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A systematic review of medicinal plants and compounds for restoring pancreatic β-cell mass and function in the management of diabetes mellitus

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ABSTRACT
Diabetes mellitus is among the most challenging public health problems worldwide due to its increasing prevalence and its associated complications, affecting individuals, healthcare systems, and economies. Insulin, a crucial hormone for maintaining glucose homeostasis, is secreted by pancreatic β-cells. The progression of both type 1 (T1D) and type 2 (T2D) diabetes is aided by dysfunction/reduced functional β-cell mass, which results in decreased insulin secretion and long-term complications. There has been a surge in interest in drug discovery programs targeted at augmenting both the quality and quantity of pancreatic islets. Several small-molecule drugs and biologics have already been proposed, and newer entities are being investigated. Importantly, plant and plant-derived compounds have a high potential for increasing the number, volume, and functionality of pancreatic islet cells. An update on the current research on the capacity of *Aloe vera*, *Momordica charantia*, *Tinospora cordifolia*, *Gymnema sylvestre*, *Panax Ginseng,* and plant-derived compounds including geniposide, berberine, phenylpropenoic acid glucoside, genistein, naringenin, baicalein, and apigenin to restore β-cell mass and function is given in this systematic review. Since β-cell deficiency is a defining feature of both T1D and T2D, it is critical to comprehend the role of some of these natural products in restoring pancreatic β-cell functionality.

INTRODUCTION

Diabetes mellitus is a chronic disease afflicting 425 million individuals worldwide, and it is expected to rise inevitably in the coming decades (IDF Diabetes Atlas 9th edition 2019). Despite significant advances in monitoring and treatment, diabetic complications continue to be a key source of morbidity and mortality (Halban *et al*., 2010). The defects that result in diabetes are diverse, but the failure of pancreatic β-cell is a large determinant of this disorder (Kahn, 2001). The progressive deterioration of glucose control in both type 1 diabetes (T1D) and type 2 diabetes (T2D) is mainly caused by the insufficient mass of β-cells and gradual dysfunction, which leads to diminished insulin secretion (Stumvoll *et al*., 2005). In T1D, immunological factors, as well as T-cells activated by immune-mediated responses damage insulin-producing β-cells (Wållberg and Cooke, 2013). T2D, on the other hand, is a degenerative condition caused by both genetic and environmental factors, resulting in insulin resistance in peripheral tissues, often culminating in β-cell death, which cannot compensate for insulin resistance (Benthuysen *et al*., 2016).

In T2D pancreatic β-cells are compromised or become non-functional as a result of persistently high levels of glucose and lipid, a phenomenon known as glucolipotoxicity (Weir, 2020). Endoplasmic reticulum stress, Reactive oxygen species (ROS) production, islet inflammation, mitochondrial dysfunction, increased synthesis of ceramides, and increased islet amyloid polypeptide (Fig. 1a–c) have all been proposed as mechanisms for glucolipotoxicity-induced β-cell dysfunction and death (Chang-Chen *et al*., 2008). Furthermore, chronic hyperglycemia can induce β-cell death by increasing the expression of proapoptotic genes,

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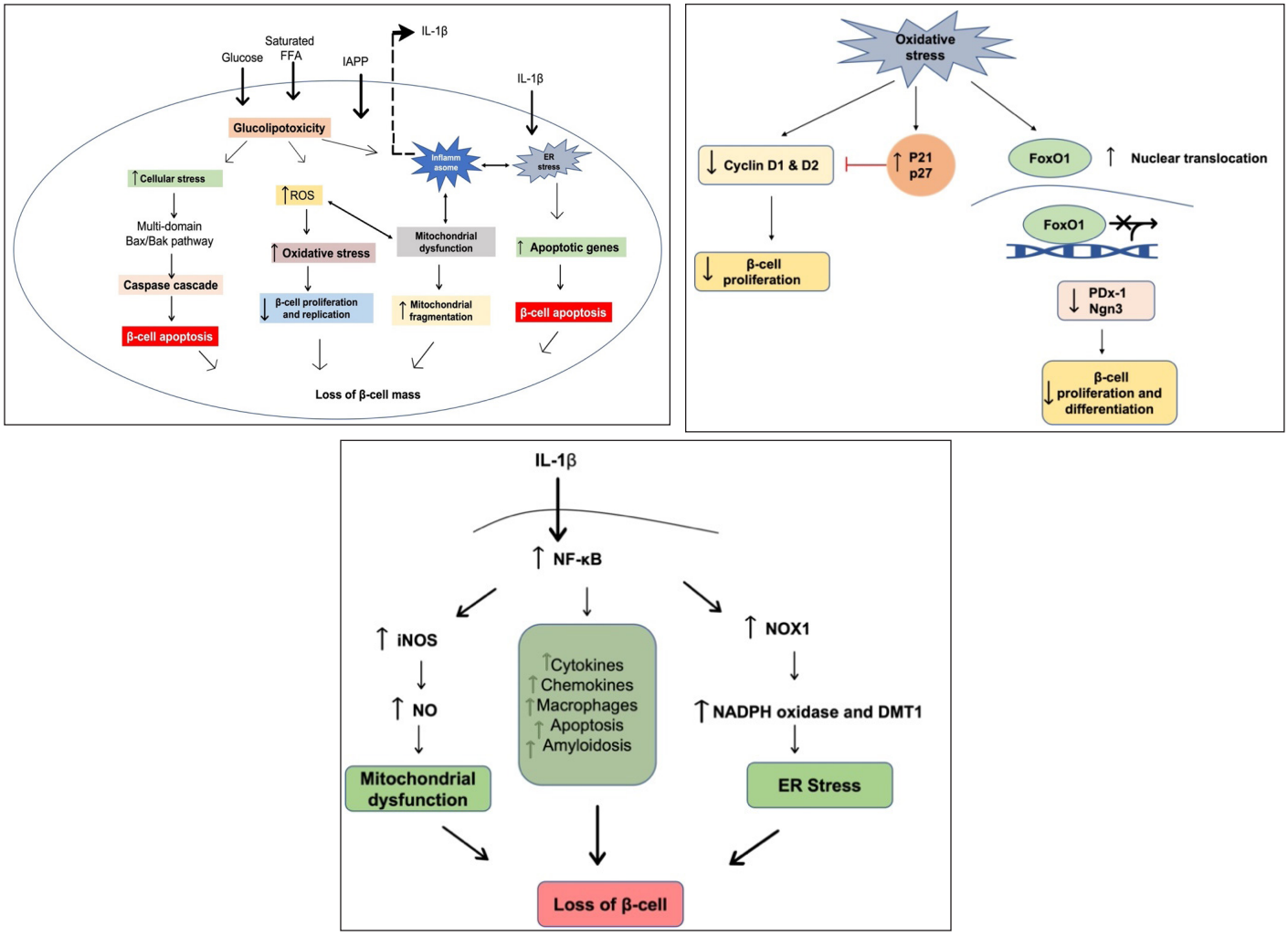

Figure 1. (a) Glucolipotoxicity leading to decreased β-cell mass and dysfunction: β-cells become dysfunctional as a result of glucolipotoxicity several mechanisms for glucolipotoxicity-induced β-cell dysfunction have been proposed, including endoplasmic reticulum stress, mitochondrial dysfunction, ROS production, islet inflammation, and increased islet amyloid polypeptide. Chronically elevated glucose levels stimulate glucose metabolism via oxidative phosphorylation. As a result, dysfunctional mitochondria and there is an increased production of ROS. ER stress has also been linked to increased biosynthetic demand, elevated FFA levels, and chronic -cell overnutrition. (b) Role of oxidative stress in beta cell cycle: ROS inhibits cyclin D1 and D2 expression while increasing cell cycle inhibitors such as p21 and p27, resulting in decreased beta cell proliferation. Furthermore, ROS promotes nuclear translocation of FoxO1, which inhibits the expression of Pdx-1, Ngn3, and other beta-cell related gene transcription, all of which are required for beta cell proliferation and differentiation. (c) Inflammatory response causing β-cell dysfunction: inflammatory mediators increases ER stress by activating Nicotinamide adenine dinucleotide phosphate oxidase and DMT-1. Also, these mediators stimulate the transcription of various cytokines, chemokines, and other inflammatory markers, exacerbating the inflammatory response. The signaling molecules involved in mitochondrial dysfunction, ER stress, oxidative stress, and inflammation all interact extensively, leading to beta cell dysfunction.

while antiapoptotic gene expression B-cell lymphoma 2 (Bcl-2) remains unaffected (Tomita, 2016). The mechanisms activated by glucolipotoxicity are strongly linked, resulting in a destructive cycle that inevitably leads to the failure of β-cells. The molecular basis of the parameters regulating β-cell mass and function, on the other hand, is a key problem for understanding diabetes, which is characterized by a near total (in T1D) or relative (in T2D) insufficiency in pancreatic β-cell number (Chen *et al*., 2017). Thus, the discovery of new therapeutics targeting the apoptotic process to delay or reverse β-cell death/dysfunction serves as an attractive strategy for the control of the disease (Venkatesan *et al*., 2011).

