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Review

Pancreatic beta cell protection/regeneration with phytotherapy

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Although currently available drugs are useful in controlling early onset complications of diabetes, serious late onset complications appear in a large number of patients. Considering the physiopathology of diabetes, preventing beta cell degeneration and stimulating the endogenous regeneration of islets will be essential approaches for the treatment of insulin-dependent diabetes mellitus. The current review focused on phytochemicals, the antidiabetic effect of which has been proved by pancreatic beta cell protection/regeneration. Among the hundreds of plants that have been investigated for diabetes, a small fraction has shown the regenerative property and was described in this paper. Processes of pancreatic beta cell degeneration and regeneration were described. Also, the proposed mechanisms for the protective/regenerative effects of such phytochemicals and their potential side effects were discussed.

Uniterms: Diabetes mellitus/treatment. Diabetes mellitus/phytotherapy. Phytotherapy/Diabetes mellitus. Islets/endogenous regeneration. Beta cells/protection. Beta cells/regeneration. Pancreas. Medicinal plants/regenerative properties.

Embora medicamentos disponíveis atualmente sejam úteis no controle de complicações da Diabetes, complicações aparecem em grande número de pacientes. Considerando-se a fisiopatologia do Diabetes, a prevenção da degeneração de células beta e o estímulo da regeneração endógena de ilhotas será abordagem essencial para o tratamento de diabetes mellitus insulino-dependente. A presente revisão aborda compostos fitoquímicos, cujo efeito é provado na proteção/regeneração de células beta de pâncreas. Entre centenas de plantas que têm sido investigadas para o diabetes, pequena fração tem mostrado propriedade regenerativa, que será descrita neste trabalho. Os processos de degeneração e de regeneração das células beta do pâncrease são descritos. Além disso, mecanismos propostos para efeitos de proteção e regeneração desses compostos fitoquímicos e seus possíveis efeitos colaterais também serão discutidos neste trabalho.

Unitermos: Diabetes mellitus/tratamento. Diabetes mellitus/fitoterapia. Fitoterapia/Diabetes mellitus. Ilhotas/regeneração endógena. Células beta/proteção. Células beta/regeneração. Pâncreas. Plantas medicinais/propriedades regenerativas.

INTRODUCTION

Diabetes mellitus is still one of the most important causes of death and disability in both developed and developing countries. According to the report by World Health Organization (WHO, 2015), 9% of adults in the world suffer from diabetes and this disease will be the 7th leading cause of death in 2030. Generally, diabetes is classified into two main types: type 1 diabetes (T1D) and type 2 diabetes (T2D), which were previously known as insulin- and non-insulin-dependent diabetes, respectively. T1D results from pancreatic beta cell degeneration and is characterized by lack of insulin production, while patients with T2D show a state of insulin resistance and usually relative insulin deficiency. Over time, diabetic patients with poor management undergo micro- and macro-vascular complications including nephropathy, retinopathy, neuropathy, and cardiovascular diseases (Deshpande, Harris-hayes, Schootman, 2008).

At present, only insulin and oral antihyperglycemic drugs are available for T1D management (Lorenzati *et al.*, 2010). Although the currently available drugs

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are useful in controlling early onset complications of diabetes, serious late onset complications appear in a large number of patients (Tzoulaki *et al.*, 2009). Considering the physiopathology of diabetes, preventing beta cell degeneration and stimulating the endogenous regeneration of islets will be essential approaches in treatment of diabetes.

Phytochemicals have always been an important source of remedies for human health problems. Numerous experimental and clinical studies have documented beneficial effects of phytotherapy for managing diabetes (Ghorbani, 2013a,b). Antidiabetic effect of phytochemicals is mediated through different mechanisms such as decreasing glucose absorption from intestine, inhibiting glucose production in the liver, increasing glucose uptake by tissues, enhancing insulin secretion from beta cells, and/or increasing pancreatic tissue regeneration (Asgary *et al.,* 2008; Kamyab *et al*., 2010; Jelodar, Mohsen, Shahram, 2007; Shafiee-Nick *et al.*, 2011; Shafiee-Nick *et al.*, 2012a). The current review focused on phytochemicals, the antidiabetic action of which has been proved, at least in part, by pancreatic beta cell protection or regeneration (Table I).

Method of literature review

Review of the related literature was carried out in the databases of Google Scholar, Medline, and Scopus. The search terms included diabetes, islets, pancreas, plant, herb, and regeneration. Cross references of the related articles were also retrieved. Papers were included if they reported the effect of a plant or phytochemical agent on histopathological features of islets of Langerhans in diabetic animals. Two authors (A.G. and A.H.) independently searched the databases and extracted data from each article.

Pancreatic beta cell degeneration/regeneration

T1D is primarily considered as an autoimmune disease resulting from the reaction of immune effector cells with endogenous beta cell antigens. Gradual invasion of T-cells, macrophages, and the released cytokines and oxidative radicals lead to insulitis. The proinflammatory cytokines, especially tumor necrosis factor alpha, interferon gamma, and interleukine-1 beta activate intracellular pathways and lead to beta cell dysfunction, apoptosis, and necrosis. Because of poor intracellular antioxidant capacity, beta cells are vulnerable to oxidative stress. Therefore, oxidative molecules are important mediators of beta cell damage induced by both T1D insulitis and T2D glucotoxicity (Sharma *et al.*, 2009).

