the reduction of oxidative stress in B-cells and the improvement of their performance (44).

3.26. Eclipta alba

Eclipta Alba is an herbaceous plant found in the tropical and subtropical regions of South America, Asia, and Africa. Many chemical compounds, including flavonoids, alkaloids, tryterpens, and other glycosides, have been purified from this plant (45). It is considered to be an important hypoglycemic agent in rural areas of southern India. Oral administration of leaf suspension of *E. alba* (2 and 4 gr/kg) for 60 days caused a significant reduction in blood glucose, glycosylated hemoglobin, glucose-6-phosphatase, and fructose-1, 6 bisphosphatase in alloxan-induced diabetic rats, however the hexokinase concentrations in the liver increased (46).

3.27. Fraxinus excersior

Intravenous injection of the aqueous extract from *Fraxinus excersior* (10 mg/kg) caused a tangible reduction in blood glucose levels in normal and streptozotocin-induced diabetic rats. The extract led to a high level of control for renal glucose, which can explain by the hypoglycemic activities of the extract (47). Another study, based on the anti-diabetic actions of *Fraxinus excersior,* showed oral administration of a single dose or 15 daily doses of the aqueous extract (20mg/kg) caused a significant reduction in blood glucose levels without changing the basal concentration of insulin (48).

3.28. Helicteres isora

The effect of the aqueous extract of the *Helicteres isora* fruit on the absorption of glucose was examined in the skeletal muscle cells of rodents. A dose of 200 mg/kg increased the absorption of blood glucose in studied cells (49).

3.29. Hypoxis hemerocallidea

The hypoglycemic effects of aqueous extract from *Hypoxis hemerocallidea* (belonging to the Hypoxidaceae family, named after the African potato) were examined in normal and in streptozotocin (STZ) treated rats. An extract dose of 800 mg/kg lead to a 48.54% reduction in normal rats blood glucose, with a 30.20% reduction in STZ treated diabetic rats (50).

3.30. Lepidium sativum

Anti-diabetic activities of the aqueous extract of the plant seeds were studied in normal and streptozonic (STZ) diabetic rats. After oral administration of a single dose (acute) or 15 times daily (chronic) of the above extract (20mg/kg), the blood glucose level significantly decreased in STZ-induced diabetic rats. After 2 weeks of chronic treatment, the glucose level did not change the basal concentration of insulin and returned to a normal state (51).

3.31. Mangifera indica

The anti-diabetic properties of *Mangifera indica* leaves were evaluated in glucose induced normoglycaemic, hyperglycaemic, and streptozotocin induced diabetic rats. The aqueous extract of this plant leaf decreased the glucose level in normoglycaemic 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 chlorpromide under the same conditions (52). In another study, during the treatment of diabetic rats with mango peel powder (MPP), there was an increase in the antioxidant activity and lipid peroxidation in the plasma, liver, and kidney decreased. Also, the glomerular filtration rate and micro albuminuria level improved with MPP treatment (53). The oral administration of the plant leaf (1 g/kg) did not change the blood glucose level in normoglycaemic or in STZ-induced diabetic rats, but, when the extract and glucose is administrated at the same time, the anti-diabetic activity of the extract is observable. The anti-diabetic activity of the extract in this study is probably due to reduced intestinal absorption of glucose (54).

3.32. Myrcia bella

This plant belongs to the Myrtaceae family and has been used by Brazilian indigenous people as a traditional medicine as an astringent, or diuretic, and in treatments for hypertension and diabetes. The hypoglycemic effects of a 70% ethanolic extract of the plant leaves were investigated in diabetic rats. During a fourteen-day treatment with extract of the plant leaf (300 or 600 mg/kg/BW), fasting blood glucose was measured weekly. The treatment with ta 600 mg/kg dose decreased the fasting blood glucose during the seventh day in diabetic mice while cholesterol and

triglyceride levels decreased in the treated diabetic group, but glycogen and the expression of IRS-1, PI3-K, and AKT in the liver increased. These results proved that the extract has hypoglycemic properties and functions by regulating glucose consumption by the liver (55).

3.33. Nigella sativa

In the study on anti-diabetic activity of *Nigella sativa* seeds, oral administration of plant capsules (at a dose of 2gr/day) significantly reduced FBG, 2 HPG, and HBA1 activities without changing the body weight of the sujects. The results of this study confirmed that applied doses can be used as an adjuvant therapy in type 2 diabetic people (56).

3.34. Ocimum sanctum

The leaves of this plant are traditionally used in treating diabetes. Consuming doses of *Ocimum sanctum* (OS) leaf at 2 gr/kg for 30 days in the group of albino rabbits caused a sharp reduction in glucose level and the level of antioxidant enzymes and glutathione increased, while lipid peroxidation decreased by using the plant leaf. For this reason, the hypoglycemic activity of the plant is believed to be related to the adjustment of the cellular antioxidant system (57). In another study, the ethanolic extract of OS leaves caused a significant reduction in blood glucose levels in normal and alloxan-induced diabetic rats (58).

3.35. Origanium vulgare

Oral administration of aqueous extract of the leaves of this plant (20mg/kg), in comparison with the standard drug glibenclamid (0.9 mg/kg/BW), caused a significant reduction in glucose level, glycosylated hemoglobin, and pancreatic amylase in STZ diabetic rats. Treatment with the extract decreased the liver/body weight ratio in diabetic rats, while the ratio of the kidney/body weight, the level of urea, uric acid, and creatinine improved slightly. Oral administration at the mentioned doses modified the reduction of body insulin, muscle, liver glycogen content, and body weight in STZ diabetic rates (59).