There are numerous anti-diabetic medications available today to treat hyperglycemia. Except for insulin, liraglutide, exenatide, and pramlintide, all other anti-diabetic drugs are administered orally. These drugs work through various mechanisms, including enhanced insulin release, improved insulin sensitivity, increased glucose uptake, and decreased carbohydrate absorption. The major downside of existing drugs is that they must be administered throughout one's life and cause undesirable side effects (Hossain and Pervin, 2018). Therefore, herbal medicines that can manage diabetes and associated complications more efficiently and safely have become increasingly popular among people and scientists working in the field both in developed and emerging nations (Kumar *et al*., 2021). Plants have proven to be an excellent source of drugs, with many currently available drugs derived explicitly or implicitly from them. The active principles derived from plants work through a wide range of pathways, including the inhibition of several key enzymes involved in glucose metabolism. The world health organization has identified

close to 21,000 plants used for a variety of medicinal purposes around the world. Nearly 800 of them have been known to possess anti-diabetic potential (Rizvi and Mishra, 2013). In a review, Salehi *et al*. (2019a, 2019b) described several medicinal plants, including *Aloe vera, Gymnema sylvestre, Ficus benghalenesis, Hibiscus rosa-sinesis, Mangifera indica, Tinospora cordifolia, Trigonella foenum-graecum, Allium sativum, Momordica charantia, Panax ginseng, Azadirachta indica Aegle marmelose* with antihyperglycemic, insulin-mimetic, anti-lipidemic, and anti-diabetic properties, with a focus on compounds of high interest from various classes such as flavonoids, terpenoids, coumarins, carbohydrates, polypeptides, and small molecules (Salehi *et al*., 2019a). Some of these medicinal plants and plant-derived compounds are discussed further in this systematic review.

METHODS USED FOR LITERATURE COLLECTION

Online databases such as PubMed, Science Direct, Google Scholar, Web of Science, Scopus, Clinical Trials.gov, and Wiley online library were used for the literature search for this systematic review. The strategy of search is based on the PRISMA guidelines and the major keywords used in various combinations included: Diabetes mellitus, the anti-diabetic activity of plant extracts and plant-derived compounds, β-cell function, proliferation, and differentiation. Based on the search 625 articles were identified. The full-length articles from peer-reviewed journals related to the subject of interest, published between (2000 and 2021) and written in English were included in the review process. Studies on the beneficial effects of crude extracts/ isolated compounds on glucose-lowering effects via restoration of islet cells using *in vivo* and/or *in vitro* studies were selected for this review. Commercial oral-hypoglycemic agents that lacked definitive evidence on pancreatic β-cell function and mass but obliquely suggested improvement of those activities were excluded from the review. Plants that have been reported for their beneficial effects on β-cells and have undergone clinical trials were included in this review. The review excluded studies that were unrelated to the research question, duplicated, had unavailable full texts or were abstract-only. Further, only plants with reported antidiabetic phytochemicals and mechanisms of action were considered for the review work. There were no restrictions on the sample size, study design, or method of exposure and outcome measurement. Of the 625 articles, 195 articles were included in this review following the criteria for inclusion. Figure 2 summarizes the strategy for the search.

IS REGENERATION POSSIBLE?

The endocrine pancreas is known to be tissue with slow turnover and reduced renewal capacity than tissues with well-defined adult stem cell niches, such as blood, skin, and gut (Aguayo-Mazzucato and Bonner-Weir, 2018) Despite this, the low frequency of both apoptosis and proliferation allows for sustained expansion of β-cell mass in rats for the initial 7 months (Montanya *et al*., 2000). For about a decade, the notion of regeneration of islets by implies apart from replication of pre-existing cells was unpopular, but neogenesis/trans differentiation has regained favor. Proliferation and the formation of newer β- cells are both likely islet regeneration mechanisms, with different emphases depending on the injury and species (Aguayo-Mazzucato and Bonner-Weir, 2018). Most of the studies on the regeneration of β-cells have been carried out using various rodent models (Kodama *et al*., 2003), and there is significant evidence of impressive proliferation capacity of post-natal rodent β-cells in situations of higher metabolic demand (Desgraz *et al*., 2011). Furthermore, it has been shown in transgenic mice that the mature pancreas can recover fully from almost complete ablation of all existing β-cells (Cano *et al*., 2008), but it is unspecified whether a similar approach applies to humans. Although it has been hypothesized for decades that the human pancreas contains progenitor cells with the potential to regenerate islets, the regenerative capacity of the human pancreas has not been conclusively demonstrated (Ku, 2008). Diabetes Research Institute reports have shown that there are progenitor cells in the human pancreas that can be induced to develop into glucose-responsive β-cells in the presence of bone morphogenic protein-7 (Qadir *et al*., 2018). These cells were also distinguished by the presence of Pancreatic and duodenal homeobox-1 (Pdx-1), a protein required for β-cell development. As a result, these findings open up the possibility for the development of regenerative therapies to combat the disease (Qadir *et al*., 2018).

RESTORATION OF PANCREATIC B-CELLS MASS AND ITS FUNCTION

The β-cells play a crucial role in human physiology since they are the only cells able to produce insulin, which can maintain glucose homeostasis by enhancing the uptake of glucose and its utilization in peripheral tissues. Therefore, dysfunctional β-cells or reduced β-cell mass, disrupt glucose homeostasis, leading to diabetes mellitus (Basile *et al*., 2019). Thus, the restoration of insulin-producing functional β-cells or transplantation of islets has been one of the major themes of treating diabetes mellitus (Tokui *et al*., 2006). Since β-cell dysfunction has been identified as a key factor in the development and progression of T1D and T2D, scientists are working on strategies to replace the destroyed β-cell. One way to do that is through β-cell replacement therapy (Butler *et al*., 2003; Rahier *et al*., 2008). However, the scarcity of donors, the need for immunosuppressive drugs, which are often toxic, and graft failure, which typically occurs within a few years (Halban *et al*., 2010) have prompted several studies on alternative means, including the use of β-cells deduced from human embryonic/induced pluripotent stem cells and/or the initiation of endogenous regeneration (Aguayo-Mazzucato and Bonner-Weir, 2018). Embryonic stem cells (ESCs) have tremendous potential for producing insulin-secreting cells because of their significant proliferation, self-renewal, and controlled differentiation capacity (D'Amour *et al*., 2006). Nevertheless, the clinical application of ESCs is limited due to their undesirable teratoma formation property (Wakitani *et al*., 2003) and the stringent ethical standards followed in their procurement (Fischbach and Fischbach, 2004). As a result, there is ongoing research into the intracellular expansion of β-cells to regenerate their mass (Bonner-Weir *et al*., 2004). Thus, (a) enhanced replication of existing β-cells (Dor *et al*., 2004) and (b) generation of new β-cells from cells not expressing insulin, either through converting from a differentiated cell type (trans differentiation) or differentiation from progenitors (neogenesis) found in regenerating pancreatic ducts, which are viewed as a possible source of β-cell regeneration, can result in increased β-cell mass (Fig. 3) (Bonner-Weir *et al*., 2004).