Many of the advances in the pathogenesis of T1D have emerged from animal studies. Streptozotocin (STZ) or alloxan-induced diabetic rat or mouse is the most currently used animal model for diabetes. A single intraperitoneal or intravenous injection of STZ is well reported to induce insulin-dependent diabetes in rats (Ghorbani *et al*., 2010; Ghorbani *et al.*, 2013; Shafiee-Nick *et al.,* 2012b). The histologic feature of islets from the pancreas of diabetic animals is characterized by a severe decrease in the number of islets, inflammation, vacuolation of the islets, and degranulation of the beta cells (Adeyemi *et al.,* 2008; Aralelimath, Bhise, 2012). In addition, regular arrangement of alpha and beta cells is disturbed and clumping of beta cells, pyknosis, and necrosis are seen in the islets (Singh *et al.,* 2008).

The subject of pancreatic beta cell regeneration is one of the most controversial topics of T1D research and treatment. It is believed that beta cell can regenerate through the replication of pre-existing beta cells or neogenesis from stem cells and progenitor cells inside or outside the islets (Bouwens, Rooman, 2005). Meier *et al.* (2006) showed a direct piece of evidence for beta cell regeneration through beta cell replication in T1D patients. Neogenesis can be originated from different cell types within pancreas: alpha cells, delta cells, duct epithelium, acinar cells, and centroacinar cells. However, this process depends on extra-pancreatic activators including hormones, growth factors, and others (Bouwens, Rooman, 2005). In adults, turnover of beta cells is slow and reduces with increasing age. However, during body growth and after injury, beta cells can replicate to maintain glucose homeostasis (Avolio *et al*., 2013). Several approaches are currently being investigated to differentiate stem/progenitor cells into beta cells; but, none has been approved for use in diabetic patients yet. Therefore, further works on this issue are warranted.

Phytochemicals with protective/regenerative effects

Allium sativum

Garlic (*Allium sativum*) has been long used as an herbal remedy in treating different diseases because of its antioxidant, antihypertensive, and anticancer effects (Afshari *et al.*, 2006; Ashraf *et al*., 2013; Benkeblia, 2005; Hajzadeh *et al.,* 2006). It is also one of the best-researched medicinal plants in terms of managing diabetes. Clinical trials have shown that the consumption of garlic decreases

TABLE I - Phytochemicals with protective/regenerative effects on pancreatic beta cells.

Plants	Animal model	Treatment	Effects on pancreas	Other effects	Reference
Abroma augusta	ALO-induced diabetic rabbits	Aqueous extract of leaves (2 mL/kg, twice daily, PO) for 21 days	↑beta cell number	↓FBG, ↓blood urea, ↓serum creatinin	Mir, Darzi, Mir, 2013
Alchornea cordifolia	ALO-induced diabetic rabbits	Ethanolic extract of leaves (250 & 500 mg/kg, PO) for 28 days	Regeneration of beta cells (at 500 mg/kg)	-	Eliakim-Ikechukwu, Obri, 2009
Allium sativum	STZ-induced diabetic rats	Aqueous extract (100 mg/kg/day) for 30 days	↑islets diameter	↓FBG, ↑serum insulin	Albajali *et al.*, 2011
		Allicin (8 & 16 mg/kg, IP) for 30 days	↓anti-islet cell antibodies; ↓beta cell degeneration	↑serum insulin, ↓FBG, ↓weight lost,	Osman *et al.*, 2012
		A. sativum oil (10 & 20 mg/kg, IP)for 30 days	Regeneration of pancreatic islets (at 20 mg/kg)	↓FBG, ↑serum insulin, ↓weight lost	Alashkham *et al.*, 2013
Amaranthus caudatus	STZ-induced diabetic rats	Methanolic extract of leaves (200 & 400 mg/kg, PO) for 21 days	Slight regeneration of beta cells (at 400 mg/kg)	↓FBG, ↓weight lost, ↓serum lipids	Girija *et al.*, 2011
Amaranthus spinosus	STZ-induced diabetic rats	Methanolic extract of leaves (200 & 400 mg/kg, PO) for 21 days	Slight regeneration of beta cells (at 400 mg/kg)	↓FBG, ↓weight lost, ↓serum lipids	Girija *et al.*, 2011
Amaranthus viridis	STZ-induced diabetic rats	Methanolic extract of leaves (200 & 400 mg/kg, PO) for 21 days	Slight regeneration of beta cells (at 400 mg/kg)	↓FBG, ↓weight lost, ↓serum lipids	Girija *et al.*, 2011
Anacardium occidentale	STZ-induced diabetic rats	*A. occidentale* extract (300 & 500 mg/kg, twice daily) for 28 days	Regeneration of pancreatic beta cells	↓FBG	Bassey, Eliakim-Ikechukw, Ihentuge, 2012
Anastatica hierochuntica	STZ-induced diabetic rats	Aqueous extract (12.5 mg/rat, PO) for 2 weeks	↑beta cell number	↓FBG	Rahmy, El-Ridi, 2002
	ALO-induced diabetic rats	Methanolic extract (100 mg/kg, PO) for 4 weeks	↑volume density of islets, ↑percentage of beta cells	↓FBG, ↓serum lipids, ↓weight lost, ↓liver enzymes activity, ↑antioxidant enzymes activity	Shaban, Al-Azzawie, Mohamme, 2011
Annona muricata	STZ-induced diabetic rats	Aqueous extract of leaves (100 mg/kg, PO) for 25 days	↑beta cell number	↓FBG, ↑serum insulin, ↓oxidative stress indexes in blood	Adewole, Caxton-martins, 2006
		Methanolic extract of leaves (100 mg/kg, IP) for 2 weeks	↑islets number, ↑beta cell number, ↓inflammatory infiltration	↓FBG	Adeyemi *et al.*, 2008

TABLE I - Phytochemicals with protective/regenerative effects on pancreatic beta cells. (cont.)

