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The Effects of Medicinal Plants on Pancreatic Beta Cells in Diabetes: A Systematic Review of Iranians' Contributions

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ABSTRACT

Introduction: Diabetes mellitus (DM) is a metabolic disorder with a high prevalence, which affects approximately 25% of the world's population. This systematic review aimed to assess the Iranian research regarding the effects of medicinal plants on pancreatic beta cells in diabetes.

Methods: This systematic review was conducted via searching in databases such as Medline, PubMed, Google Scholar, and ScienceDirect until April 2018. The studied that were published in Iran, peer-reviewed, and designed as a randomized control trial on type I diabetes were retrieved and screened.

Result: The initial search results of the electronic databases yielded 822 relevant articles. After two stages of screening, checking the references, and removing the duplicate articles in various databases, 18 articles were finally selected for the review.

Conclusion: According to the results, medicinal plants have a positive impact on the performance of pancreatic beta cells in animal models through various mechanisms, such as increasing the number, size, regeneration, and reduction of the inflammation of beta cells.

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Introduction

Diabetes mellitus (DM) is a metabolic disorder with a high prevalence, which affects approximately 25% of the world's population. Type I diabetes is a chronic, autoimmune disease caused by the continuous injury of self-tolerance to the insulin-generating cells of the pancreas.

Today, several medical treatments (e.g., insulin therapy) and several chemical antidiabetic drugs are available for DM, such as sulfonylureas, thiazolidinedione, and α-glucosidase inhibitors. However, antidiabetic drugs give rise to adverse side-effects in various human organs (1-4). Currently, herbal medicines are used more frequently since they have fewer side-effects compared to synthetic drugs (5), while they also contain more effective compounds; the World Health Organization (WHO) recommendations also attest to the use of pharmaceutical herbs.

Medicinal plants have long been administered for the treatment of various diseases (6). In this regard, extensive research has been focused on these plants for the treatment of DM. The present study aimed to investigate the effects of medicinal plants on pancreatic beta cells based on the Iranian studies in this regard. According to the findings, medicinal plants have a positive impact on the performance of pancreatic beta cells through increasing the number, size, regeneration, and

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reducing the inflammation of beta cells. Furthermore, medicinal plants could be beneficial in the treatment of type I diabetes through various mechanisms.

Recently, the American Diabetes Association (ADA) has classified DM into four categories of type I DM, type II DM, gestational DM, and other types (1-5). DM encompasses several diseases of abnormal carbohydrate metabolism (7) and is the most prevalent metabolic disorder worldwide (8). Type I DM is a severe, chronic, autoimmune disease characterized by the progressive loss of self-tolerance to the insulin-producing cells of the pancreas (9). This condition is often associated with microvascular and macrovascular complications (10, 11), which could reduce the life expectancy of the patients by up to 10-15 years (12) and diminish their quality of life (13).

DM is a common disease in both developing and developed countries (14). It is predicted that the number of the diabetic patients in developing and developed countries will reach 69% and 20% of the population by 2030, respectively (15). Furthermore, DM will become the seventh main cause of mortality by 2030 (16). The International Diabetes Federation (IDF) Diabetes Atlas shows that the Middle East and North Africa have the highest worldwide prevalence of the disease (17). Diabetes imposes a substantial socioeconomic burden on the community. In 2017, the costs of diagnosed diabetes were estimated at 327 billion dollars in the United States (18). Based on the costs, prevalence, and morbidity of the disease (9), researchers have been attempting to discover more effective and economical antidiabetic drugs (19).

Historically, medicinal plants have been administered for the treatment of DM worldwide (20). In recent decades, attention has been paid to the use of medicinal plants for diabetes treatment in both developed and developing countries. The application of medicinal plants has resulted in the expansion of complementary and alternative medicine for DM treatment (21, 22).

Evidence attests to the high effectiveness of medicinal plants in the treatment of DM and its complications. The beneficial biological impacts of these medicines are attributed to chemical compositions such as phenolic compounds, alkaloids, flavonoids, terpenoids, coumarins, and glycosides. In addition, these plants could affect hypoglycemia induction through the modulation of the secretion, synthesis or regeneration of insulin, expanding islets in size or number, and antioxidant effects. Some of these plants could also prevent or treat complications such as hypertension, nephropathies, and retinopathies (20-23).