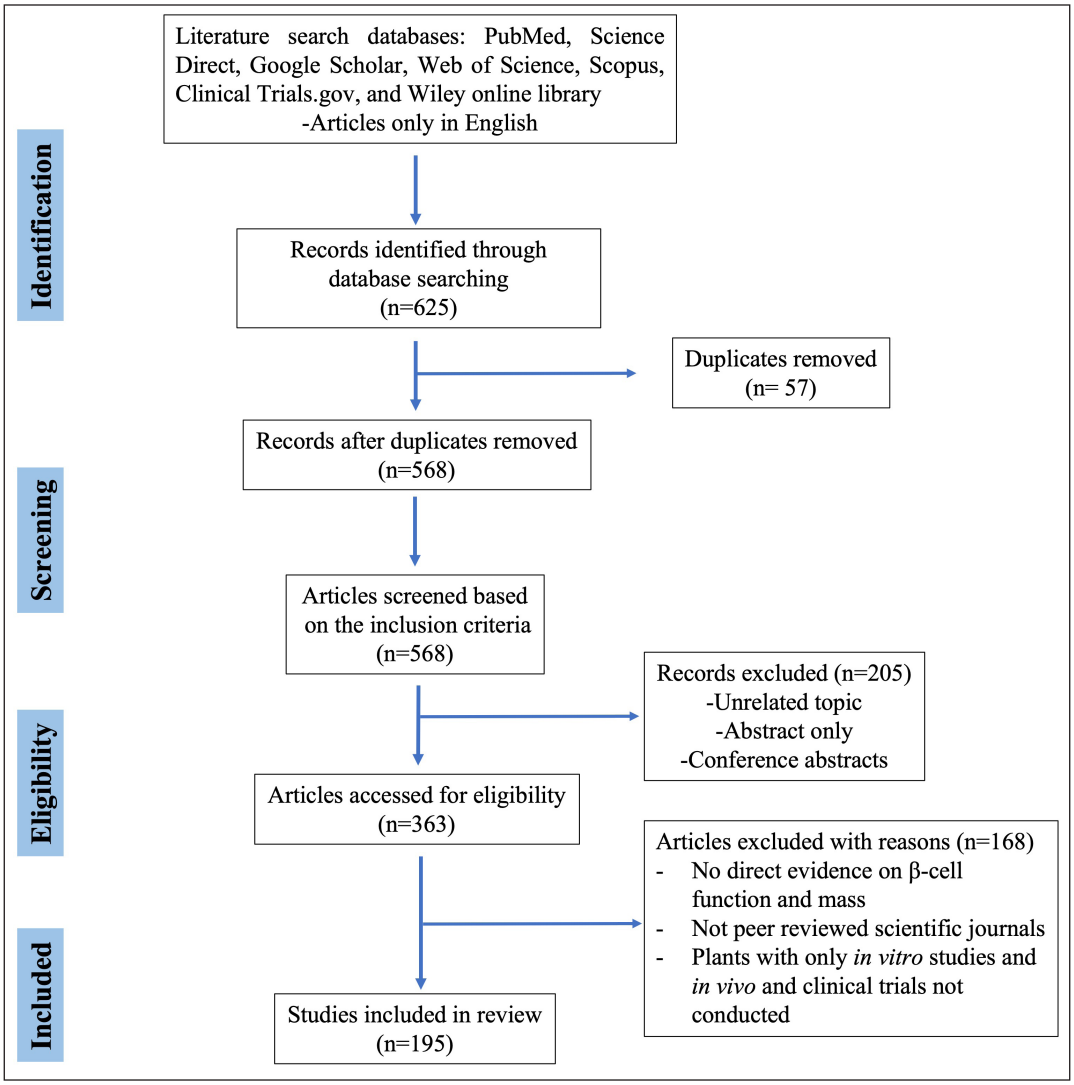

Figure 2. Search strategy.

Transdifferentiation is the process through which one specialized cell type is transformed into some other mature cell type via a dedifferentiation intermediate. It has emerged as the most alluring method of generating β-cell sources for cell replacement therapies (Kim and Lee, 2016). This process is contingent on cellular reprogramming, such as the neogenesis of β-cells and alternative progenitor cells as the source for regeneration of new β-cells from the adult pancreas. Acino-ductal trans differentiation is one such example. Given their abundance, proximity, and shared developmental origin with endocrine cells, acinar cells appear to be a viable source for producing large numbers of β-cells. Acinar cell subpopulations have increased expression of the transcription factor sex-determining region Y-Box 9, a progenitor cell marker for the pancreas, indicating the existence of differentiated acinar cells (Furuyama *et al*., 2011). Furthermore, during the initial stages of pancreatic development in mice, the trans differentiation process was initiated by ductal cells towards the endocrine lineage, acting as a progenitor for an islet cell (Solar *et al*., 2009). Interestingly, ductal cells positive for immature β-cell indicators

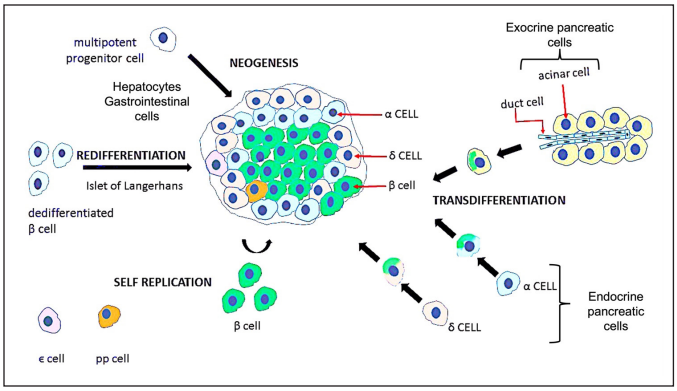

Figure 3. Expansion of functional beta-cell mass: expansion of the population of functional β-cells represents one of the difficult strategies for compensating for insulin deficiency and improve glucose homeostasis. Cells producing insulin can be derived from either multipotent progenitor cells (hepatocytes or gastrointestinal cells), pancreatic exocrine cells, or endocrine pancreatic islet cells, by inducing cell identity switches termed as trans differentiation. Also, via enhanced replication of existing β-cells (self-replication).

were observed in pregnant women and T2D, indicating this as a reparative mechanism to enhance β-cells mass in physiological and pathophysiological conditions with increased metabolic demand (Dirice *et al*., 2019).

The potential of α-cells to differentiate into β-cells is yet another example of pancreatic trans differentiation. Some of the benefits of considering α-to-β trans differentiation as a potential intervention are the close lineage associations and extensive overlap of transcriptomes between α and β-cells, as well as the evident better resistance of α-cells to metabolic stressors (Hancock *et al*., 2010). It was also found that pancreatic insulin-glucagon-positive cell populations increased in response to an increase in Glucagon like peptide-1 (GLP-1) exposure via an increase in the Pdx-1 expression (Zhang *et al*., 2019).

Because, hepatocytes and gastrointestinal cells are obtained from the primitive foregut endoderm and share initial developmental stages, they are viewed as a plausible endogenous source of insulin-producing cells. Multiple studies have developed reliable methods for obtaining cells like β-cells from hepatocytes by increasing the expression of transcription factors that are important for β-cell development, resulting in improved expression of biologically active insulin and restoration of glycemic control in various diabetic models (Ber *et al*., 2003; Kojima *et al*., 2003). Similarly, transient transgenic expression of genes such as Pdx-1, MafA, and nuclear factor E2-related factor (Nrf2) can induce insulin expression in gastrointestinal cells *in vivo* (Chen *et al*., 2014). Another study found that demonstrated that increasing HNF-6-induced Ngn-3 expression with GLP-1 improved insulin-producing cell conversion in rodent and human intestinal epithelial cells (Suzuki *et al*., 2003). A large number of studies in this research area, however, are based on findings made in rodents and proof-of-concept studies on human cells *in vitro*. As a result, it remains a significant challenge to determine whether reprogramming of β-cells from extra-pancreatic cells can be stimulated in human patients with the ultimate goal of increasing their mass and treating diabetes.

PHARMACOLOGICAL AGENTS THAT PROMOTE B-CELL MASS AND IMPROVE THEIR FUNCTION

The search for strategies to enhance β-cell function and its regeneration has resulted in the discovery of several small molecules that have been demonstrated to protect and stimulate human β-cell proliferation. Table 1 lists some of the molecules involved in increased islet cell mass, the proliferation of beta cells, and glucose-stimulated insulin secretion (GSIS). Once all safety concerns have been addressed, these pharmacological agents could be used as a strategic approach to reducing the amelioration of this disorder. However, the shortcomings of presently available oral hypoglycemic agents in terms of their efficacy and/or safety, short-term hypoglycemia, and the emergence of diabetes as a global epidemic have prompted the development of alternative therapies that can manage diabetes more efficiently and safely. Dietary composition is considered to be one of the stimuli for pre-existing cell multiplication; different components may trigger this differentiation individually or synergistically. As a result, it is worthwhile to research natural

Table 1. Pharmacological agents that aid in the regeneration and function of β –cells.

S.No.	Molecules	Salient feature	Mechanism of action	Reference
1	GLP-1	Potentiated GSIS Increased β -cell proliferation and a decrease in beta-cell apoptosis	Pancreas-specific mediator of incretin response in islet beta cells through cyclic AMP (cAMP)/Ca(2+)-dependent pathway	(Nie *et al*., 2013) (Liu *et al*., 2017)
2	Gamma-aminobutyric acid (GABA)	Immuno protective and regenerative effects on islet beta cells in preventing T1D in NOD mice.	Activation of PI3-K/Akt-dependent growth and survival pathways	(Soltani *et al*., 2011)
3	Betacellulin (Epidermal growth factor)	Neogenesis of beta cells and amelioration of glucose intolerance	Promoted beta-cell differentiation from nonendocrine precursor cells residing in the duct lining and from acinar cells	(Yamamoto *et al*., 2000)
4	PPAR gamma agonists	Potentiated GSIS and increase in islet insulin content.	Protect β -cells from the deleterious effects of glucolipotoxicity	(Lupi *et al*., 2004)
5	Combined treatment of GABA and Sitagliptin	Prevents damage of beta cells and promotes regeneration of β-cells	Suppressive effect on alpha cell mass and increase in Pdx-1^{+} cells and reduced Tunel^{+} beta cells.	(Liu *et al*., 2017)
6	Combined treatment of GABA and Exendin-4	Cytokine-induced apoptosis was reduced and improved β-cell function	Activated Akt pathway signaling	(Son *et al*., 2019)
7	GABA	Increased grafted β-cell proliferation, while decreasing apoptosis, leading to enhanced β-cell mass.	Activated calcium-dependent signaling pathway through both GABA A and B receptors, further activating PI3-Akt and CREB–IRS-2 pathways responsible for β-cell proliferation and survival.	(Purwana *et al*., 2014)
8	Aminopyrazine compound (GNF4877)	β-cell proliferation, increased β-cell mass, and insulin content	inhibition of DYRK1A and GSK3B promotes NFATc-dependent β-cell proliferation	(Shen *et al*., 2015)
9	Thiadiazine	β-cell proliferation	Inhibition of DYRK1A	(Belgardt and Lammert, 2016)
10	5-iodotubercidin (5-IT)	Increases human β-cell proliferation *in vitro* and *in vivo* and GSIS	Inhibition of DYRK1A	(Dirice *et al*., 2016)

products that can assist in overcoming some of these limitations and alleviate this disorder.