Plants	Animal model	Treatment	Effects on pancreas	Other effects	Reference
Artanema sesamoides	STZ-induced diabetic rats	Methanolic extract of aerial parts (200 & 400 mg/kg, PO) for 14 days	↓necrosis of islet cells, ↓degeneration of the islets	↓FBG, ↓serum lipids, ↓liver enzymes activity, ↓liver and kidney damage, ↑antioxidant defense in liver and kidney	Selvan *et al.,* 2008
Azadirachta indica	ALO-induced diabetic rats	Alcoholic extract of leaves (400 mg/kg, twice daily, PO) for 14 days	Regeneration of new islets	↓FBG	Ebong *et al.*, 2006
	STZ-induced diabetic rats	Ethanolic extract of leaves (500 mg/kg, twice daily, PO) for 50 days	↑beta cell density; ↓pancreatic lipid hydroperoxide levels	↓FBG	Akinola, Caxton-Martins, Dini, 2010
Bauhinia variegata	ALO-induced diabetic rats	Ethanol extract of bark (500 mg/kg, PO) for 15 days	Restored the cellular size and number of islets towards normal	↓FBG, ↓serum lipids	Koti *et al*., 2009
Berberine	ALO-induced diabetic rats	berberine (100 & 200 mg/kg, PO) for 21 days	Moderate expansion of islets, ↓damage scores	↓FBG, ↓serum lipids, ↓oxidative stress in the heart	Tang *et al.*, 2006
	STZ- and high carbohydrate/ fat diet-induced diabetic rats	berberine (75-300 mg/kg, PO) for 16 weeks	↑beta cells number, ↑insulin expression, ↓oxidative stress indexes	↑serum insulin	Zhou *et al.*, 2009
Cassia alata	STZ-induced diabetic rats	Ethanolic extract of leaves (500 mg/kg, twice daily, PO) for 28 days	Regeneration of beta cells	↓FBG	Eliakim-Ikechukwu *et al.*, 2013
Cassia occidentalis	ALO-induced diabetic rats	Aqueous extract of whole plant (200 mg/kg, PO) for 21 days	Partial restoration of cellular population and size of islet cells	↓FBG, ↓serum lipids	Verma *et al.*, 2010
Clitoria ternatea	STZ-induced diabetic rats	Ethanolic extract of aerial parts (200 mg/kg, PO) for 21 days	↓necrosis of islets, ↓fibrosis of islets, improvement in beta cell granulation	↓FBG, ↓weight lost, ↓serum lipids	Verma, Itankar, Arora, 2013
Curcumin	STZ-induced diabetic mice	Curcumin (200 mg/kg, IP) for 12 weeks	↓lymphocytes infiltration in the islets, ↑islets number	↓FBG, ↓weight loss	Chanpoo, Petchpiboonthai, 2010
	STZ-induced diabetic rats	Curcumin derivative (150 mg/kg, PO) for 40 days	↑islet cells number, ↑insulin positive cells	↓FBG, ↑serum insulin, ↑C-peptide	Abdel Aziz *et al.,* 2013
Crocus sativus	ALO-induced diabetic rats	Ethanolic extract of stigmas (40 mg/kg, IP) for 14 days	↑beta cell number, ↑immunoreactivity of insulin in beta cells	↓FBG, ↑serum insulin	Mohajeri, Mousavi, Doustar, 2009
		Ethanolic extract (200 - 600 mg/kg, PO) for 4 weeks	The animals had normal histological structure (at 600 mg/kg)	↓FBG, ↓serum lipids, ↓weight lost, ↑serum insulin, improved kidney and liver function	Elgazar *et al.*, 2013

TABLE I - Phytochemicals with protective/regenerative effects on pancreatic beta cells. (cont.)