Currently, insulin injection and pramlintide administration have been approved for the management of type I DM (16, 24). On the other hand, the ethnobotanical information have also reported approximately 800 beneficial plants for DM treatment (14). These plants have fewer side-effects and are more cost-efficient compared to chemical drugs (25). In general, the impact of these plants on beta cells has been confirmed (25), and Iranian studies have shared about 0.72% of the global diabetic articles (26).

The present study aimed to assess the effects of medical plants on the beta cells histology in diabetic rats based on Iranian research to lay the groundwork for the further investigations in this regard.

Methods

This systematic review was conducted on April 4, 2018. Article selection and data collection were based on the Preferred Reporting Items for Systematic Reviews (PRISMA), and the literature search was conducted in databases such as Medline, PubMed, Google Scholar, and Science Direct using various keywords and phrases, including “medicinal plants”, “β cells”, “islets of Langerhans”, “type I diabetes”, and “Iran”. The search had no time limits, and only the articles published in the English language were selected.

The database results are presented in Table 1. The collected data of the studies performed in Iran included peer-reviews, randomized control trials on type I diabetes, effects of plants on diabetic rats, reduced blood glucose levels using medicinal plants, use of drug causing diabetes, and effects of medicinal plants on beta cells based on histological examinations. The articles that were not published in full text (conference proceedings excluded) were not reviewed.

In the present study, four strategies were adopted to screen the articles; initially, the titles and abstracts were evaluated for the elimination of irrelevant articles. Afterwards, the full text of the remaining articles were assessed by three reviewers independently (D. O., A. A., and M. G.), and irrelevant articles were excluded. Following that, the same articles from different databases were excluded (P. A. S., S. S. S., and Z. E.). Finally, two reviewers independently reviewed the references lists of the articles to evaluate their eligibility for inclusion (A. A., D. O., and M. G.). Figure 1 shows the flow diagram of the database search and article review.

Results

The initial results of the electronic databases search yielded 822 articles. After two stages of screening, checking the references, and removing

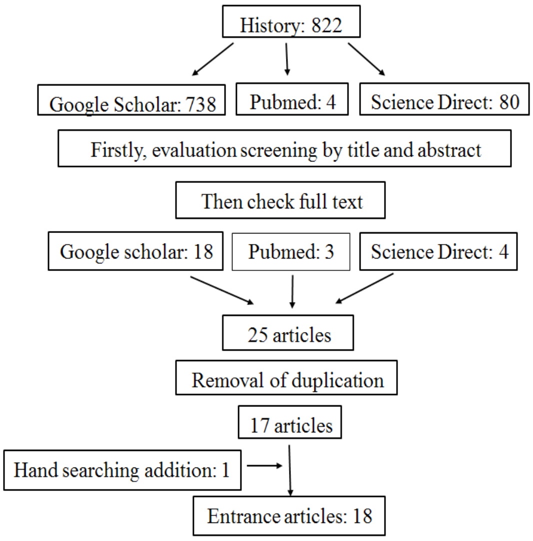

Figure 1. Research Methodology

Table 1. Plants Stimulatng Beta Cell Regenaration

Authors	Animal Model	Treatment	Duration	Dose
Gohari A.	STZ-induced Diabetic Rats	*Urtica dioica*	28 days	12.5 ml/kg/day
Golalipour M. J.	STZ-induced Diabetic Rats	*Urtica dioica*	35 days	100 mg/kg/day
Tashakori Sabzevar F.	STZ-induced Diabetic Rats	Celery	33 days	100 and 200 mg/kg
Mohammadi J.	STZ-induced Diabetic Rats	*Morus alba*	35 days	400 and 600 mg/kg
Alimohammadi S.	STZ-induced Diabetic Rats	*Nigella sativa*	32 days	5, 10, and 20 mg/kg
Soleimani S.	STZ-induced Diabetic Rats	*Equisetum arvense* L.	35 days	50 and 250 mg/kg
Mohajeri D.	Alloxan-induced Diabetic Rats	*Crocus sativus* L.	30 days	40 mg/kg
Azarmi M.	Alloxan-induced Diabetic Rats	*Lavandula officinalis* L.	21 days	200 mg/kg
Soltani Band K.	STZ-induced Diabetic Rats	*Prangos ferulacea* (L.) Lindl	30 days	100 mg/kg
Taghizadeh M.	STZ-induced Diabetic Rats	*Rosa canina* L.	42 days	250 and 500 mg/kg
Ebrahimi E.	STZ-induced Diabetic Rats	*Citrullus colocynthis*	21 days	75 mg/kg
Yazdanparast R.	STZ-induced Diabetic Rats	*Teucrium polium*	42 days	0.5 g /kg
Javidanpour S.	STZ-induced Diabetic Rats		28 days	200 mg/kg