TRADITIONAL MEDICINE CONTRIBUTING TO THE RESTORATION OF B-CELL MASS AND ITS FUNCTION

Complementary or herbal medicine draws the attention of many diabetics to manage and/or prevent diabetes and its ramifications. Numerous popular herbs are asserted to lower blood glucose levels, and therefore the possibility of improving glucose control or reducing the dependency on insulin therapy via the use of traditional medicine is undeniably appealing (Dey *et al*., 2002). Herbal medicine is based on the comprehensive and integrated theory, that emphasizes the whole body. In contrast to conventional treatments, which typically contain a single bioactive molecule that targets a particular mechanism, herbal concoctions may include a variety of bioactive components that act synergistically through different mechanisms (Ceylan-Isik *et al*., 2008).

These medications can have a diverse range of beneficial effects, including increased insulin responsiveness, insulin release, β-cell regeneration, reduced carbohydrate absorption, and so on (Choudhury *et al*., 2018). However, caution should be exercised before administering any herbal medicine treatment (Watson and Preedy, 2012), as the selection of herbs may be dependent on a variety of factors, such as the stage of diabetes advancement, the types of comorbidities that the patients have, cost and availability, and the health impact of the herbs (Surya *et al*., 2014). As a result, researchers must increase their efforts in investigating alternative preventive and therapeutic measures, such as the utilization of locally accessible functional plants with novel action mechanisms. Such measures may be useful in a variety of communities where their use is accepted and considered a pivotal customary practice (Njume *et al*., 2019). Some of the commonly used plants and plant-derived compounds that have been researched extensively for their anti-diabetic potential, with a focus on β-cell function and β-cell preservation, and have undergone clinical trials are discussed further in the review. Table 2 summarizes the role of some of these medicinal plants in restoring pancreatic β-cells functionality in terms of T1D and T2D. In this table, animals induced with chemicals such as streptozotocin (STZ) and alloxan, which can damage pancreatic beta cells, are classified as T1D models, while diet-induced ones are classified as T2D models. Figure 4 depicts the multiple pathways by which medicinal plants and compounds derived from plants may regenerate pancreatic β-cells.

PLANTS FOR RESTORING PANCREATIC B-CELL MASS AND ITS FUNCTION

Aloe vera

Aloe vera, a succulent plant has a long history of use by many cultures because of its medicinal properties (Sahu *et al*., 2013). The anti-diabetic potential of *A. vera* have been studied by various researchers (Rajasekaran *et al*., 2004; Tanaka *et al*., 2006), wherein, administration of different preparations results in a significant decrease in plasma glucose levels in different models (Beppu *et al*., 2006). The antihyperglycemic potential of *A. vera* was suggested to be mediated via increased insulin synthesis and its secretion, attenuation of oxidative damage, and the associated pancreatic β-cell destruction (Boudreau and Beland, 2006). Furthermore, administration of the ethanolic extract (300 mg/kg body weight) to STZ-induced rats resulted in a 50% reduction in fasting blood glucose (FBG) levels, as well as the prevention of the pancreatic β-cell damage or the recovery of partially destroyed β-cells (Noor *et al*., 2017, 2008). Many of its medicinal properties are believed to be due to polysaccharides observed in the inner leaf gel (Ni *et al*., 2004; Yin *et al*., 2008) anthrachinonic derivatives, phenolic compounds that are metabolized in the intestine and enter the circulatory system to show physiological effects, including protection against β-cell damage (Beppu *et al*., 2006).

Dyslipidemia is well known to play a crucial role in impaired β–cell function which contributes to the onset of T2D (von Eckardstein and Sibler, 2011). Oral administration of phytosterols-rich fraction of *A. vera* to Zucker diabetic fatty rats has significantly improved random blood glucose, glycated hemoglobin (HbA1c) levels, serum free fatty acids (FFA) and triglycerides (TG) levels, indicating increased insulin sensitivity and secretion, but no effect was observed on total cholesterol (TC) levels (Misawa *et al*., 2008). The lack of effect of the fraction on TC levels is thought to be attributable to the low dosage of phytosterols administered by (Misawa *et al*., 2008). For the treatment of diabetic patients, *A. vera* in conjunction with metformin could prevent diabetes-associated dyslipidemia, improve cellular integrity, and increase high-density lipoprotein (HDL) levels, reducing cardiovascular disease risk and renal failure. The histopathology studies on the pancreas and kidney demonstrated signs of recovery, in contrast to the diabetic group, which had necrotic pancreatic cells and total glomeruli erosion in the kidney (Atanu *et al*., 2018).

GLP-1/DPP-IV (Dipeptidyl peptidase- I V) pathway is considered important in restoring the deranged islet-cell balance and various studies have demonstrated beneficial effects on functional β–cell mass and pancreatic insulin content (Gilbert and Pratley, 2020). A dipyrrole derivative from *A. vera* demonstrated *in vitro* inhibition of the DPP-IV enzyme in a non-competitive manner suggesting one of the mechanisms by which *A. vera* extract restores β–cell mass in a diabetic model (Prasannaraja *et al*., 2020). Furthermore, the polypeptide-rich fraction from *A. vera* has shown protective effects on β–cells via the GLP-1/DPP-IV pathway, as evident from histopathological studies (Babu *et al*., 2021). Another study demonstrated that ethanolic *A. vera* extract alleviated diabetes symptoms by improving β–cell function and lipid metabolism. Scanning electron microscope analysis demonstrated decreased surface irregularities on islet cells in the treated group (Deora *et al*., 2021). However, it is continued to believe that all these therapeutic effects must be attributed to the synergism of compounds rather than a single chemical entity.

Clinical studies

A 5-year clinical study involving 5,000 patients with coronary artery disease confirmed that including *A. vera* gel in the diet resulted in a significant reduction in fasting and post-prandial blood glucose levels in diabetics, as well as total serum cholesterol, TG, and an increase in HDL levels was observed (Agarwal, 1985). Surprisingly, the majority of those who benefited were diabetics who were not taking any anti-diabetic medication, and no side effects were observed during the study (Agarwal, 1985). Another study found *A. vera* to have anti-diabetic activity in new cases of diabetes mellitus, with improved triglyceride levels

Table 2. Effects of medicinal plants on diabetes mellitus through pancreatic β–cell regeneration.