Plants	Animal model	Treatment	Effects on pancreas	Other effects	Reference
Elephantopus scaber	ALO-induced diabetic rats	Aqueous extract of root and leaves (0.3 g/kg, PO) for 12 weeks	↑beta cell number per islet	↓FBG, ↓serum lipids, ↓serum urea, ↓creatinine	Daisy, Rayan, Rajathi, 2007
Epicatechin	ALO-induced diabetic rats	Epicatechin (30 mg/kg, twice daily, IP) for 4-5 days	↑beta cell number per islet	↓FBG, ↑serum insulin	Chakravarthy, Gupta, Gode, 1982
Gymnema sylvestre	STZ-induced diabetic rats	Water soluble extract of leaves	↑islets number, ↑beta cell number	↓FBG, ↑serum insulin	Shanmugasundaram *et al.*, 1990
		Standardized extract of leaves (200 & 400 mg/kg, PO) for 40 days	↓congestion, ↑normal beta cells	↓FBG, ↓HbA1c, ↓serum lipids, ↓weight lost, ↑serum insulin, ↑glycogen content in liver	Aralelimath, Bhise, 2012
	ALO-induced diabetic rats	Methanol extract of leaves and callus for 45 days	↑beta cell regeneration	↑body weight, ↑glycogen content in liver	Ahmed, Rao, Rao, 2010
Juglans regia	ALO-induced diabetic rats	Diet supplemented with 60 g/kg of leaves for 15 days	↑islets density, ↑percent of beta cells, ↑islets size	↓FBG	Jelodar, Mohsen, Shahram, 2007
		Ethanolic extract of leaf (200 mg/kg)	Enlargement of islets size	↑serum insulin, ↓HbA1c	Asgary *et al.*, 2008
	STZ-induced diabetic rats	Methanolic extract of leaves or peel (200 mg/kg, PO) for 4 weeks	↑beta cell number	↓FBG, ↑serum insulin, ↓HbA1c	Javidanpour *et al.*, 2012
		Aqueous extract of shell septum (200 - 800 mg/kg, PO) f or 4 weeks	No effect	↓FBG	Dehghani, Mashhoody, Panjehshahin, 2012
Leucaena leucocephala	STZ-induced diabetic rats	Extract of seed (0.25 - 1 g/kg, PO) for 14 days	↑beta cell number per islets, ↑islets diameter	↓FBG, ↓serum lipids	Darmono Syamsudin, Simanjuntak, 2006
Mangiferin	Partial pancreatectomy-induced diabetic mice	Mangiferin (30 & 90 mg/kg, IP) for 14 days	↑beta cell hyperplasia, ↑beta cell proliferation, ↓beta cell apoptosis	↓FBG, ↑serum insulin, ↑glucose tolerance	Wang *et al*., 2014
Momordica charantia	STZ-induced diabetic rats	Fruit juice (10 mL/kg, PO) for 10 weeks	↑beta cell number	↑serum insulin	Ahmed *et al.*, 1998
	ALO-induced diabetic rats	Acetone extract of fruit (250-750 mg/kg, PO) for 30 days	Recovery of beta cells of the islets of Langerhans	Hepatoprotection	Singh, Gupta, 2007b
		Alcoholic extract of fruit (250-750 mg/kg, PO) for 30 days	Recovery of beta cells of the islets of Langerhans	↓FBG	Singh *et al*., 2008
	Neonatal STZ-induced type-2 diabetic rats	Aqueous extract of fruit (20 mg/kg, PO) for 4 weeks	↑beta cell number per islet	↓FBG, ↑ serum insulin	Abdollahi *et al.*, 2011

TABLE I - Phytochemicals with protective/regenerative effects on pancreatic beta cells. (cont.)

Plants	Animal model	Treatment	Effects on pancreas	Other effects	Reference
Momordica charantia	Neonatal STZ-induced type-2 diabetic rats	Ethanolic extract of fruit (400 mg/kg, PO) for 4 weeks	↑islet size, ↑total beta cell area, ↑beta cell number	↓FBG, ↑serum insulin	Hafizur, Kabir, Chishti, 2011
Morus alba	STZ-induced diabetic rats	Ethanolic extract of leaves (400 & 600 mg/kg, PO) for 35 days	↑islets diameter, ↑beta cell number	↓FBG	Mohammadi, Prakash, 2008
Nigella sativa & Thymoquinone	STZ-induced diabetic rats	Volatile oil (0.2 mL/kg, IP) for 30 days	Regeneration/ proliferation of pancreatic β-cells	↓FBG, ↑serum insulin	Kanter *et al.*, 2003
		Volatile oil (0.2 mL/kg, IP) for 30 days	Preserving beta cell numbers, ↓oxidative stress	↓oxidative stress parameters in blood	Kanter *et al.*, 2004
		Thymoquinone (50 mg/kg, PO) for 4 weeks	↓islet degeneration and necrosis	↓FBG, ↑serum insulin	Kanter, 2009
		N. sativa oil (0.2 mL/kg) for 30 days	↑islets diameter	↓FBG, ↑serum insulin	Albajali *et al.*, 2011
		Aqueous extract (2 mL/kg, IP), oil (0.2 mL/kg, IP) or thymoquinone (3 mg/kg, IP) for 30 days	↓oxidative stress indexes, partial regeneration of the islets and beta cells	↓FBG, ↑serum insulin	Abdelmeguid *et al.,* 2010
	STZ + nicotinamide-induced diabetic rats	Thymoquinone (80 mg/kg) for 45 days	Preservation of islet cells against beta cell damage	↓oxidative stress in liver and kidney	Sankaranarayanan, Pari, 2011
Prangos ferulacea	STZ-induced diabetic rats	Hydroalcoholic extract of leaves, stem and root (100 mg/kg, PO) for one month	↓lymphocytes infiltration, ↓necrotic cells, regeneration of islets	↓FBG, ↓weight loss, ↓HbA1c	Soltani Band *et al.,* 2011
Pterocarpus marsupium	ALO-induced diabetic rats	A flavonoid fraction extracted from the bark	Regeneration of beta cells	↓FBG	Chakravarthy *et al.*, 1980
Sansevieria trifasciata	ALO-induced diabetic rats	Decoction of leaves (100 - 200 mg/kg, PO) for 30 days	↑granule density in beta cells of islets	↓FBG	Qomariyah, Sarto, Pratiwi, 2012
Solanum nigrum	ALO-induced diabetic rats	Aqueous extract of leaves (400 mg/kg) for 21 days	Partial restoration of islets population and hyperplasia of islet cells	↓FBG	Maniyar, Umamageswari, Karthikeyan, 2012
Syzygium cumini	ALO-induced diabetic rats	Alcoholic extract of seeds (250-750 mg/kg, PO) for 30 days	Hypertrophy of certain islets, ↑granule density in beta cells	↓FBG, ↑body weight,	Singh, Gupta, 2007a

TABLE I - Phytochemicals with protective/regenerative effects on pancreatic beta cells. (cont.)

