ScienSage

Journal of Advanced Scientific Research

Available online through http://www.sciensage.info

ISSN
0976-9595
Review Article

A PERSPECTIVE ON REGENERATIVE POTENTIALS OF HERBS FOR DIABETES THERAPEUTICS

Abhay Srivastava, Mitul Vakani, Gurprit Bhardwaj, Sarita Gupta*

Molecular Endocrinology and Stem Cell Research Lab, Department of Biochemistry, Faculty of Science, The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India

**Corresponding author: sglmescrl@gmail.com*

ABSTRACT

Diabetes Mellitus, one of the leading metabolic disorders, has become a worldwide pandemic and socioeconomic challenge where one in eleven adults are suffering from this condition. India is among the leading country that due to its populace's changing lifestyle and genetic predisposition is harboring nearly 77 million diabetic patients. Current hypoglycemic drugs in the market that are used in the treatment of diabetes can merely manage the condition and have side effects. Hence, improved and effective strategies harboring herbal medicinal plants and bioactive drugs are needed in the paradigm of diabetes therapeutics. Various neutraceutical plants/bioactive focusing on anti-hyperglycemic, increased insulin secretion, pancreatic/beta cell regenerative properties, islet-neogenic properties, are stated. The positive antidiabetic effect and nutritional value of *Enicostemma littorale* have been extensively explored. Pancreatic/beta cell regenerative properties combined with the current stem cell/ regenerative technology demonstrating differentiation potential into insulin producing cells can thus become an attractive strategy for the therapeutic intervention. The traditional nutraceutical/ herbal medicines can provide an effective alternative to the synthetic side effects of the existing diabetes drugs which will not only improve our existing knowledge but will provide a novel effective clinically acceptable diabetic cure.

Keywords: Herbal therapy, Diabetes Mellitus, Stem cells, Bio-active molecules.

1. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder that affects a large number of people. Patients suffering from diabetes continue to increase worldwide. The prevalence of both Type 1 and Type 2 diabetes mellitus is increasing throughout the world along with the ensuing morbidity and early mortality because of premature microvascular and macrovascular disease. The international diabetes federation in the year 2019 stated that around 463 million adults were suffering from diabetes. Statistically, India is severely afflicted by DM, there were over 77 million cases of diabetes in India in 2019 [1]. Diabetes is a complex metabolic disorder associated with hyperglycemia, hyperlipidemia, and oxidative stress either due to decreased insulin secretion (type 1) or lack of insulin response (type 2). In type 1 diabetes, there is the self-destruction of insulin producing pancreatic β-cells whereas in type 2, long term insulin resistance gets transformed into type 1 with loss of β-cells, which creates a chaotic state for β-cells [2,3]. There are different approaches for the treatment of diabetes; first and foremost is insulin itself, apart from this, many other drugs are in the market which target different levels such as Sulfonylurea, which efficiently releases insulin from β-cells by blocking the ATP-sensitive potassium channels. Meglitinides like repaglinide and nateglinide are other important insulin secretagogues [4, 5]. Biguanides, decrease insulin resistance, a thiazolidinedione, increase insulin sensitivity; alpha-glucosidase inhibitors like acarbose, decreases glucose absorption from the intestine, and Sodium-Glucose Cotransporters inhibitors (SGLT) cause increased glucosuria thereby decreasing hyperglycemia. Clinical trials indicate that, in some instances, control of blood glucose can be restored by transplantation of cadaveric derived and *in vitro* newly differentiated islets.

2. TRADITIONAL NUTRACEUTICAL/HERBAL PLANTS WITH ANTIDIABETIC ACTIVITY

In recent years, the popularity of complementary medicine such as traditional herbal therapy, described

by ayurvedic and indigenous systems of medicine in India has increased. Herbal preparations/agents are preferred, antidiabetic agents. Table 1 demonstrates traditional Nutraceuticals/herbal plants with anti-diabetic activity.

Table 1: Summarizing traditional Nutraceuticals/herbal plants with antidiabetic activity

Anti-Hyperglycaemic effect	Increased Insulin secretion
Azadirachta indica [6]	*Allium sativum* and *Allium cepa* [7]
Aegle marmelos [8]	*Aloe vera* [9]
Curcuma longa Linn [10]	*Acacia Arabica* [11]
Catharanthus roseus [12]	*Gymnema sylvestre* [13]
Emblica officinalis Gaertn [14]	*Ocimum sanctum* [15]
Ginseng species [16,17,18]	Insulin-mimetic property *Coccinia indica* [19]
Momordica charantia [20,21]	
Mangifera indica L [22]	
Pterocarpus marsupium [23]	
Silibummarianum [24,25]	
Trigonella foenum-graecum [26,27]	

3. COALESCING MEDICINAL PLANT/BIO-ACTIVE MOLECULES WITH REGENERATIVE MEDICINE FOR DIABETES TREATMENT

Currently, commercially available drugs manage the diabetic condition but portray health risks hence medicinal plants or natural bioactive molecules derived from herbs with pancreatic/islet regenerative properties with regards to differentiation potential from various stem/progenitors into insulin producing islets like clusters with minimal to no side effects gives an improved edge to the regenerative medicines.