Name	Extract	Model	Reference
Aloe vera	Reduced FPG, decreased insulitis, inhibits intestinal glucose absorption, attenuation of oxidative damage, and associated pancreatic beta cell destruction Restoration of FBG, Improved insulin secretion, quantitative and qualitative increase in beta cell mass Amelioration of hyperglycemia, hyperlipidemia, atherogenic index, improved cellular integrity PF showed protective effects on β–cells via the GLP-1/DPP-IV pathway	T1D (STZ or Alloxan)	(Beppu *et al*., 2006) (Noor *et al*., 2017, 2008) (Atanu *et al*., 2018) (Babu *et al*., 2021)
	Reduced RBG, HbA1c levels, Improved glucose intolerance, reduced FFA and TG	T2D (Diet-induced rats)	(Misawa *et al*., 2008).
	Improving β–cell function and lipid metabolism. Decreased surface irregularities on islet cells	Genetically obese STZ induced	(Deora *et al*., 2021)
Momordica charantia	Anti-hyperglycemic and anti-oxidative effects, reduced TBARS Reduced the Na+- and K+-dependent absorptions of glucose, Normalized structural abnormalities of peripheral nerves, promoted glucose uptake Normalized FBG, improvement in islets Reduced FBG, Increased serum insulin, alleviated pancreatic damage, and increased the number of beta cells Increases expression of insulin, Pdx-1, and lowers Glut-2 expression. Increase in the number and size of pancreatic islets Neoformation of islets from pre-existing islets reversed degeneration of the liver Regeneration in pancreatic islet cells, normalizes blood glucose, Insulin, and cholesterol levels	T1D (STZ or Alloxan)	(Tripathi and Chandra, 2010) (Ahmed *et al*., 2004) (Singh *et al*., 2008) (Abdollahi *et al*., 2011) (Malekshahi *et al*., 2019) (Singh and Gupta, 2007) (Almarzooq and Moussa, 2009)
	Normalized FBG, reduced TG, LDL, and increased HDL levels Lowers cholesterol, LDL, TG, and increased HDL. Reduced serum glucose and increased serum insulin levels, increases PPAR-γ	T2D (Diet-induced rats)	(Chaturvedi, 2005) (Gadang *et al*., 2011)
Tinospora cordifolia	Decreased FBG and HbA1c levels, enhanced insulin and C-peptide levels, regeneration of β–cell, restored enzymes involved in glucose metabolism Improved β–cell function, insulin-mimicking activity, and inhibiting the gluconeogenesis process β-cell regenerative properties modulated the expression of Glut-4	T1D (STZ or Alloxan)	(Rajalakshmi *et al*., 2009) (Patel and Mishra, 2011) (Rajalakshmi and Anita, 2016)
	Regulated blood glucose, increased insulin secretion, suppressed oxidative stress marker, and TBARS levels	T2D (Diet induced rats)	(Sangeetha *et al*., 2011)
Gymnema sylvestre	Normalized blood glucose increased insulin levels, islet, and beta cell number β-endocrinocytes nuclei were significantly enlarged Reduced blood glucose, increased insulin levels, and β-cell regeneration Hypoglycemic and hypolipidemic activity and significant recovery of damaged β-cells Neoformation of beta cells with improved beta cell function Normoglycemic and hypolipidemic activity and β-cell regeneration Reduced blood glucose, increase plasma insulin	T1D (STZ or Alloxan)	(Shanmugasundaram *et al*., 1990a) (Chattopadhyay, 1998) (Ahmed *et al*., 2010) (Aralelimath and Bhise, 2012) (Fatima, 2015) (Daisy *et al*., 2009)|(Sugihara *et al*., 2000)
Panax Ginseng	Reduced FBG and improved islet deterioration and insulin deficiency in rats. Inhibited apoptosis of β-cells by increasing the expression of Bcl-2 and decreasing the expression of Bax and caspase-3 Reduced blood glucose levels and improved glucose tolerance; increased insulin secretion increased pancreatic β-cell proliferation Reduced FBG, increased insulin levels, improved glucose tolerance, reduced cholesterol levels Reduced FBG levels, attenuated gluconeogenesis by activating adenosine-5 ′monophosphate kinase activity, insulin-sensitizing capabilities	T1D (STZ or Alloxan)	(Xu *et al*., 2017) (Park *et al*., 2012) (Attele *et al*., 2002) (Li *et al*., 2012; Wei *et al*., 2015)
	Reversed insulin resistance, increased expression of PPARγ- 2 and its responsive genes, inhibiting TNF-α production and restoring insulin-stimulated GLUT4 translocation to the cell surface Alleviated hyperglycemia, hyperlipemia, and insulin resistance	T2D (Diet-induced rats)	(Gao *et al*., 2013; Han *et al*., 2012) (Liu *et al*., 2013)

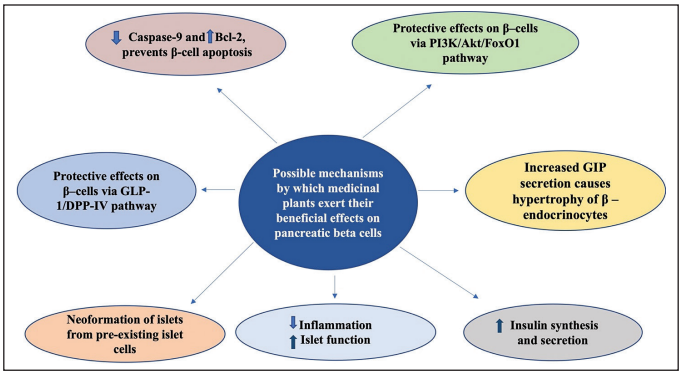

Figure 4. Possible mechanism for β- cell regeneration: medicinal plants and plant-derived compounds can regenerate pancreatic beta cells through multiple pathways; Inhibition of DPP-IV and increasing shelf life of GLP-1, reduced islet inflammation potentiates GSIS; Prevents beta cell apoptosis by inhibiting Caspase-9 and increasing Bcl-2; Preventing nuclear translocation of Fox-1 increases expression of genes involved in beta cell regeneration and have protective effects on beta cells; reduced cytokine, chemokine production increases insulin synthesis and secretion.

(Yongchaiyudha *et al*., 1996). As previously stated, dyslipidemia is known to play an important role in impaired β–cell function, which contributes to the T2D onset. Improving triglyceride, cholesterol, and total lipid levels must therefore be one of the mechanisms for improved β–cell function. Furthermore, in diabetics, oral administration of a high-molecular-weight fraction (AHM-0.05 g) containing acemannan and verectin daily thrice for 12 weeks resulted in a decrease in FBG levels (Yagi *et al*., 2009). Acemannan, which is digested by intestinal microbiota into oligosaccharides and is responsible for obstructing glucose absorption, was discovered to be responsible for the biological effect of AHM (Boban *et al*., 2006; Jain *et al*., 2007; Yagi *et al*., 2001). In addition, T2Dwho received acemannan (600 mg capsule/day) for 60 days demonstrated a decrease in blood glucose, TC, and Low-density lipoprotein (LDL) levels (Huseini *et al*., 2012). In a randomized trial, *A. vera* was considered to be superior to the placebo in reducing FBG levels HbA1c, and TC levels, and also improvement in HDL levels was observed (Alinejad-Mofrad *et al*., 2015; Devaraj *et al*., 2013). Another study observed that Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was found to be lower in an intervention group (Choi *et al*., 2013).

Although the antidiabetic activity of *A. vera* has been reported in various studies, not all of this included preparation are identical. Furthermore, the variability in daily dose makes it difficult to determine the minimum optimal dose of *A. vera* that can bring glucose homeostasis. Large-scale, multicenter, randomized-controlled long-term trials must be robustly designed to corroborate the recent findings and investigate the long-term impact of *A. vera* supplementation on managing prediabetes and T2DM with a focus on improved β–cell function (Zhang *et al*., 2016).

Momordica charantia

Momordica charantia (MC), also known as bitter gourd (karela), is a flowering vine that has been used to treat diabetes since antiquity. (Lucas *et al*., 2010). Numerous *in vitro*, and *in vivo* studies, and clinical trials validated its anti-hyperglycemic potential by significantly lowering blood glucose levels, glycosylated hemoglobin, and insulinotropic activity (Chaturvedi, 2005; Tripathi and Chandra, 2010). MC extract has been shown to restore plasma glucose levels in various animal models and a significant change in pancreatic islet morphology (increase in islet size, total β-cells area, number of cells) was observed, which may be due to the renewal of β-cells or the recovery of partially destroyed β-cells (Ahmed *et al*., 2004; Almarzooq and Moussa, 2009). The alcoholic extract of whole fruit improved islets significantly and blood glucose levels remained static even after discontinuation of the drug for 15 days (Singh *et al*., 2008). The regeneration/renewal property of the extract was also demonstrated in alloxan-induced diabetic rabbits (Tahira and Hussain, 2014) and Sprague-Dawley neonatal rats (Abdollahi *et al*., 2011) where oral administration alleviated pancreatic damage and increased the number of β-cells. In STZ-induced diabetic rats, MC extract upregulated the expression of Insulin and Pdx-1 genes while decreasing the expression of glucose transporter-2 (GLUT2) and the number and size of pancreatic islets increased significantly (Malekshahi *et al*., 2019). The presence of small scattered islets among the acinar tissue after administering acetone MC extract in alloxan-induced diabetic rats was the most significant finding, which may reflect the neoformation of islets from pre-existing islet cells. Because dietary composition is one of the stimuli for pre-existing cell multiplication, various components present in the acetone fraction may trigger this differentiation (Singh and Gupta, 2007). The reparative effects of the MC extract were also observed in HIT-T15 hamster pancreatic β-cells (Xiang *et al*., 2007) and MIN6N8 cells via the downregulation of MAPKs and NF-κB pathway (Kim and Kim, 2011) and modulation of Peroxisome proliferator- activated receptor gamma (PPAR-γ) gene expression (Gadang *et al*., 2011). It was recently reported that saponins from MC improved β-cell morphology and its function in a concentration-dependent manner via the PI3K/Akt/FoxO1 signaling pathway (Liu *et al*., 2021). These findings imply that this plant has the potential to either repair or prevent the death of damaged pancreatic β-cells.

Clinical studies

Even though the multiple mechanisms underlying bitter melon's beneficial effects, as well as the results reported in previous *in vitro* and *in vivo* studies, provide a strong base for well-designed randomized controlled trials to evaluate bitter melon as a treatment option for diabetes mellitus, only a few randomized, double-blind controlled studies of bitter melon have been conducted. The majority of bitter melon clinical studies have focused on blood glucose management (Fuangchan and Ingkaninan, 2009), a substantial reduction in HbA1c levels after four months of intervention (Zanker *et al*. 2012), fructosamine reduction following a 4-week regimen of 2,000 mg/day (Fuangchan *et al*., 2011), reduced glucose area under the curve (AUC), weight, BMI, fat percentage, and waist circumference, with an increment of insulin AUC, first phase and total insulin secretion (Cortez-Navarrete *et al*., 2018). The clinical potential of MC extract and its components shows convincing results in normalizing blood glucose levels, however, studies based on regenerating effects are needed in a larger population to use this dietary supplement for the management of diabetes. The clinical potential of MC extract and

its components demonstrates convincing results in normalizing blood glucose levels; however, more research on the regeneration and stimulation of β-cells is needed before using this dietary supplement for diabetes management.