Plants	Animal model	Treatment	Effects on pancreas	Other effects	Reference
Teucrium polium	STZ-induced diabetic rats	Hydroalcoholic extract (equivalent to 0.5 g plant/kg, PO) for 6 weeks	↑islets number, ↑beta cell number, ↓lymphocytes and macrophages number	↓FBG, ↓bilirubin, ↓glutamate oxaloacetate transferase, ↓glutamate pyruvate transferase, ↑serum insulin	Yazdanparast, Esmaeili, Ashrafi, 2005
Tinospora cordifolia	STZ-induced diabetic rats	Methanolic extract of stem (250 mg/kg, PO) for 100 days	Regeneration of beta cells	↓FBG, ↓HbA1c, ↑serum insulin, ↑C-peptide	Rajalakshmi *et al.*, 2009
Trigonella foenum-graceum	Neonatal STZ-induced type-2 diabetic rats	Hydroalcoholic extract of seeds (100 mg/kg, PO) for 28 days	↑beta cell number, ↑islet size	↓FBG, ↓weight lost, ↓HbA1c, ↑serum insulin	Kulkarni *et al.,* 2012
Thunbergia laurifolia	ALO-induced diabetic rats	Extract of leaves (60 mg/rat, PO) for 15 days	Recovery of some beta cells	↓FBG	Aritajat, Wuteerapol, Saenphet, 2004
Vernonia amygdalina	ALO-induced diabetic rats	Pre-treated with aqueous extract (250 mg/kg, PO) for 21 days	Moderate regeneration of islets	↓FBG	Sunday *et al*., 2012
		Ethanolic extract of leaves (400 mg/kg, PO) for 14 days	Regeneration of new islet cells	↓FBG, ↓serum alpha-amylase activity	Atangwho *et al.,* 2007
Vinca rosea		Methanolic extract of leaves (300 & 500 mg/kg, PO) for 14 days	Partial restoration of normal cellular population and enlarged size of beta cells	↓FBG, ↑glucose tolerance, ↓serum lipids, ↓weight lost, ↓creatinine, ↓urea, ↓alkalin phosphatase	Ahmed *et al.,* 2010
Urtica dioica	STZ-induced diabetic rats	Hydroalcoholic extract (100 mg/kg, IP) for 5 days before induction of diabetes	↑beta cells number	↓FBG	Golalipour *et al.,* 2010
Urtica pilulifera	STZ-induced diabetic rats	Lectin isolated from seeds (100 mg/kg, IP) for 4 weeks	↓cellular damage in pancreas	↓FBG, ↓weight lost	Kavalali *et al.,* 2003

ALO: alloxan; FBG: fasting blood glucose; HDL: high density lipoprotein; IP: intraperitoneal injection; PO (*Per os)*: oral administration; STZ: streptozotocin; TG: triglyceride; ↓: decrease; ↑: increase

fasting blood glucose (FBG) and lipids in diabetic patients (Ghorbani, 2013a, b). According to the animal studies, it may also induce a protective/regenerative effect on pancreatic beta cells. Albajali *et al.* (2011) reported that the aqueous extract of *A. sativum* increased the diameter of pancreatic islets in STZ-induced diabetic rats. In another study, intraperitoneal injection of *A. sativum* oil decreased beta cell degeneration and level of anti-islet antibodies in the animals with T1D (Osman *et al.,* 2012). Alashkham *et al.* (2013) also showed regenerative action of this oil in the pancreatic islets of diabetic rats. Yet, in another study, there was no significant difference between the histopathology of the pancreas of garlic treated and untreated diabetic rats (Jelodar *et al.,* 2005).

Allicin is the major active component of *A. sativum* and a precursor of many secondary compounds formed in crushed garlic preparations or aged garlic. This compound has been proposed to be responsible for the health promotion benefits of *A. sativum* and protective actions in pancreatic islets (Osman *et al.,* 2012).

Anastatica hierochuntica

Anastatica hierochuntica from Brassicaceae family is commonly called "Kaff Maryam" or "Rose of Jericho" and is one of the folk medicinal plants, which is widely used in Arab countries (Daur, 2012; Shaban, Al-Azzawie, Mohamme, 2011). Experimental studies have demonestrated that aqueous and methanolic extracts of *A. hierochuntica* have antioxidative, hypoglycemic, and hypolipidemic effects in diabetic rats (Rahmy, El-Ridi, 2002; Shaban, Al-Azzawie, Mohamme, 2011). This hypoglycemic action may be due to its beneficial effects on pancreatic beta cells. Rahmy, El-Ridi (2002) reported that *A. hierochuntica* increased the number of beta cells in pancreatic islets of diabetic rats. Similarly, Shaban, Al-Azzawie, Mohamme (2011) showed that this plant enhanced volume density of islets and percentage of beta cells in diabetic rats.