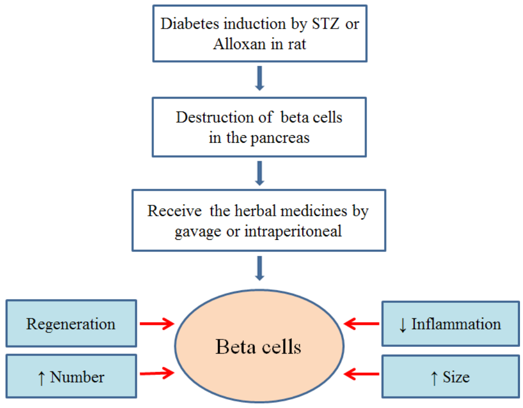

Figure 2. Diabetes Induction and Effects of Medicinal Plants on β Cells in Diabetic Rats

the duplicate articles in various databases, 18 articles were selected for the current review. All the articles were published during 2005-2018.

Discussion

The results of the current review indicated that the extracts of medicinal plants have an impact on beta cells through four mechanisms (Figure 2).

Effect of Herbal Extracts on the Regeneration of Beta Cells

In the retrieved articles, 12 medicinal plants were reported to affect the regeneration of beta cells as (Table 1).

Urtica dioica

Urtica dioica belongs to the Urticaceae family (27). This plant has proven effective in the treatment of disorders such as rheumatoid arthritis, prostatic hyperplasia, inflammation, and hypertension (28). Furthermore, Urtica dioica could decrease the blood glucose levels (28, 29). Gohari A. et al. conducted a study during four weeks and confirmed that the intragastric gavage of Urtica dioica hydrodistillate (12.5 ml/kg/day) leads to the regeneration of beta cells. In addition, they reported that Urtica dioica could increase serum insulin levels (29). In another study, Golalipour M. J. et al. intraperitoneally injected the hydroalcoholic extract of Urtica dioica leaves (100 mg/kg/day) to rats for five weeks, and the histological examination confirmed the increased number of β cells.

Celery

Apium graveolens (celery) belongs to the Apiaceae family (30). In a study, Tashakori-Sabzevar F. et al. reported that treatment with the hexane extract of celery seeds for 33 days could increase beta cells. In addition, the intraperitoneal injection of 100 and 200 mg/kg of the plant resulted in the regeneration of beta cells. The results of the mentioned study also confirmed that celery affects triglycerides, cholesterol, and high-density lipoprotein (31).

Morus alba

Morus alba belongs to the Moraceae family (32). In a research, Mohammadi J. et al. investigated the impact of Morus alba on pancreatic tissues. In the mentioned study, rats were administered with 400 and 600 mg/kg of the oral alcoholic extract of Morus alba leaves for 35 days. According to the findings, the number of beta cells increased in both groups, while the increase was more significant in the group receiving the dose of 600 mg/kg. In addition, both doses of the extract could enhance the size of beta cells, while the diameter increased more significantly with the dose of 400 mg/kg compared to 600 mg/kg (33).

Nigella sativa

Nigella sativa is from the Ranunculaceae family (34). Pharmacological studies have confirmed the antidiabetic, antioxidant (35), anti-inflammatory, antispasmodic, cardiovascular, gastrointestinal, and hepatoprotective properties of Nigella sativa seeds (36). According to Alimohammadi S. et al., the injection of the hydroalcoholic extract of Nigella sativa seeds to diabetic rats for 32 days caused the number of beta cells to increase. In the mentioned study, three doses of Nigella sativa were used (5, 10, and 20 mg/kg). The count of beta cells increased with the doses of 10 and 20 mg/kg, while the increase was more significant with the dose of 10 mg/kg compared to 20 mg/kg (37).