Tinospora cordifolia

Tinospora cordifolia, also known as Guduchi (Giloy), is an extremely potent herb that is extensively used in Ayurveda to combat diabetes and keep the function of various organs in balance (Sharma *et al*., 2015). The anti-diabetic potential of this herb is mediated by a slew of biologically active phytocompounds isolated from different parts of the plant (Sudha *et al*., 2011).

Various studies demonstrate amelioration of experimental diabetes in various animal models (Upadhyay *et al*., 2010) and this effect is mediated by reducing oxidative stress, increasing insulin secretion, and inhibiting gluconeogenesis and glycogenolysis, all of which help to regulate blood glucose levels (Sangeetha *et al*., 2011). *Tinospora cordifolia* extract supplementation significantly lowers glycated hemoglobin while increasing insulin and C-peptide levels. This increase in C-peptide levels suggests that pancreatic β–cell regeneration could be one of the possible mechanisms for this effect (Rajalakshmi *et al*., 2009). When compared with diabetic controls, histological examination of the pancreas in TCS methanol extract-treated groups support the regenerative capacity of the extract (Rajalakshmi *et al*., 2009). Sharma *et al*. (2019) suggested that *T. cordifolia* stem water extract had beneficial effects on pancreatic β–cells and increased glucose uptake in 3T3-L1 adipocytes, which may regulate glucose metabolism in diabetic rats. The signaling mechanism of isoquinoline alkaloids isolated from the plant (Palmatine, jatrorrhizine, and magnoflorine) was studied in vitro and in vivo for their insulinotropic effect using the RINm5F and rat pancreatic-cell line (Sudha *et al*., 2011). Further, an alkaloid-rich fraction from *T. cordifolia* extract had antihyperglycemic activity by improving β–cell function, insulin-mimicking activity, and inhibiting the gluconeogenesis process (Patel and Mishra, 2011). Purified polysaccharide from TC methanolic extract showed β-cell regenerative properties in STZ-induced Wistar rats, and the compound treatment positively modulated the Glut-4 expression in the gastrocnemius muscle, pointing to the development of anti-diabetic drugs with few side effects (Rajalakshmi and Anita, 2016).

Clinical studies

The studies mentioned above confirm the hypoglycemic effect of *T. cordifolia* and the isolated compound (s) by either promoting glucose uptake, inhibiting hepatic gluconeogenesis, or absorption of glucose into muscle and adipose tissues via stimulation of regeneration and rejuvenation of β-cells. All of this active component(s) with different physiological roles demonstrate the versatility of the plant.

Despite the anti-diabetic activities observed in pre-clinical studies, there have been very few clinical trials reported. The decrease in lipoproteins was accompanied by stimulation of the plasma lecithin cholesterol acyltransferase levels (Kumar, 2015). Importantly, no herb-drug interaction has been reported (Sharma *et al*., 2015). However, more research on the β-cell regenerating capacity of the plant is needed before this plant could lead its way to clinical use.

Gymnema sylvestre

Gymnema sylvestre, also known as Gurmar, is an indigenous herb that is officially mentioned in the Indian Pharmacopoeia for the treatment and/or prevention of diabetes (Tiwari *et al*., 2014). Gymnema leaves' hypoglycemic action was first documented in the late 1920s (Mhaskar and Caius, 1930). Numerous *in vivo* studies have since confirmed the hypoglycemic activity of *G. sylvestre* root and leaf extracts (Sugihara *et al*., 2000). The antidiabetic array of molecules has been identified as a family of closely related gymnemic acids and gymnemasaponins, which are classified as oleanane saponins (Kaur *et al*., 2011). Furthermore, the leaves of this plant contain anthraquinones, tannins, flavonoids, phenols, cardiac glycosides, and other compounds (Senthilkumar, 2015) exhibiting therapeutic potential.

The insulinotropic activity of *G. sylvestre* leaves has been demonstrated in numerous diabetic models, with a concurrent reduction in fasting and postprandial glucose levels (Shanmugasundaram *et al*., 1990a), increasing endogenous insulin levels, presumably due to the pancreas β -cells regeneration (Murakami *et al*., 1996). Microscopy examination on GS extract-treated animals revealed that the nuclei of β-endocrinocytes nuclei were significantly increased in size in all sections of the organ with the same volume fraction and area of pancreatic islets (Chattopadhyay, 1998). This means that the effect of GS extract on gastric inhibitory polypeptide secretion is most likely responsible for β-endocrinocytes hypertrophy (Flier, 2001).

In vitro, GS extract induced insulinogenesis in HIT-T15, MIN6, and RINm5F β-cell lines as well as isolated islets of Langerhans, and these effects were mediated by increased cell permeability (Persaud *et al*., 1999a). In wistar rats, *G. sylvestre* leaf and callus extract showed a beneficial effect on β-cell regeneration, and gymnemic acid was found to be the active ingredient responsible for pancreatic β-cell regeneration and restoration of function (Ahmed *et al*., 2010). Similarly, long-term treatment with standardized dry extract of *G. sylvestre* leaves resulted in regenerative effects in diabetic rats (Aralelimath and Bhise, 2012). The number of β-cells increased significantly following GS treatment in STZ-induced diabetic rats. The immunohistochemical evidence revealed pancreatic islet regeneration and/or neoformation (Fatima, 2015). A cluster of β-cells without any α-cells was observed in GS-treated diabetic rats, implying β-cells regeneration rather than stem-cell-induced growth (Fatima, 2015). According to a recent study, *G. sylvestre* extract (Om Santal Adivasi) protects islets from cytokine-induced apoptosis *in vitro* and *in vivo* by upregulating cell survival pathways and the free radical scavenger system (Al-Romaiyan *et al*., 2020). Several compounds isolated from GS extract have been shown to have beneficial effects on blood glucose levels, TC levels, and TG levels suggesting that this plant has the potential to regenerate and/or neo-form pancreatic islets (Daisy *et al*., 2009).

Clinical studies

Gymnema sylvestre has been tested in humans as an anti-hyperglycemic agent in combination with other drugs

with promising results (Shanmugasundaram *et al*., 1990b). Fasting plasma glucose, glycated hemoglobin, and glycosylated plasma proteins were reduced significantly in T2D patients after administering GS extract or Beta Fast GXR (supplement), and some of them were able to decrease the dosage or even discontinue the use of available hypoglycemic agents (Baskaran *et al*., 1990). Endogenous insulin appears to be improved by GS therapy, possibly through β-cell regeneration. In T2D patients, oral administration of GS extract (Om Santal Adivasi) revealed an insulinotropic effect, as well as a significant improvement in glycemic control. *In vitro* measurements using patient-derived islets derived revealed a stimulatory effect on insulin secretion, which corresponded to the *in vivo* mode of action (Al-Romaiyan *et al*., 2010). In addition to the above action, a decrease in the HOMA-IR, and an increase in the Homeostatic model of beta cell function Homeostasis Model Assessment of β-cell function (HOMA-B) were observed upon administration of GS extract, suggesting its beneficial effect in the management of diabetes (Kumar *et al*., 2010). Further research should be conducted to determine the drug's long-term effect in larger populations, as well as to understand the mechanism of action of purified compounds so that their therapeutic applications can be widely explored.

Panax ginseng

For thousands of years, *P. ginseng* has been used as a tonic and reparative remedy in traditional Chinese medicine (Hou, 1977). Ginsenosides, widely recognized as ginseng saponins, are a type of natural triterpene saponin that is considered to be accountable for the antihyperglycemic potential of ginseng (Yang and Wu, 2016). Near about 200 ginsenosides are identified in ginseng and heat-processed ginseng products so far (Attele *et al*., 1999).

Ginseng has gained a great deal of attention for its anti-diabetic efficacy. Oral administration of *P. ginseng* berry extract and its major constituent, ginsenoside Re, demonstrated a hypoglycemic effect in obese diabetic C57BL/6J ob/ob mice, and that ginsenoside Re plays a crucial role as an anti-hyperglycemic agent (Attele *et al*., 2002). High glucose and fatty acid levels upregulate uncoupling protein-2 (UCP2) expression, which is relatively high in diabetic models (Reilly and Thompson, 2000; Zhang *et al*., 2011). Furthermore, superoxide stimulates UCP2 activity (Krauss *et al*., 2003). According to these findings, UCP2 may have a significant role in beta-cell pathology and the advancement of T2D. Interestingly, American ginseng water extract inhibited UCP-2 expression, which has been linked to insulin synthesis and β-cell survival (Luo and Luo, 2006). Further, the level of pro-apoptotic protein caspase-9 was reduced while the anti-apoptotic protein Bcl-2 level was increased, contributing to ginseng's ability to protect against β-cell death and improve insulin synthesis (Luo and Luo, 2006). Ginseng extract (GE) and several ginsenosides were reported to inhibit cytokine-induced pancreatic cell death in MIN6N8 cells by reducing the production of nitric oxide and ROS. Also, the expression of p53/p21, caspase, and poly (ADP-ribose) polymerase cleavage was inhibited, which may contribute to antidiabetic influence in T1D (Kim and Kim, 2007). Similar results were reported by another group where GE increased GSIS in MIN6 cells while protecting pancreatic β-cell from apoptosis (Park *et al*., 2008). Furthermore, in STZ-induced diabetic mice, administration of ginseng berry extract (150 mg/kg) substantially lowered levels of blood sugar and improved glucose tolerance; enhanced insulin secretion was potential because of increased pancreatic β-cell proliferation (Park *et al*., 2012).