Annona muricata

Annona muricata from Annonaceae family (commonly called Soursop) is a small tree, all parts of which are used in natural medicine in the tropical areas in South and North America and west of Africa (Adewole, Caxton-Martins, 2006). According to the animal studies on STZ-induced diabetic rats, the administration of extract of *A. muricata* leaves can increase the number of islets and beta cells in pancreas (Adewole, Caxton-Martins, 2006; Adeyemi *et al.*, 2008).

Azadirachta indica

Neem (*Azadirachta indica*), a tree in the mahogany family, is among the well-known medicinal plants in Africa. Using a clinical study, its hypoglycemic and hypolipidemic effects among diabetic patients have been shown in recent years (Kochhar, Sharma, Schdeva, 2009; Kumari, 2010). Two animal studies have demonstrated that *A. indica* has also a regenerative effect on the islets of Langerhans. According to the report by Akinola, Caxton-Martins, Dini (2010), oral feeding of ethanolic extract of *A. indica* leaves increased beta cell density and decreased oxidative stress in the pancreas of STZ-induced diabetic rats. Ebong *et al.* (2006) also showed regenerative action of this extract in alloxan-induced diabetic rats.

Berberine

Berberine is an isoquinoline alkaloid which is present in the root, rhizome, and stem bark of many plants, such as *Berberis vulgaris*, *Coptidis rhizoma*, *Hydrastis canadensis*, *Mahonia aquifolium*, and *Mohonia nervosa* (Ye *et al.,* 2009). Berberine has been demonstrated to have beneficial effects on hyperglycemia and dyslipidemia in diabetic patients (Yin *et al*., 2008). Regarding its protective/regenerative effect on pancreas, Tang *et al.* (2006) demonstrated that oral administration of berberine decreased the levels of FBG and serum lipids and restored the damage of pancreas tissue in alloxan-induced diabetic rats. Another study reported that berberine increased insulin sensitization, insulin secretion, and beta cell regeneration in STZ- and high carbohydrate/fat diet-induced diabetic rats (Zhou *et al.,* 2009).

Crocus sativus

Saffron (*Crocus sativus*) is a perennial stemless herb of the Iridaceae family which is widely cultivated in Iran and also in some other countries such as India. Crocin (crocetin glycoside) and safranal ($C_{10}H_{14}O$) are the main constituents of *C. sativus* and responsible for the pharmacological effects of this plant. Safranal has been reported to have a number of medicinal attributes including antioxidative and cytoprotective effects (Alinejad, Ghorbani, Sadeghnia, 2013; Sadeghnia *et al.*, 2013). Safranal, *C. sativus*, and crocin show antihyperglycemic, hypolipidemic, and blood insulin elevating effects in insulin-dependent diabetic animals (Kianbakht, Hajiaghaee, 2011; Mohajeri, Mousavi, Doustar, 2009; Samarghandian *et al*., 2013). In addition, *C. sativus* has beneficial effects on the histological structure of pancreas in alloxan-induced diabetic rats (Elgazar, Rezq, Bukhari, 2013). Recovery of beta cells and increase of insulin immunoreactivity are of beneficial effects induced by *C. sativus* in the islets of Langerhans of diabetic rats (Mohajeri, Mousavi, Doustar, 2009).

Curcumin

Curcumin (diferuloylmethane) is an active ingredient of *Curcuma longa*, a spice employed as a flavoring and coloring supplement in foods. Evidence has suggested that it has potent antioxidant and cytoprotective effects (Alinejad, Ghorbani, Sadeghnia, 2013; Park *et al.*, 2008). In diabetic rats, curcumin inhibits lymphocytes infiltration in the islets of Langerhans and keeps the number of islets and beta cells (Chanpoo, Petchpiboonthai, 2010; Abdel Aziz *et al.,* 2013). These effects are accompanied by decreased FBG and increased serum insulin and C-peptide (Abdel Aziz *et al.,* 2013).

Gymnema sylvestre

Accumulating evidence has demonstrated that *G. sylvestre* (commonly known as Gurmar in India) improves glycemic control in both T1D and T2D. Clinical trials have demonstrated that the administration of this herb decreases FBG, PPBG, and HbA1c in diabetic patients (Ghorbani,

2013b). The potential ability of *G. sylvestre* in regenerating pancreatic beta cells has been tested in recent years. It has been shown that aqueous extract of *G. sylvestre* leaves increases serum insulin level in streptozotocin treated rats. This effect is accompanied by a double increase in the number of beta cells (Shanmugasundaram *et al.,* 1990). Regenerative effect of *G. sylvestre* has been also observed following long-term treatment of diabetic rats using a standardized dry extract of leaves (Aralelimath, Bhise, 2012). Gymnemic acid is considered to be the active ingredient responsible for the regenerative action of *G. sylvestre* on beta cells (Ahmed, Rao, Rao, 2010).

Juglans regia

Juglans regia (walnut) has been widely used in the traditional medicine of Asian countries as a remedy for various ailments. Its leaves have shown a significant hypoglycemic effect in diabetic animals. Increase of hepatic glycogenolysis, decrease of gluconeogenesis, inhibition of glucose absorption from the intestine, and enhancing serum insulin are the proposed mechanisms for hypoglycemic effect of *J. regia* (Asgary *et al.,* 2008; Kamyab *et al*., 2010; Jelodar, Mohsen, Shahram, 2007). Increase of insulin level can be mediated through regenerative actions of *J. regia* on pancreatic islets. It has been shown that density of islets, percent of beta cells, and islets size significantly increase in pancreatic tissue of diabetic rats receiving walnut leaf (Jelodar, Mohsen, Shahram, 2007). Regenerative property of *J. regia* is accompanied by increase in the serum insulin level (Asgary *et al.,* 2008; Javidanpour *et al.,* 2012). Yet, in contrast to leaf, treatment with the shell septum of *J. regia* has no effects on the pancreatic structure of diabetic rats (Dehghani, Mashhoody, Panjehshahin, 2012).