4. STEM CELLS IN ISLET REPLACEMENT THERAPY

Stimulation of endogenous tissue regeneration is an important avenue that is being examined for β-cell replacement therapy. The capacity to repair tissue following an insult has been demonstrated in many tissues, including the skin, liver, and heart [28]. This mechanistic tissue regeneration has also been demonstrated in many animal models of pancreas injury such as partial duct ligation and partial pancreatectomy or by β-cell specific injury with alloxan and Streptozotocin [29]. These studies have attempted to identify the source of new β-cells following regeneration as a means to generate an increased supply of β-cells. There are three main sources of new β-cells: replication, islet ductal neogenesis, and stem/ progenitor cell differentiation.

The islet transplantation therapy for type 1 diabetes patients pioneered in 2000 by the Edmonton group [30] demonstrated its potential with remarkable freedom from exogenous insulin-dependence for the majority of patients for up to 1-2 years. Although there are limitations of this approach because more than 50% of the patients were back on insulin in five years, some continuing function of residual grafts is required [31]. Islet therapy is a promising approach. Stem cells both embryonic and adult, along with induced pluripotent stem cells (iPSCs) opens new vistas in pancreatic regenerative or islet replacement therapy. These cell-based therapies may eventually provide new rays of hope for curative treatment for diabetes. The availability of this treatment option is limited due to (i) the death of cadaveric islet donors [32], (ii) generation of new islets from stem cell pool, and (iii) availability of islet neogenic or differentiating agents [33]. However, hurdles of islet transplantation can be significantly improved. Medical practitioners had started using islet transplantation therapy to treat diabetes in the year 2000 [34]. Various methods have been developed to create *in vitro* large quantities of glucose-responsive functional islets from the pancreatic stem or precursor cells under well-defined stimulus conditions [35, 36]. Another more famously used technique is the use of human embryonic stem cells by "Novocell protocol". This when used in a defined sequence, and with specific differentiating agents helps to direct the stem cells finally towards hormone expressing group of endocrine cells which represent "islets" [37]. It is ideal that islets created *in vitro* have all the cells present in natural islets, but at least they must have majority of insulin-releasing

β-cells mixed with a small fraction of α-cells so that the "new islet cluster" can independently maintain glucose homeostasis by tightly regulating the release of insulin in response to glucose. Various differentiating agents for this rationale are now being rummaged around for. Biological growth factor like Keratinocyte growth factor (KGF), Fibroblast growth factor (FGF), Glucagon-like peptide-1(GLP-1) and Betacellulin [38-40] and chemical agents like Nicotinamide, Activin-A, Exendin-4 [41-43] are conveniently used by researchers. But the yield of islets after differentiation is not sufficient to overcome the verge of demand and the high cost of therapy. Hence scientists are now shifting towards the use of dramatic medicinal properties of herbal plants that may possess islet neogenic activity.

5. MEDICINAL PLANTS IN PANCREATIC REGENERATION AND ISLET NEOGENESIS:

5.1. Citrullus colocynthis

According to the findings of one of the studies, the application of 125 mg *C. colocynthis* once per day for 2 months can lead to a considerable decrease in the mean levels of HbA1c and FBS among patients with type II diabetes without any side effects [44]. *C. colocynthis* aqueous seed extract stabilized animal body weight and ameliorated hyperglycemia in a dose- and time-dependent manner which was attributable to regenerative effect on β cells and intra-islet vasculature. It increased the islet diameter and β cell count [45].

5.2. Tinospora cordifolia

Authors have reported that treatment with *T. cordifolia* stem powder caused a reversal in the level of fasting blood sugar by 9 % in Type 2 diabetic patients compared to control human controls [46]. The novel polysaccharide from *T.cordifolia* possesses hypolipidemic and hypoglycemic properties. It also has glucose oxidizing and β cell regenerative properties. Regeneration of β cells in the pancreatic sections was found in the histological studies of Streptozotocin-induced Diabetic Wistar Rats [47].

5.3. Moringa oleifera

Kumari *et al*. demonstrated the treatment of type 2 diabetic subjects with 8 g of powdered *M. oleifera* leaf in a tablet form per day for 40 days. A total of 46 subjects were involved in the study. At the end of the study, fasting blood glucose and postprandial blood glucose were 28% and 26% lower, respectively, in the treated subjects [48]. Aqueous extract of *M. oleifera* leaves possesses potent hypoglycemic effects through the normalization of elevated hepatic pyruvate carboxylase enzyme and regeneration of damaged hepatocytes and pancreatic cells via its antioxidant properties. Moreover, it restored the normal histological structure of the liver and pancreas damaged by alloxan in diabetic rats [49].

5.4. Ephedra sinica Stapf, and Ephedra distachya

Glycans and ephedrans A, B, C, D, and E, isolated from *Ephedra distachya* herbs have been confirmed to have anti-hyperglycemic activity in alloxan-induced diabetic mice by regenerating atrophied endocrine pancreas and restoring insulin secretion [50].