Another study found that rats fed an high fat diet (HFD) reversed insulin resistance in muscle glucose transport quickly. This was attained by increased and improved expression of PPARɣ-2 and its responsive genes, adiponectin, and Insulin receptor substrate-1 (IRS-1), impeding tumor necrosis factor- α (TNF-α) production and restoring insulin-stimulated GLUT4 translocation to the cell surface (Gao *et al*., 2013; Han *et al*., 2012). Compound K, a metabolite of protopanaxadiol-type ginsenosides demonstrated the hypoglycemic effect by reducing FBG levels, attenuating gluconeogenesis by activating adenosine-5 ′monophosphate kinase activity (Li *et al*., 2012; Wei *et al*., 2015). Malonyl ginsenosides are naturally occurring ginsenosides found both in fresh and air-dried ginseng that can alleviate hyperglycemia, hyperlipemia, and insulin resistance in STZ-induced diabetic rats fed a high-fat diet (Liu *et al*., 2013). Another study found that feeding GE to C57BL/6 mice significantly reduced HOMA-IR and fasting insulin levels, as well as alleviated pancreatic islet hypertrophy, implying that reduced insulin resistance may contribute to reduced insulin demand (Seo *et al*., 2015). As per the histopathological and immunohistochemistry studies, ginseng oligopeptides (GOPs) treatment significantly decreased FBG in induced animals and improved islet deterioration and insulin deficiency in rats. GOPs inhibited β-cell apoptosis by decreasing the expression of pro-apoptotic Bax and caspase-3 while increasing the levels of anti-apoptotic Bcl-2 (Xu *et al*., 2017). As previously stated, an increasing amount of research from *in vitro* and *in vivo* studies indicates that the hypoglycemic action of ginseng is complex due to a variety of mechanisms. Furthermore, clinical trials evaluating the safety and efficacy of GE in diabetics are needed.

Clinical studies

Panax ginseng has been used in Asia for a long time. Several clinical studies studying the impact of ginseng on parameters related to diabetes have been published, with widely disparate results. *Panax ginseng* (6 g/day) consumption for 12 weeks ameliorates hyperglycemia in T2D (Vuksan *et al*., 2000). Another study by the same group found that Korean red ginseng (KRG) treatment improved glycemic control and insulin levels in T2D patients (Vuksan *et al*., 2008). Bang *et al*. (2014) reported similar results, where 12 weeks of KRG supplementation improved blood glucose levels and decreased HOMA-IR in newly diagnosed T2D (Bang *et al*., 2014). In diabetics, regular supplementation with fermented red ginseng reduced postprandial glucose levels while increasing postprandial insulin levels (Oh *et al*., 2014). Ginsam, a vinegar extract of *P. ginseng*, improved blood glucose and HbA1c levels in T2Dwith poor glycemic control (Yoon *et al*., 2012). Also, the evaluation of hydrolyzed GE (HGE) in Korean participants was effective in treating people with impaired fasting glucose levels (Park *et al*., 2014). Furthermore, in another study ginseng berry extract reduced fasting glucose levels by 3.7%, postprandial glucose at 60 minutes, and the AUC for glucose by 7.7% in a double-blind placebo-controlled study; however, this study failed to show anti-diabetic potential concerning other blood glucose and lipid metabolism-related parameters. Importantly, no adverse

effects from long-term berry extract consumption were reported by (Choi *et al*., 2018). Reeds *et al*. (2011) on the other hand, found that oral ginseng or ginsenoside Re therapy has no effect on β-cell function in morbidly obese subjects with poor glucose tolerance or recently diagnosed diabetes. The lack of a therapeutic effect could be attributed to poor systemic bioavailability (Reeds *et al*., 2011) and differences in ginsenoside concentrations may also have contributed to outcome variability. Standardization of ginsenosides types and ratios is required to achieve consistent efficacy and use it as a prospective drug for the treatment of diabetes mellitus.

COMPOUNDS IMPLICATED IN THE RESTORATION OF PANCREATIC B -CELL MASS AND ITS FUNCTION

Different natural compounds, such as flavonoids and alkaloids, have been shown in preclinical and clinical studies to have anti-diabetic potential.

Geniposide

Geniposide, a natural dietary pigment obtained from gardenia fruits, has emerged as an exciting candidate due to its ability to significantly increase T-cell factor 7-like 2 (TCF7L2) mRNA levels in cells exposed to high glucose levels. Blood glucose levels were normalized following geniposide treatment in db/db and HFD mice, accompanied by an increase in *β*-cell mass (Yao *et al*., 2015). Wnt/*β*-catenin signaling is an important regulator for *β*-cell insulin secretion. TCF7L2, a key transcription factor of Wnt signaling, mediates its effects through GLP- 1 receptor. Increased expression of TCF7L2 may enhance GLP-1R expression and activate the AKT pathway (Shu *et al*., 2009) promoting β-cell regeneration in vivo (Shu *et al*., 2012). Numerous studies have confirmed the role of TCF7L2 in improving β-cell function, survival, and regeneration (da Silva Xavier *et al*., 2009; Figeac *et al*., 2010). Furthermore, geniposide could prevent β-cell apoptosis in lipotoxicity-induced INS-1 cells via GLP-1R (Liu *et al*., 2012) and protect *β*-cell mass from pro-inflammatory cytokine-mediated toxicity by upregulating TCF7L2 expression (Yao *et al*., 2015).

Berberine

Berberine is an isoquinoline alkaloid found in different parts of the plant. Berberis has been used to treat various disorders including diabetes. The effect of berberine on insulin production is controversial. Prolonged treatment with berberine increased insulin secretion in various cell lines and mouse islets of Langerhans in a dose-dependent manner (1–10 μM) (Leng *et al*., 2004), whereas acute administration with high concentrations (50 M for 1 hours) lowered insulin secretion (Zhou *et al*., 2008). Even though its effects on insulin release *in vitro* have been debated, berberine has been shown to reduce hyperglycemia, enhance insulin sensitivity, and stimulate pancreatic β-cell regeneration in T2D animal models. Oral administration of berberine (380 mg/kg) resulted in weight reduction and a substantial improvement in glucose homeostasis in db/db mice (Lee *et al*., 2006). It has also been shown to have a protective effect against STZ-induced β-cell death (Zhou *et al*., 2009). Unpublished data from our lab showed that berberine isolated from natural resources inhibits DPP-IV activity *in vitro*, and the results were confirmed by *in silico* studies.

Phenylpropenoic acid glucoside

Phenylpropenoic acid glucoside (PPAG) from rooibos (*Aspalathus linearis*) extract increases *in vitro* glucose uptake and improves glycemic control in the T2D animal rat model, suggesting that the anti-hyperglycemic effect of rooibos is attributable to PPAG and thus it has the potential to be a new class of antidiabetic therapeutics (Muller *et al*., 2013). Furthermore, oral administration of PPAG to mice fed a high fat and fructose diet (similar to an unhealthy western diet) for 12 weeks prevented diabetes. PPAG increased β-cell mass in this chronic, long-term treatment by decreasing lipotoxic β-cell apoptosis. PPAG also protected β-cells from palmitate-induced apoptosis *in vitro* and from ER stress by increasing the expression of the anti-apoptotic BCL2 protein while not affecting proapoptotic signals (Mathijs *et al*., 2014). PPAG also protects pancreatic β-cells against the harmful effects of STZ, oxidative stress, and glucotoxicity, in addition to having anti-apoptotic and anti-necrotic properties and protecting human beta cells from a diabetogenic insult. The cytoprotective effect was preceded by the normalization of anti-apoptotic protein BCL2 expression in pancreatic islets (Himpe *et al*., 2016).

Genistein

Genistein is the most extensively researched isoflavone for the management of diabetes (Gilbert and Liu, 2013) and can be found in a wide range of plants, including lupine, fava beans, soybeans, and soybean products. It has been researched in several diabetic models and has consistently demonstrated hypoglycemic potential across experimental models (Elmarakby *et al*., 2011; Fu *et al*., 2010). Numerous *in vitro* studies using isolated islets and insulinoma cell lines have evidenced that genistein has anti-diabetic properties due to its direct effect on β-cells (Elliott *et al*., 2002; Liu *et al*., 2006; Ohno *et al*., 1993). However, genistein's beneficial effects are limited to a certain concentration. Chronic treatment (100 mol/l) with genistein prevented the cultured islet cell proliferation, whereas acute treatment (5 mol/l) resulted in increased proliferation of β-cells *in vitro* and *in vivo* (Sorenson *et al*., 1994).