3.36. Phyllanthus amarus

Phyllanthus amarus is a medicinal plant known as a hypoglycemic factor in central and southern India. Oral administration of ethanolic extract from the leaves (400 mg/kg/BW) for 45 days caused a significant reduction in blood glucose levels in alloxan-induced diabetic mice and led to a significant improvement in the body weight of diabetic mice. Also, there was a reduction in glucose-6-phosphatase and fructose 1, 6 di phosphatase activities in the liver. The glucokinase activity, in comparison with control group, increased during treatment in the liver of the diabetic rats (60).

3.37. Prangos ferulacea (L.) lindl.

This plant is used in traditional medicine to relieve pain, inflammation, and help treat diabetes. The major components of extracts from this plant are monoterpenes compounds. The presence of monoterpenes, sesquiterpenes, coumarins, flavonoids, tannins, saponins, alkaloids, terpenoids, and antioxidants are factors in the antioxidant, anti-diabetic, anti-microbial, anti-viral, and antispasmodic properties (61). In a study on the properties of this plant, it was found that, in diabetic rats, a dose of 100mg/kg of the hydro-alcoholic extract of plant root causes a significant reduction in blood glucose levels, total cholesterol, triglyceride, LDL, glycosylated hemoglobin, and a significant increase in HDL levels. In addition, it adjusts the number of white blood cells to normal. This extract is also effective in improving liver and kidney damages and leads to a significant increase in blood indicators of liver function, such as creatinine, AST, and ALT (62).

3.38. Rhus coriaria (sumac)

Effects of sumac seeds on reproductive systems were examined in nicotinamide streptozotcin induced type 2 diabetic rats. Glibendamide and sumac extract were used orally for 28 days. The weight of the body and testis, number and viability of sperm, and the level of luteinizing hormone of serum, follicle, and testosterone significantly decreased in diabetic rats, but this reduction was alleviated in diabetic rats treated with the above extract (400mgkg). Glibenclamide also helped recovery of the reduction of sperm count and hormones in diabetic rats (63).

3.39. Salacia reticulate

The effects of *Salacia reticulate* aqueous extract on glucose absorption were examined in normal type 1 diabetic mice. Simultaneous oral administration of the extract (1mg/kg) with maltose or sucrose lead to increased levels of

plasma glucose after a meal (postprandial), and inhibited insulin and intestinal alpha glycosidase activities in the mice. Also, a 0.01 solution of the extract given as drinking water prevented an increase in insulin glucose levels and intestinal alpha glycosidase activities in type 1 diabetic mice. This treatment helped prevent an increase of lipid peroxidation in the plasma, pancreas, and kidney and prevented a decrease in plasmas insulin level and anincrease in aldose reductase activity in kidney (64).

3.40. Securinegra virosa

The anti-diabetic effects of the methanolic extract of the leaves of *Securinegra virosa* was examined in streptozocin induced diabetes rats. Intraperitoneal administration of 3 doses (100, 300, 600mg/kg) of the extract were administered and after 2 hours, no changes in blood glucose level were observed with all 3 doses. After 4, 8, and 24 hours, all doses caused a significant reduction in glucose level in the experimental group. This extract may increase the absorption and metabolism of glucose or may inhibit the hepatic gluconeogenesis (65).

4. More in-depth discussion

Diabetes is considered to be a metabolic disorder that mainly occurs due to defects in either insulin secretion, insulin action, or both. Diabetes is a disease that can lead to serious problems affecting human health. In the long term, effects can causes micro and macro vascular problems (66). In addition, uncontrolled diabetes can cause many chronic complications, including blindness, heart disease, and renal failure (67). A significant change occurs in the structure and metabolism of lipid in diabetes. Lipid peroxidation is associated with hyperlipidemia. The liver plays a critical role in glucose, lipid homeostasis, and has an important effect on diabetes. The liver and kidneys participate in the absorption, oxidation, and metabolism of free fatty acids and synthesize cholesterol, phospholipids, and triglycerides. Despite the presence of anti-diabetic drugs in the pharmaceutical market, the treatment of diabetes with medicinal plants is often successful. Herbal medicines and plant components with insignificant toxicity and no side effects are notable therapeutic options for the treatment of this disease around the world (12). Most tests have demonstrated the benefits of medicinal plants containing hypoglycemic properties in diabetes management. The most common herbal active ingredients used in treating diabetes are flavonoids, tannins, phenolic, and alkaloids (67). The existence of these compounds implies the importance of the anti-diabetic properties of these plants (12). For example, tannin improves the function of pancreatic Beta-cells and increases insulin secretion. Quercetin is an antioxidant that acts in several mechanisms related with the removal of oxygen radicals, so prevents lipid peroxidation and metal ion chelation (12). In fact, the mechanisms of actions for hypoglycemic plants include: increasing of insulin secretion, increasing of glucoses absorption by muscle and fat tissues, prevention of glucose absorption from the intestine, and prevention of glucose production from liver cells (11). These factors are mostly responsible for the reduction or elimination of diabetes complications. It is worth noting that in this study, STZ rats are the most common animal model used to investigate anti-diabetic activity of plant extracts.

5. Conclusions

Plants are natural antioxidants and effective herbal medicines, in part due to their anti-diabetic compounds, such as flavonoids, tannins, phenolic, and alkaloids that improve the performance of pancreatic tissues by increasing the insulin secretion or decreasing the intestinal absorption of glucose. More researches are needed in order to separate the active components of plants and molecular interactions of their compounds for analysis of their curative properties.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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