5.5. Oreocnide integrifolia:

Here, the study examined the potential of the flavonoid-rich fraction of *Oreocnide integrifolia* in pancreatic regeneration of 70% pancreatectomized BALB/c mice. Although they explained that the ductal progenitors were responsible for the pancreatic regeneration, they did not comment on either the active principle responsible for the flavonoid fraction or its mechanism of action for the same [51]. Figure 1 depicts the islet neogenic activity of various herbal plants and table 2 describes medicinal plants with pancreatic/ β cell regenerating ability.

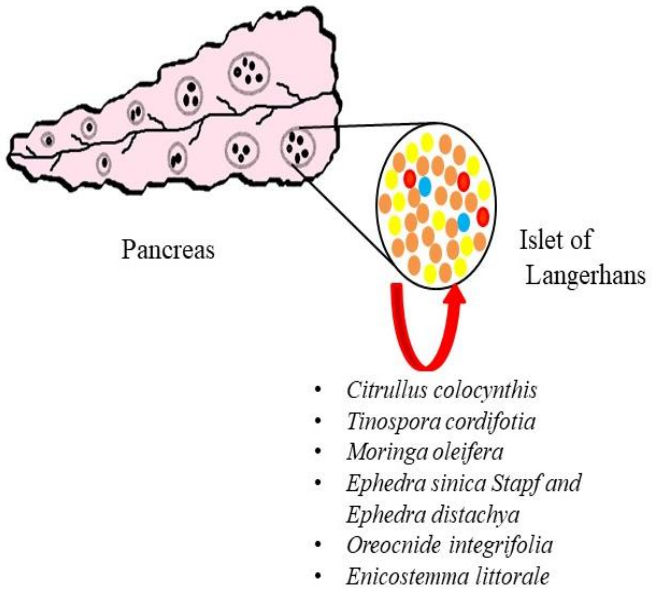

Fig. 1: Islet neogenic activity of various herbal plants

Table 2: Plants with pancreatic/ β cell regenerating ability

Plants with pancreatic/β cell regenerating ability	Mode of action	Reference
Citrullus colocynthis	Regenerative effect on β cells and intra-islet vasculature	[45]
Tinospora cordifolia	β cell regenerative properties	[47]
Moringa oleifera	Regeneration of damaged pancreatic cells via its antioxidant properties	[49]
Ephedra sinica Stapf, and Ephedra distachya:	Acts by regenerating atrophied endocrine pancreas and restoring insulin secretion	[50]
Oreocnide integrifolia	Pancreatic regeneration of 70% pancreatectomized BALB/c mice.	[51]

6. *ENICOSTEMMA LITTORALE:* ANTI DIABETIC EFFECTS AND A NEW TARGET FOR ISLET NEOGENESIS

Enicostemma littorale (Gentianaceae) belonging to the family Gentianaceae is a glabrous perennial herb. It grows throughout India up to 1.5 feet high and more frequently near the sea. It is called Chota-kirayat or Chota chirayata in Hindi, Mamejavo in Gujarati, Nagajivha in Bengal, and Vellarugu or Vallari in Tamil.

As for the high nutritional value of EL, 2 g of EL fresh leaves is daily recommended in diabetes [52]. A 100 g of fresh EL contains 140 kcal energy with 26.5g of carbohydrate, 7g of protein, 0.7g of fat, 8.4 g of minerals, 1.641 mg of calcium, 49.9 mg of iron, 81mg of phosphorous, and 4.2 g of fiber as per the nutritional analysis report of Indian Council of Medical Research [53].

Traditionally aqueous extract and dried powder of this herb have been used for the treatment of malaria and diabetes, however was not evaluated scientifically till the year 2000. Taking lead from the reverse pharmacology approach, studies with aqueous extract of this plant were initiated [54, 55]. Alloxan-induced diabetic rats showed increase in serum insulin levels owing to hypoglycemic and antidiabetic effects of aqueous extract of *Enicostemma littorale* along with insulin secretagogue action in isolated rat pancreatic islets [54, 56, 57]. The methanolic extract imparts an insulinotropic effect, normalizes dyslipidemia, and reduces oxidative stress [54, 55]. In another study, diabetic rats when treated with plant extract for 45 days showed a reduction in blood glucose levels and also provided nephron, neuro, and cardioprotective effects [58-60].

It is also reported that the EL extract improved lipid profile at a small dose of 0.5 g/kg [61]. Our group has also suggested that the methanolic extract of *Enicostemma littorale* imparts cytoprotective and anti-apoptotic effects to the islet of Langerhans against oxidative stress [62]. Apart from animal studies, we have also reported the antidiabetic effect of EL in Non-insulin dependent diabetes mellitus (NIDDM) patients showing hypoglycemic, antioxidant, and hypolipidemic actions with aqueous extract [63]. Table 3 demonstrates *Enicostemma littorale* extracts and its anti diabetic properties

Table 3: *Enicostemma littorale* Plant extracts & anti diabetic properties

Enicostemma littorale	**Aqueous Extract** Hypoglycemic effect, insulin secretagogue action & Cardioprotective.	[54,56,57]
	Methanolic Extract The hypoglycemic, insulinotropic effect, Hypolipidemic, antioxidant as well as preventive effects of Nephrotoxicity & Neuropathy. Moreover, Methanolic extract recently demonstrated Cytoprotective and anti-apoptotic effects on the islet of Langerhans against oxidative stress.	[54,55] [58-60] [62]