Another study reported that acute treatment with genistein (5 μM for 30 m) potentiated GSIS in islets of mice and the INS-1 β-cell line (Liu *et al*., 2006) and that moderate concentration of genistein (50 μM for 1 hour) also produced similar results in isolated islets of the mice (Persaud *et al*., 1999b). In addition, genistein has been shown to modulate both β-cell proliferation and apoptosis. A low concentration of genistein-induced proliferation was detected using the incorporation of BrdU in INS-1 cells (0.1–10 M for 24 hours) and isolated human islets (1 and 5 M for 24 hours) respectively. (Fu *et al*., 2010). In contrast, a higher concentration of genistein (100 μM for 24 hours) increased β-cell death in RINm5F cells at 4 hours (Elliott *et al*., 2001) and 24 hours (Elliott *et al*., 2002). It is believed that the insulinotropic and proliferative effects of genistein are mediated partly via the accumulation of cAMP and activation of protein kinase A (Fu *et al*., 2010). Also, the observed increase in cell death associated with higher concentrations of genistein could be due to the inhibition of topoisomerase-II (Elliott *et al*., 2001). Inhibiting

topoisomerase-II can cause fragmentation of DNA, cell death, and G2/M cell cycle arrest (Collier *et al*., 2006).

Naringenin

Naringenin is a bioactive flavonoid that is found primarily in citrus fruits like grapes, oranges, lemons, and tomatoes (Sumathi *et al*., 2015). Nrf2 is a leucine zipper transcription element that regulates the expression of intracellular antioxidant enzymes, preventing cell death from oxidative stress (Lacher *et al*., 2015). It is theorized that targeted Nrf2 activation will protect pancreatic cells from oxidative damage, thereby reducing diabetes complications (Lu *et al*., 2016). Naringenin showed protective effects against STZ-induced apoptosis in MIN6 cells by increasing Nrf2 expression and its target genes GST and NQO1 and decreasing the expression of caspase-3 (Rajappa *et al*., 2018). Further, *in vivo* studies revealed that 45 days of oral naringenin administration significantly decreased blood glucose levels, improved lipid profile, and increased the level of antioxidants in pancreatic tissues (Rajappa *et al*., 2018). It also improved glucose homeostasis and response to insulin in STZ-treated mice. Immunohistochemical analysis demonstrated that insulin expression was restored in control animals. In addition, naringenin increased glycolysis while inhibiting gluconeogenesis. These *in vitro* and *in vivo* results highlight the potential of naringenin to enhance the expression of Nrf2 and protect pancreatic β-cells from STZ-induced oxidative damage (Rajappa *et al*., 2018).

Baicalein

Baicalein is a flavonoid extracted from the roots of the medicinal plant Scutellariae baicalensis Georgi (SBG), which is generally grown in Asian countries (Bruno *et al*., 2002). Baicalein, baicalin, wogonin, and wogonoside are supposedly the major biologically active components in SBG, accounting for 5.41%, 10.11%, 1.3%, and 3.55% of the dry material respectively (Li-Weber, 2009). Because of the potential health benefits of baicalein and its glucuronide baicalin, they have received a great deal of attention. *In vivo* studies demonstrated oral administration of baicalin for 30 days, decreased hyperglycemia-induced mitochondrial damage in *β*-cells (Waisundara *et al*., 2009). Baicalein has been shown to have positive effects on diabetes-associated health complications (Pu *et al*., 2012). Further, it has been shown to improve glycemic control and GSIS in HFD-induced middle-aged obese mice. However, no significant change was observed in the intake of food, body weight, lipid profile, and insulin sensitivity in obese mice. However, in the HFD model with a low dose of STZ, baicalein treatment improved glucose homeostasis and blood insulin levels, which are linked to enhanced *β*-cell survival and mass. Furthermore, baicalein significantly improved GSIS and increased the effectiveness of insulin-secreting cells and cultured islets either in the basal medium or under prolonged hyperlipidemic conditions. These findings suggest that baicalein may be involved in modulating pancreatic *β*-cell function (Fu *et al*., 2014). Baicalein may have anti-diabetic properties by increasing glucose uptake and glycolysis and inhibiting gluconeogenesis in hepatocytes, possibly through regulation of the Ins/IRS-1/PI3K/AKT pathway (Yang *et al*., 2019). Baicalein has been shown *in vivo* to improve glucose and fat metabolism in T2D rats by normalizing the MAPK/PI3K/AKT signaling pathway, thereby improving insulin sensitivity (Cui *et al*., 2018).

Apigenin

Apigenin is a flavonoid derived from plants with innumerable nutritional and organoleptic properties. It is mostly found in the glycosylated form in vegetables, fruits, herbs, and plant-based beverages and oils (Marrano *et al*., 2021; Salehi *et al*., 2019b). The antihyperglycemic potential of apigenin may be due to its ability to inhibit the activity of α-glucosidase, enhance insulin secretion (Pamunuwa *et al*., 2016), and neutralize ROS in the cell (Shay *et al*., 2015), all of which help to prevent diabetes and its complications. Furthermore, it has been shown to have a protective effect against cytokine-induced β-cell damage via suppression of nuclear factor kappa B activation (Kim *et al*., 2007) and was able to reverse the cytotoxic effects of STZ and inhibit β-cell apoptosis. The protective effects of apigenin were related to ameliorating the loss of antioxidant enzymes (Wang *et al*., 2017). Apigenin present in extra virgin olive oil augmented beta-cell proliferation and enhanced GSIS in INS-1E cells and human islet cells (Marrano *et al*., 2021). Protein kinase B (AKT) activation and cAMP response element-binding protein (CREB) is important for the regulation of β-cell mass and its function (Dalle *et al*., 2011; Elghazi *et al*., 2007). Apigenin was found to significantly increase both AKT and CREB phosphorylation, suggesting that it can foster β-cell health and may increase insulin release and improve glycemic control (Marrano *et al*., 2021).

CONCLUSION

β-cell death contributes to the progression of T1D and T2D by reducing the mass of β-cells and, as a result, endogenous secretion of insulin. Therapeutics to impede or even reverse the apoptosis and dysfunction of β-cells are urgently needed. Several studies have demonstrated that the average contributions of β-cell proliferation, neogenesis, and apoptosis to overall β-cell mass vary with age and in response to stress. We reviewed some medicinal plants and plant-derived compounds, inspired by traditional healthcare systems. Several pieces of scientific evidence suggested that these plant extracts and/or phytochemicals have anti-hyperglycemic properties. Some of these extracts such as *A. vera*, *P. ginseng*, *M. charantia,* and a few compounds, such as Geniposide, Baicalein, and Apigenin, demonstrated highly promising effects. The extracts and the phytochemicals described in this review are believed to ameliorate diabetic symptoms via multiple pathways including increased half-life of GLP-1 and inhibiting DPP-IV, decreasing β-cell apoptosis by inhibiting caspase 9 and increasing the expression of Bcl-2, enhancing the expression of genes involved in β-cell proliferation, decreasing islet inflammation and increasing insulin synthesis and secretion. However, the most significant limitation is the paucity of controlled clinical trials. The short duration of these studies, small sample size, lack of randomization, and dose variation. Thus, further investigation and clinical trials are needed to determine the correct dosage for diabetes prevention and its complications, as well as to better comprehend the mechanisms through which these extracts impart their therapeutic benefits. Importantly, prospective anti-diabetic plants should be evaluated for toxicity to ensure they are therapeutically safe and effective phytomedicines.

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LIST OF ABBREVIATIONS

AUC, Area under curve; BCL2, B-cell lymphoma 2; cAMP, Cyclic adenosine monophosphate; DPP-IV, Dipeptidyl peptidase -IV; ESCs, Embryonic stem cells; FFA, Free fatty acid; *GABA,* Gamma-aminobutyric acid; GLP-1*,* Glucagon-like peptide-*1;* Glut2, Glucose transported-2; Glut-4, Glucose transporter-4; GOPs, Ginseng oligopeptides; *GSIS, Glucose stimulated insulin secretion; Gymnema sylvestre*, *G. sylvestre*; HbA1c, Glycated hemoglobin; HDL, High-density lipoprotein; HFD, High fat diet; HOMA-B, Homeostasis model assessment of β-cell function; HOMA-IR, Homeostatic model assessment of insulin resistance; IRS-1, Insulin receptor substrate-1; KRG, Korean red ginseng; LDL, Low-density lipoprotein; *Momordica charantia*, *M. charantia* (MC); Nrf2, Nuclear factor E2-related factor; *Panax Ginseng*, *P. ginseng*; Pdx-1, Pancreatic and duodenal homeobox 1; PPAG, Phenylpropenoic acid glucoside; PPAR-γ, Peroxisome proliferator- activated receptor gamma; STZ, Streptozotocin; T1D, Type 1 diabetes; T2D, Type 2 diabetes; TCF7L2, T-cell factor 7-like 2; *Tinospora cordifolia*, *T. cordifolia;* TNF-α, Tumor necrosis factor alpha.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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