Equisetum arvense L.

Equisetum arvense L. (Equisetaceae) mainly grows in Ardebil, Iran. Previous findings have confirmed that this plant has hypoglycemic properties. According to Soleimani S. et al., oral treatment with the alcoholic extract of Equisetum arvense L. with two doses of 50and 250 mg/kg for 35 days increased the number of beta cells. In addition, both doses could increase the islets cells, while regeneration was higher with the dose of 250 mg/kg compared to 50 mg/kg (38).

Crocus sativus L.

Crocus sativus L. (saffron) is from the Iridaceae family (39). This plant is known for its hypolipidemic, anti-inflammatory, and anticancer properties. In a study in this regard, Mohajeri D. et al. reported that the intraperitoneal injection of the alcoholic extract of saffron at the dose of 40 mg/kg for 30 days resulted in the regeneration of β cells in the pancreas (40).

Lavandula officinalis L.

Lavandula officinalis (lavender) belongs to the Lamiaceae family (41). According to the study by Azarmi M. et al., the intraperitoneal injection of the alcoholic extract of this plant at the dose of 200 mg/kg for 21 days enhanced the islets of Langerhans in rats (42).

Prangos ferulacea (L.) Lindl

Prangos ferulacea (L.) Lindl belongs to the Apiaceae (Umbelliferae) family (43). This plant is effective in the treatment of gastrointestinal disorders and has antioxidant potential. In a study in this regard, Soltani Band K. et al. reported the antidiabetic impact of this plant through the intraperitoneal injection of 100 mg/kg of the hydroalcoholic extract to diabetic rats for 30 days. In addition, the histological examination indicated that the number of beta cells increased in the treatment group (44).

Rosa canina L.

Taghizadeh M. et al. assessed the impact of Rosa canina L. (rose hip) on beta cells. In the mentioned study, oral treatment with the alcoholic fruit extract of Rosa canina L. was provided to diabetic rats for 42 days. The histological examination revealed that both doses of 500 and 250 mg/kg could increase beta cells, while the increase was more significat with the dose of 250 mg/kg compared to 500 mg/kg (45).

Citrullus colocynthis

Citrullus colocynthis is from the Cucurbitaceae family (46). Ebrahimi E et al. (2016) demonstrated that oral treatment with 75 mg/kg of the hydroalcoholic leaf extract of Citrullus colocynthis for 21 days could increase the count of beta cells (47).

Teucrium polium

Teucrium polium L. is from the Lamiaceae family (48). Yazdanparast R. et al. confirmed that the ethanol-water extract of this plant could enhance the regeneration of pancreatic islets in the rats administered with 0.5 g/kg of the plant powder via gavage for 42 days (49).

Juglans regia L.

Juglans regia L. (walnut) is a member of the Juglandaceae family. Javidanpour S. et al. reported that the alcoholic extract of the leaves and fruit peel of Juglans regia L. could increase beta cells. In the mentioned study, one group of diabetic rats was orally treated with 200 mg/kg of the fruit peel, and the other groups orally received 200 mg/kg of the leaves of the plant for 28 days. The histological examination confirmed that both extracts could increase the number of beta cells, while fasting blood sugar only decreased in the the leaf extract group (50).

Among the 12 plants affecting the regeneration of beta cells, the shortest treatment time for beta cell regeneration was reported with Lavandula officinalis L., which could stimulate regeneration in 21 days at the dose of 100 mg/kg. In addition, Rosa canina L. and Teucrium polium could stimulate beta cell regeneration at the doses of 250-500 and 500 mg/kg within 42 days, which is the most time-consuming process compared to the other plants.

Plants Increasing the Size of Beta Cells

According to the current review, only one plant affects the size of beta cells (Table 2).

Juglans regia L.

Studies have confirmed that J. regia leaves have antiproliferative, anti-inflammatory, and antimicrobial properties. In this regard, Asgari S. et al. designed a study to investigate the impact of Juglans regia L. on pancreatic islets via the intraperitoneal injection of the alcoholic extract of the leaves (200 mg/kg) to diabetic rats for 28 days. In the mentioned study, the histological examination showed that the herbal extract increased the size of beta cells (51).