7. PANCREATIC REGENERATIVE AND ISLET-NEOGENIC PROPERTIES OF HERBAL AGENTS (BIOACTIVE)

7.1. Geniposide

Geniposide significantly decreased the blood glucose, insulin as well as triglyceride levels in diabetic mice. It also promotes β cell regeneration and survival in i*n vitro* study in isolated mouse islets & mouse pancreatic cell line (MIN6). Further, mouse pancreatic islets *in vitro* as well as mouse *in vivo* study identified a role of geniposide in enhancing β-cell survival and regeneration

by mechanisms involving the activation of β-catenin/T-cell factor 7 like-2 signaling pathways [64].

7.2. Kinsenoside

Kinsenoside from *A. roxburghil* is a major component of its n-butanol fraction, exhibited glucose lowering effect in STZ rats at 15 mg/kg dose along with increased glucose tolerance. Enhanced integrity of islets of Langerhans was observed in the Kinsenoside treated rats, which indicated pancreatic β-cell regeneration. Thus, rendering Kinsenoside as a promising antidiabetic agent for therapy [65].

7.3. Silymarin

Silymarin recovers the normal morphology and endocrine function of damaged pancreatic tissue in alloxan induced diabetic rats. Moreover, the Silymarin treatment induced an increase in both Pancreas/ duodenum homeobox protein 1 (*Pdx1*) and insulin gene expression as well as β-cell proliferation in Wistar rats, partially pancreatectomized (60%) model [66]. Five randomized human clinical trials on 270 diabetic patients showed that routine silymarin administration regulates a momentous reduction in fasting blood glucose levels as well as HbA1c levels [67].

7.4. Genistein

Genistein enhances insulin secretion & inhibits pancreatic β-cell apoptosis. Genistein treatment increased β-cell proliferation in cell culture models as well as in the pancreas of Genistein-treated diabetic mouse model. The effects appear to involve cAMP/ PKA (cyclic Adenosine monophosphate/Protein kinase A) signaling. Genistein treatment was also associated with increases in intracellular cAMP, PKA activity, and active ERK1/2 (extracellular signal-regulated kinases), suggesting that the cAMP/PKA and ERK1/2 pathways are stimulated by Genistein treatment. Identical effects were observed in human islet β-cells that were exposed to Genistein, suggesting non-species-specific and human-relevant effects [68]. Randomized Human clinical trials revealed that 1-year genistein treatment significantly reduced fasting glucose and fasting insulin as well as HOMA-IR (Homeostatic model assessment (HOMA) insulin resistance (IR)) without any side effects [69].

7.5. Quercetin

Commonly found in plants (In many fruits, vegetables, leaves, and grains) enhances insulin secretion and inhibits pancreatic β cell apoptosis. Quercetin potentiated both glucose and Glibenclamide-induced insulin secretion in the insulin-secreting cell line INS-1 and rat isolated pancreas. The ERK1/2 signaling pathway played a crucial role in the potentiation of glucose-induced insulin secretion by quercetin. Also, quercetin protected β-cell function and viability against oxidative damage induced by H_2O_2 and induced major phosphorylation of ERK1/2 [70].

7.6. Berberine

Berberine is isolated from *Rhizoma coptidis*. It enhances insulin secretion and lowers hyperglycemia. It stimulated pancreatic β cell regeneration in type 2 diabetic animals [71]. Moreover, the pilot human clinical trials study on 36 types 2 diabetic patients for 3-month treatment of berberine revealed that significant decreases in hemoglobin A1c, fasting blood glucose, postprandial blood glucose [72].

7.7. Nymphayol

Nymphayol enhances insulin secretion. Nymphayol isolated from Nymphaeastellata (Wild.) flowers demonstrated Partial regeneration of β cells [73].

7.8. Ginsenoside

Ginsenoside Rg3 (Rg3), an active ingredient of ginseng saponins, has been reported to enhance insulin secretion stimulating anti-apoptotic activities in pancreatic beta cells. Ginsenoside administration might be a prospective management approach to enhance- islet function and ameliorate early inflammation after islet transplantation. Also, anti-obesity effects were observed in diabetic patients and diabetic animal models [74].

7.9. Conophylline

Conophylline is a vinca alkaloid. It is extracted from the tropical plant *Ervatamia microphylla*. Conophylline addition to pancreatic rudiments in culture as well as to AR42J cells (a model of pancreatic progenitors) increased the number of insulin, and *Pdx-1*-positive cells. Treatment with Conophylline of neonatal Streptozotocin diabetic rats increased as well the number of insulin-positive clusters budding from ductal structures. This resulted in glucose normalization and improved glucose tolerance for 2 months. The data supports the role of Conophylline in β-cell regeneration, which has also been described in the same animal model treated with glucagon-like peptide and Exendin-4. Moreover, the same group also previously

demonstrated that the number of islet-like cell clusters and pancreatic duodenal homeobox-1-positive ductal cells were greater in 2-month conophylline-treated rats. These results propose that conophylline induces differentiation of pancreatic progenitors' cells and increases the formation of Pancreatic β-cells. [75]. This compound acts as well in the *Shh* pathway, mimicking the effect of Activin-A. Besides, Activin-A, when bound to its receptor, can activate p38 mitogen-activated protein kinase inducing the expression of neurogenin3. Conophylline acting as a ligand for Activin-A was later proved by performing differentiation in presence of Activin-A antagonist. The antagonist blocked islet generation when incubated with Conophylline confirming the mode of differentiation [76]. This was the first evidence that provided some clue that herbal compounds possess islet neogenic property, thus playing a crucial role in islet differentiation.