Momordica charantia

Momordica charantia (Karela, Ampalaya, bitter melon) has acquired a reputation for the management of diabetes. It has passed several animal and clinical studies and its beneficial effects on blood glucose and lipids have been shown in diabetic patients since 36 years ago (Ghorbani, 2013b). Effect of *M. charantia* fruit on pancreatic histopathological changes has been determined by at least five experimental studies. In adult diabetic animals, the results indicate that *M. charantia* increases the number of beta cells per islets and leads to the neoformation of islets from the pre-existing islet cells (Ahmed *et al.,* 1998; Singh, Gupta, 2007b; Singh *et al.*, 2008). In addition, the hypoglycemic effect of *M. charantia* remains after the cease of treatment (Singh *et al*., 2008). In neonatal diabetic rats, administration of aqueous or ethanolic extract of *M. charantia* fruit alleviates pancreatic damage and induces the renewal of pancreatic beta cells (Abdollahi *et al.*, 2011; Hafizur, Kabir, Chishti, 2011).

Nigella sativa

N. sativa (black seed) has been used for centuries as a natural remedy for various ailments. Hypoglycemic and hypolipidemic effects of black seed have been reported in diabetic patients (Ghorbani, 2013a). Kanter *et al*. (2003) investigated the effect of *N. sativa* volatile oil on histopathology of pancreatic beta cells in diabetic rats and found that *N. sativa* treatment decreased the elevated serum glucose, increased the insulin concentration, and partially regenerated pancreatic beta cells in these animals. Afterward, they showed that the beneficial effect of *N. sativa* on the number of beta cells was accompanied by decreasing lipid peroxidation and increasing antioxidant enzyme activity (Kanter *et al*., 2004). In another experiment, it was represented that the administration of *N. sativa* oil to STZ-induced diabetic rats increased the diameter of islets of Langerhans (Albajali *et al.*, 2011). The protective effect of *N. sativa* against beta cell destruction is attributed to its active constituent, thymoquinone. Treatment with thymoquinone inhibits STZ-induced islet degeneration and necrosis and leads to the partial regeneration of the islet and beta cells of diabetic animals (Abdelmeguid *et al.*, 2010; Kanter, 2009; Sankaranarayanan, Pari, 2011).

Vernonia amygdalina

Vernonia amygdalina, also called bitter leaf, is a vegetable from compositae family and is commonly used in west of Africa for treating various diseases including diabetes (Atangwho *et al.,* 2007). Pre-treatment with the aqueous extract of *V. amygdalina* protects the islets of Langerhans against alloxan-induced pancreatic degeneration (Sunday *et al*., 2012). Also, administration of *V. amygdalina* induces regeneration of the islet cells and decreases FBG in diabetic rats (Atangwho *et al.*, 2007).

Other plants with protective effects on pancreas

In addition to the above-mentioned herbs, a number of others has been found to have potential protective or regenerative properties on beta cells: *Abroma augusta* (Mir, Darzi, Mir, 2013), *Alchornea cordifolia* (Eliakim-Ikechukwu, Obri, 2009), *Amaranthus caudatus* (Girija *et al.*, 2011), *Amaranthus spinosus* (Girija *et al.*, 2011), *Amaranthus viridis* (Girija *et al.*, 2011), *Artanema sesamoides* (Selvan *et al.,* 2008), *Bauhinia variegata* (Koti

et al., 2009), *Cassia alata* (Eliakim-Ikechukwu *et al.*, 2013), *Cassia occidentalis* (Verma *et al.*, 2010), *Clitoria ternatea* (Verma, Itankar, Arora , 2013), *Elephantopus scaber* (Daisy *et al.,* 2007), Epicatechin (Chakravarthy, Gupta, Gode, 1982), *Leucaena leucocephala* (DarmonoSyamsudin, Simanjuntak, 2006), Mangiferin (Wang *et al*., 2014), *Morus alba* (Mohammadi, Prakash, 2008), *Prangos ferulacea* (Soltani Band *et al.,* 2011), *Pterocarpus marsupium* (Chakravarthy *et al.*, 1980), *Sansevieria trifasciata* (Qomariyah, Sarto, Pratiwi, 2012), *Syzygium cumini* (Singh, Gupta, 2007a), *Teucrium polium* (Yazdanparast, Esmaeili, Ashrafi, 2005), *Thunbergia laurifolia* (Aritajat, Wuteerapol, Saenphet,, 2004), *Tinospora cordifolia* (Rajalakshmi *et al.*, 2009), *Trigonella foenum-graceum* (Kulkarni *et al.*, 2012), *Vinca rosea* (Ahmed *et al.*, 2010), *Urtica dioica* (Golalipour *et al.*, 2010), and *Urtica pilulifera* (Kavalali *et al.*, 2003). However, for each one, only one study from independent authors was found to support their protective or regenerative effects on beta cells. Therefore, further studies are needed to establish the therapeutic value of these herbs in the management of insulin-dependent diabetes.