Plants Increasing the Size and Count of Beta Cells

Among the reviewed articles, two plants and two compositions were reported to affect the size and count of β cells (Table 3).

Mixed Walnut Leaf, Coriander, and Pomegranate Seeds

In a study, Jelodar G. et al. ground walnut leaf (Juglans regia L.), coriander leaf (Coriandrum sativum L.), and pomegranate (Punica granatum L.) seed and mixed and homogenized the portion with a normal diet. During 15 days, rats were fed with 15 grams (60 g/kg) of the plants through food, and the results showed that they had potential effects on increasing the size and count of β cells (52).

Pistacia atlantica and Amygdalus scoparia

Hashemnia M. et al. performed a study to assess the impact of the hexane extract of these plants on beta cells. In the mentioned study, the plants were evaluated separately, and 200 mg/kg of each extract was administered to a specific diabetic rat group via an intragastric tube for 15 days. The obtained results showed that both extracts increased the size and count of pancreatic islets, while the P. atlantic extract was more effective in the regeneration process (53).

Citrullus colocynthis

Citrullus colocynthis is also known as 'bitter apple', 'colocynth', 'vine of Sodom', and 'tumba' (54) and grows in Africa, the Middle East, and Arab countries (40). This plant has been used for the treatment of skin diseases and has antitumor, antibacterial, anti-inflammatory, and antidiabetic effects (40). Oryan A. et al. conducted a study on the rats administered with 300 mg/kg of the alcoholic extract of C. colocynthis fruit seeds via an intragastric tube for 12 days, and the histological findings confirmed that the number and size of beta cells increased as a result (54).

Cucurbita pepo L.

Cucurbita pepo L. is aslo known as pumpkin and belongs to the Cucurbitaceae family. Asgari S. et al. utilized two doses of the plant powder, confirming that the gavage of pumpkin fruit powder (2 g/kg) could increase beta cells, while the dose of 1 g/kg enhanced the diameter of pancreatic islets within 28 days (55).

Plants Reducing the Inflammation of Beta Cells

Among the reviewed articles, one plant was reported to influence the inflammation of beta cells (Table 4).

Hibiscus esculentus L.

Hibiscus esculentus L. is also known as Okra and belongs to the Hibiscus family. Hajian S. et al. carried out a research to evaluate the effects of the Hibiscus esculentus L. seeds and mucilage extract on diabetic rats in two treatment groups, one of which received the Hibiscus esculentus L. seed powder via gavage (2 g/kg) for 35 days, and the other received Hibiscus esculentus L. mucilage via gavage (2 g/kg) for 35 days. According to the findings, the inflammation markers reduced in both groups, while the reduction was more significant in the group receiving the seed (56).

Table 2. Plants Increasing Beta Cell Size

Author	Animal model	Treatment	Duration	Dose
Asgari S.	Alloxan- induced Diabetic Rats	*Juglans regia* L.	28 days	200 mg/kg

Table 3. Plants Increasing Beta Cell Size and Count

Author	Animal Model	Treatment	Duration	Dose
Jelodar G.	Alloxan-induced Diabetic Rats	Mixed Walnut Leaf, Coriander and Pomegranate Seeds	15 days	60 g/kg
Hashemnia M.	STZ-induced Diabetic Rats	*Pistacia atlantica* and *Amygdalus scoparia*	15 days	200 mg/kg
Oryan A.	Alloxan-induced Diabetic Rats	*Citrullus colocynthis*	12 days	300 mg/kg
Asgari S.	Alloxan-induced Diabetic Rats	*Cucurbita pepo* L.	28 days	1 and 2 g/kg

Table 4. Plants Reducing Beta Cell Inflammation

Author	Animal model	Treatment	Duration	dose
Hajian S.	STZ-induced Diabetic Rats	*Hibiscus esculentus* L.	35 days	2 g/kg

Conclusion

According to the results, medicinal plants have a positive impact on the function of pancreatic beta cells in animal models through various mechanisms, such as increasing the number, size, regeneration, and reduction of inflammation of beta cells. However, further investigations are required regarding the molecular and intracellular mechanisms affecting the function of beta cells.

Conflict of Interest

The authors declare no conflict of interest.

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