7.10. Resveratrol

Differentiation protocols incorporating Resveratrol (RSV) treatment yielded numerous insulin-positive cells, induced significantly higher PDX1 expression, and were able to transiently normalize glycemia when transplanted in streptozotocin (STZ) induced diabetic mice thus promoting its survival [77]. A Human clinical study showed that daily resveratrol treatment for 3 months significantly decreased HbA1c levels in 28 Type-II diabetic patients [78].

7.11. Curcumin

Several studies highlight curcumin's benefit as a hypoglycemic agent as enhances insulin secretion. Researcher suggests pancreatic islets regeneration in diabetic rats when treated with Curcumin for forty days (Long term study). Anti-inflammatory and antioxidant effects of curcumin create a favorable environment to promote islet neogenesis [79, 80]. A 9-month curcumin clinical trial on humans demonstrated that Curcumin has a positive effect on the prediabetic population. Besides, the curcumin treatment appeared to recover the overall function of pancreatic β-cells, with very lesser adverse effects [81]. Figure 2 demonstrates the islet neogenic activity of various plant bioactive.

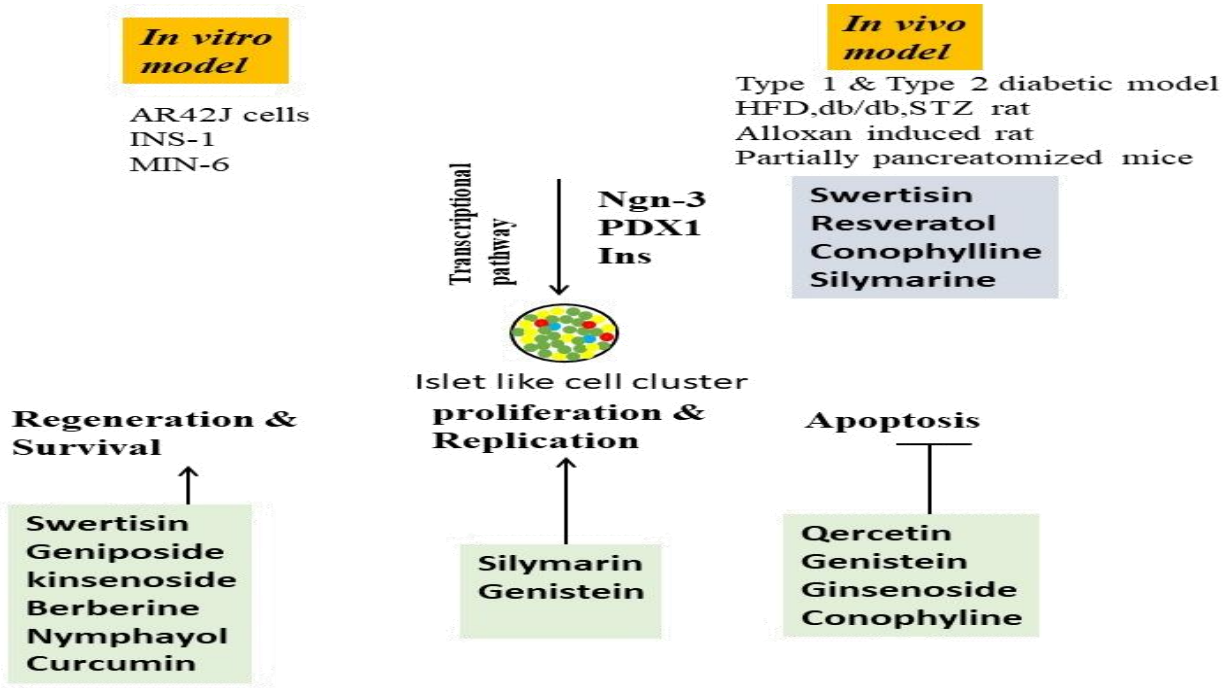

Fig. 2: Islet neogenic activity of various plant bioactives

8. ANTIDIABETIC ACTIVITY OF ISOLATED COMPOUNDS FROM *ENICOSTEMMA LITTORALE*:

Many compounds have been isolated and reported from *Enicostemma littorale*. Five alkaloids, two sterols, and volatile oil have been reported by Natarajan and Prasad [82]. Seven flavonoids including swertiamarin have been reported by Ghoshal *et.al*. [83] and swertiamarin a gentiopicroside was isolated from ethyl acetate extract [84]. Further swertisin and swertiamarin were

successfully isolated from EL and proved potent insulin sensitizer and adipogenic inhibitor property of swertiamarin in NIDDM rats and hepatic steatosis models [85,86]. Swertisin has been proved as a potent inducer of islet differentiation from stem/progenitors.