Proposed mechanisms for protective/regenerative effect of phytochemicals

In this review, the protective effects of several plants on drug-induced β-cells destruction, increasing islets size, and beta cell population were presented. Although these pieces of evidence did not fully reveal the involved molecular mechanisms, decreasing apoptosis, increasing cells' antioxidant capacity, and immunomodulation wee the postulated mechanisms of action.

Beta cell apoptosis and replication rates, islet size, and islet neogenesis are the major determinants of pancreatic endocrine capability for insulin secretion and glucose homostasis (Montanya, Tellez, 2009). Changing the balance of beta cell replication and apoptosis alters the length of beta cell cycle which contributes to the islet size and insulin release. Decreasing apoptosis results in the enhancement of beta cell viability and increase in insulin production.

Intrinsic and extrinsic pathways are considered as two general routes for the activation of apoptosis. The former is activated by stress factors including growth factor deprivation, cell cycle disturbance, and DNA damage, which lead to mitochondrial release of cytochrome *c* and subsequent stimulation of caspase-9. The latter begins with cell death receptors and the associated activation of caspase-8. Finally, both pathways stimulate effector caspases (3, 6, and 7) which target the substrates that promote DNA fragmentation and cell death (Sharma *et al.*, 2009; Forouzanfar *et al.*, 2013).

It has been well documented that oxidative stress plays an important role in beta cell dysfunction and apoptosis (Yang *et al.*, 2011). Because of poor antioxidant capacity, beta cells are vulnerable to the oxidative stress induced by both T1D insulitis and T2D glucotoxicity (Sharma *et al.,* 2009). Therefore, drugs and phytochemicals that improve glycemia and/or oxidative stress ameliorate or prevent islet lesions. In this regard, protective effect of some phytochemicals on pancreas has been found to be mediated through their antioxidant effects. Zhou *et al.* (2009) reported that treatment with berberine restored the reduced superoxide dismutase activity and increased lipid peroxidation of pancreas of diabetic animals to the near control level. These antioxidant effects of berberine, therefore, mediate its anti-apoptotic action against beta cell apoptosis in insulin-resistant animal models and against palmitate-induced lipoapoptosis in HIT-T15 insulin producing cells (Gao, Zhao, Li, 2011; Wu, Lu, Dong, 2011). Similarly, the beta cell protective effect of *N. sativa* can be attributed to the antioxidant properties of this plant, which increases superoxide dismutase activity, inhibites lipid peroxidation, and decreases the generation of reactive oxygen species (ROS) in pancreas tissue (Abdelmeguid *et al.*, 2010). Also, reduction of lipid peroxidation in the pancreas of diabetic rats treated with *A. indica* suggests the beneficial potential of this plant in the amelioration of ROS-induced pancreatic islet lesions (Akinola, Caxton-Martins, Dini, 2010). In addition to the direct evidence for pancreas, protective/regenerative effects of the phytochemicals on other tissues may support their beneficial actions on pancreatic structure of diabetic rats. For example, hepatoprotective property of Allicin (Vimal, Devaki, 2004), *N. sativa* (Al-Ghasham *et al.*, 2008), and *A. indica* (Oyewole, 2011; Ezz-Din *et al.*, 2011) and nephroprotective action of *N. sativa* (Al-Ghasham *et al.,* 2008) and *A. indica* (Ezz-Din *et al.*, 2011) have been demonstrated. Also, berberine can promote axonal regeneration in the injured nerves of rats' peripheral nervous system (Han, Heo, Kwon, 2012).

Immunomodulatory action and stimulation of proliferation and differentiation of progenitor cells may be also among the mechanisms involved in beta cell protective/regenerative effects of some phytochemicals (Abiramasundari, Sumalatha, Sreepriya, 2012; Ghazanfari, Hassan, Ebrahimi, 2002).

CONCLUSION

Destruction of pancreatic islets is the major determinant for the onset of hyperglycemia and development of complications in insulin-dependent diabetic patients.

Preventing beta cell degeneration, stimulating endogenous regeneration of islets, and islet transplantation will be of essential approaches for T1D management. At present, the limited supply of donor islets prevents tissue transplantation from being used in the patients. Therefore, development of phytochemical products with beta cell regenerative property can be a promising option for the patients who have lost their mass of functional islet cells. Among the hundreds of plants that have been investigated for diabetes, a small fraction has shown the regenerative property, which was described in this paper. For most of these herbs, however, the number of studies supporting their beneficial effects on pancreas is not enough. Only *A. sativum*, *A. indica*, berberine, *C. sativus*, *G. sylvestre*, *J. regia*, *M. charantia*, and *N. sativa* had more than one piece of evidence for their regenerative property so that their consumption may decrease insulin dependence on diabetic patients. The exact mechanism responsible for the protective/regenerative effects of phytochemicals on pancreatic islets is yet to be elucidated. However, antioxidant property of phytochemicals may in part mediate their protective action against pancreatic beta cell apoptosis. Regardless of the molecular mechanisms, it seems that patients at the earliest stages of diabetes can be treated with these plants to delay or prevent the full destruction of pancreatic islets. Also, construction of polyherbal compounds through the combination of these phytochemicals may yield more potent regenerative agents for beta cells. Upcoming clinical trials on this topic are particularly warranted.

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