8.1. Swertisin imparts Islet neogenic activity to *E. littorale:*

Recently stem/progenitor differentiation activity of *Enicostemma littorale* has also been reported where human pancreatic carcinoma cells Panc-1 and mouse embryonic fibroblast cells NIH3T3 were converted to functional insulin producing islet clusters [87]. Dadheech et al., in 2015 identified the active principle molecule Swertisin, a flavonoid that was responsible for the above islet neogenic property. Swertisin, not only gave a better yield of islets but it was also superior in terms of the amount of insulin released after a glucose challenge. Further, the islets generated using Swertisin were transplanted into Streptozotocin treated diabetic BALB/c mice, which became normoglycemic after the transplantation. Further, the molecular mechanism of Swertisin was extensively studied and was found to follow Activin A mediated MEPK-TKK pathway during islet Neogenesis. Insulin transcript levels increased owing to swertisin. It also decreased expression of Nestin, Ngn-3 (Neurogenin-3), and Pancreatic Duodenal Homeobox Gene-1 (PDX-1) in a post (PPx) partial pancreatectomised mice model [88]. Swertisin when administered into STZ diabetic mice (*in vivo*) also triggered the resident pancreatic progenitors to replenish and recover the endocrine function by increasing islet formation [89]. All these properties of Swertisin make it an ideal candidate for a novel therapeutic intervention in treating diabetes mellitus. Hence, presently islet differentiating activity of swertisin has been explored with human mesenchymal stem cells and further our efforts are in the direction of designing potent islet therapy using plant-derived compounds for effective diabetes treatment. Table 4 demonstrates Plant bioactive with pancreatic/ β cell regenerating ability. Figure 3 depicts islet neogenic activity of swertisin.

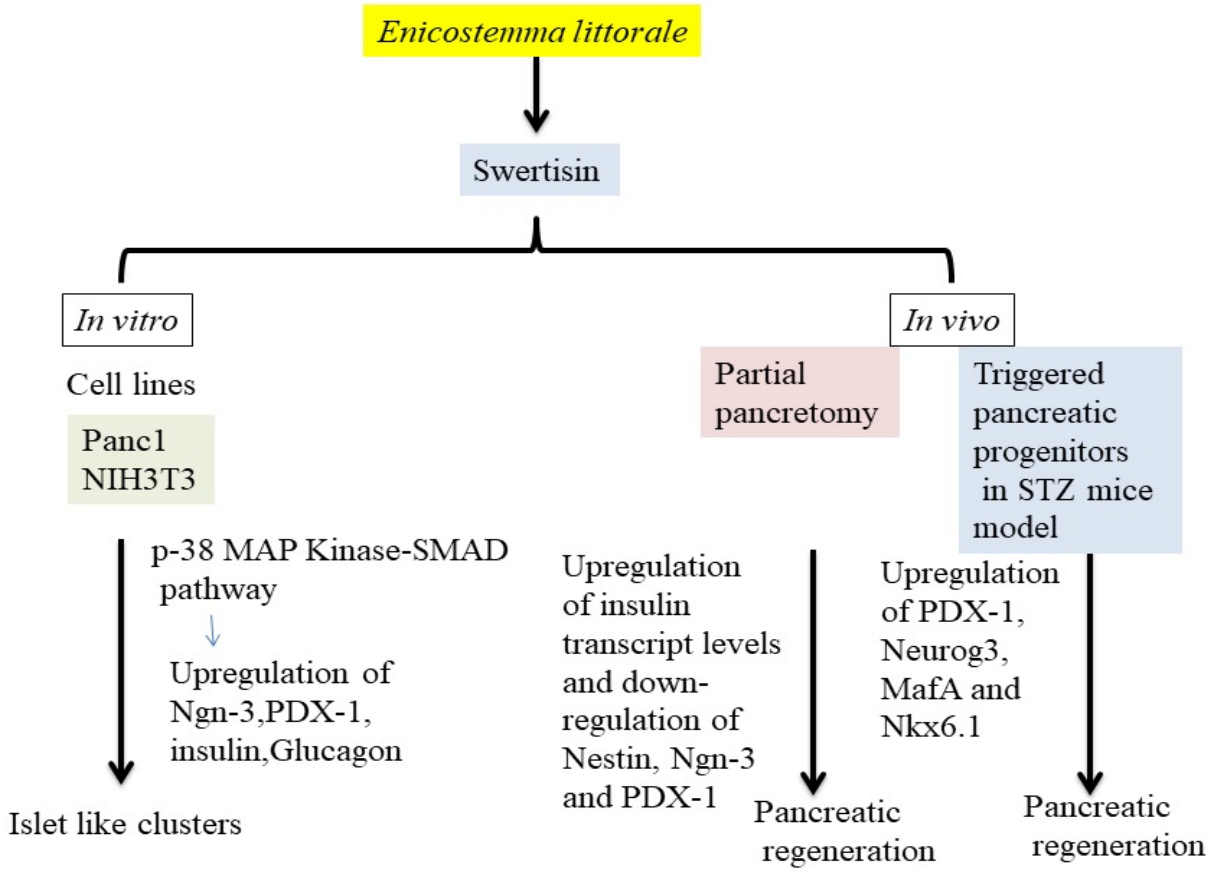

Fig. 3: Islet neogenic activity of swertisin

Table 4: List of pancreatic/ β cell regenerating bioactive agents

Sr no.	pancreatic/β cell regenerating agents	Mode of action	Reference
1.	Geniposide	Promotes β cell regeneration and survival	[64]
2.	Kinsenoside	Enhanced integrity of islets of Langerhans was observed in the Kinsenoside treated rats, which indicated pancreatic β-cell regeneration. Thus, rendering Kinsenoside as a promising antidiabetic agent for therapy	[65]
3.	Silymarin	Effect of Silymarin in *Pdx-1* expression and the proliferation of pancreatic β-cells in a pancreatectomy model.	[66]
4.	Genistein	Enhances insulin secretion & Inhibits pancreatic β cell apoptosis	[68]
5.	Quercetin	Commonly found in plants(in many fruits, vegetables, leaves, and grains) enhances insulin secretion & inhibits pancreatic β cell apoptosis	[70]
6.	Berberine	Berberine enhances insulin secretion and stimulated pancreatic β cell regeneration in Type 2 diabetic animals	[71]
7.	Nymphayol	Nymphayol enhances insulin secretion. Nymphayol isolated from *Nymphaeastellata* (Wild.) flowers demonstrated Partial regeneration of β cells.	[73]
8.	Ginsenoside	Ginsenoside Rg3 (Rg3), an active ingredient of ginseng saponins, has been reported to enhance insulin secretion stimulating anti-apoptotic activities in pancreatic beta cells.	[74]
9.	Conophyllin	Increased the number of insulin, and *Pdx-1*-positive cells *in vitro* resulted in glucose normalization and improved glucose tolerance. β-cell regeneration. Conophylline acting as a ligand for Activin-A was later proved by performing differentiation in presence of Activin-A antagonist.	[76]
10.	Resveratrol	Differentiation protocols incorporating Resveratrol (RSV) treatment yielded numerous insulin-positive cells, induced significantly higher PDX1 expression.	[77]
11.	Curcumin	Anti-inflammatory and antioxidant effects of curcumin create a favorable environment to promote islet neogenesis	[79,80]
12.	Swertisin	A flavonoid which is responsible for islet neogenic property. Swertisin, not only gave a better yield of islets but it was also superior in terms of the amount of insulin released after a glucose challenge. Further, the islets generated using Swertisin were transplanted into Streptozotocin treated diabetic BALB/c mice, which became normoglycemic after the transplantation. Further, the molecular mechanism of Swertisin was extensively studied and was found to follow Activin-A mediated MEPK-TKK pathway during islet neogenesis. Swertisin was extensively studied and was found to follow Activin-A mediated pathway during islet neogenesis. Swertisin when administered into STZ diabetic mice (*in vivo*) also triggered the resident pancreatic progenitors to replenish and recover the endocrine function by increasing islet formation.	[54,55,56, 57] [88,89]

9. CHALLENGES IN IPC DIFFERENTIATION

There are far too many inducers and various sources of stem/precursor cells used for differentiating insulin producing cells. The major challenge thus faced by the clinicians is the combination of the stem cell source and the differentiating inducer. The molecular mechanism of most of the naturally derived molecules is not well established and even if they are known, it is concerning a particular type of cellular system. Hence, the mechanistic pathway involved might differ from one cellular system to the other. Thus, it is an imperative challenge to understand the effect of these inducers not only at the pancreatic level but at the systemic level by using these molecules *in vivo*. Further cost effectiveness is another important issue for translation into clinical therapy.

10. CONCLUSION

There is enough literature and experimental evidence to suggest antidiabetic effects of various bioactive derived from herbs with few reports with regards to differentiation potential from various stem/progenitors into insulin producing islets like clusters. We have successfully demonstrated the role of bioactives from *Enicostemma littorale* having this potential and thus become the basis of a successful regenerative therapeutic strategy for treating diabetes mellitus. However, there is still a need to find more such compounds in perfect combination which can optimize the generated Islet like cluster (ILCs) in terms of yield, size, insulin production, and glucose homeostasis.

Declarations of interest

None declared

11. REFERENCES

1. International Diabetes Federation. *Diabetes Atlas*, 2019; **9th edn**.
2. Korsgren O, Nilsson B, Berne C, Felldin M, Foss A, Kallen R. et al. *Transplantation*, 2005; **79(10):**1289-1293.
3. Bailes BK. *Aorn J*, 2002; **76(2):**266-276, 278-282.
4. Kadarian C, Broussalis AM, Miño J, Lopez P, Gorzalczany S, Ferraro G. et al. *Pharmacol Res*, 2002; **45(1):**57-61.
5. Andrade Cetto A, Wiedenfeld H. *J Ethnopharmacol*, 2004; **90(2-3):**217-220.
6. Srivastava S, Lal VK, Pant KK. *Phytopharmacology*, 2012; **2(1):**1-15.
7. Bailey C, Day C. *Diabetes care*, 1989; **12(8):**553-564.
8. Singh A, Singh K, Saxena A. *Int J Res Ayurveda Pharm*, 2010; **1(1):**212-224.
9. Ajabnoor M. *J Ethnopharmacol*, 1990; **28(2):**215-220.
10. N Arun, N Nalini. *Plant Foods Hum Nutr*, 2002; **57(1):**41-52.
11. Rajesham VV, Ravindernath AD, Bikshapathi VRN. *Indo Am J Pharm Res*, 2012; **2(10):**1200-1212.
12. Nammi S, Boini MK, Lodagala SD, Behara RBS. *BMC Complement Altern Med*, 2003; **3(1):**4.
13. Shanmugasundaram ERB, Gopinath KL, Shanmugasundaram KR, Rajendran V M. *J Ethnopharmacol*, 1990; **30(3):**265-279.
14. Manjunatha S, Jaryal AK, Bijlani RL, Sachdeva U, Gupta SK. *Indian J Physiol Pharmacol*, 2001; **45(1):**71-79.
15. Agrawal P, Rai V, Singh RB. *Int J Clin Pharmacol Ther*, 1996; **34(9):**406-409.
16. Yuan C, Wu J, Lowell T, Gu M. *Am J Chin Med*, 1998; **26(01):**47-55.
17. Ohnishi Y, Takagi S, Miura T, Usami M, Kako M, Ishihara E. *Biol Pharm Bull*, 1996; **19(9):**1238-1240.
18. Kimura M, Waki I, Chujo T, Kikuchi T, Hiyama C, Yamazaki K. et.al. *J Pharmacobiodyn*, 1981; **4(6):**410-417.
19. Kamble SM, Kamlakar PL, Vaidya S, Bambole VD. *Indian J Med Sci*, 1998; **52(4):**143-146.
20. Baldwa VS, Bhandari CM, Pangaria A, Goyal RK. *Upsala journal of medical sciences*, 1977; **82(1):**39-41.
21. Khanna P, Jain SC, Panagariya A, Dixit VP. *J Nat Prod*, 1981; **44(6):**648-655.
22. Gray AM, Flatt PR. *Br J Nutr*, 1998; **80(1):**109-114.
23. Mathew PT, Augusti KT. *Indian J Physiol Pharmacol*, 1975; **19(4):**213-217.
24. Flora K, Hahn M, Rosen H, Benner K. *Am J Gastroenterol*, 1998; **93(2):**139-143.
25. Laura SM. *Diabetes spectrum*, 2001; **14(4):**199-208.
26. Madar Z. *Nutr Rep Int*, 1984; **29(6):**1267-1273.
27. Raghuram TC, Sharma RD, Sivakumar B, Sahay BK. *Phytother Res*, 1994; **8(2):**83-86.
28. Mimeault M, Hauke R, Batra SK. *Clin Pharmacol Ther*, 2007; **82(3):**252-264.
29. Bouwens L, Rooman I. *Physiol Rev*, 2005; **85(4):**1255-1270.
30. Shapiro AM, Lakey J, Ryan EA, Korbutt GS, Toth E, Warnock GL. et al. *N Engl J Med*, 2000; **343(4):**230-238.

31. Ryan EA, Paty BW, Senior PA, Bigam D, Alfadhli E, Kneteman NM. et al. *Diabetes*, 2005; **54(7):**2060-2069.
32. Holland AM, Elefanty AG, Stanley E G. *Cell Res*, 2009; **19(4):**395-396.
33. Zhang YQ, Kritzik M, Sarvetnick N. *J Cell Mol Med*, 2005; **9(2):**331-344.
34. Bretzel RG, Eckhard M, Brendel MD. *Panminerva Med*, 2004; **46(1):**25-42.
35. Hardikar AA, Marcus-Samuels B, Geras-Raaka E, Raaka BM, Gershengorn MC. *Proc Natl Acad Sci*, 2003; **100(12):**7117-7122.
36. Ramiya VK, Maraist M, Arfors KE, Schatz DA, Peck AB, Cornelius JG. *Nat Med*, 2000; **6(3):**278-282.
37. D'Amour KA, Bang A, Eliazer S, Kelly OG, Agulnick AD, Smart NG. et al. *Nat. Biotechnol,* 2006; **24(11):**1392-1401.
38. Abraham EJ, Leech CA, Lin JC, Zulewski H, Habener JF. *Endocrinology*, 2002; **143(8):**3152-3161.
39. Katdare MR, Bhonde RR, Parab PB. *J Endocrinol,* 2004; **182(1):**105-112.
40. Banerjee M, Kanitkar M, Bhonde R R. *Rev Diabet Stud*, 2005; **2(3):**165-176.
41. Chandra VGS, Phadnis S, Nair PD, Bhonde RR. *Stem Cells*, 2009; **27(8):**1941-1953.
42. Banerjee M, Bhonde RR. *Jop*, 2003; **4(4):**137-145.
43. Xu G, Stoffers DA, Habener JF, Bonner-Weir S. *Diabetes*, 1999; **48(12):**2270-2276.
44. Barghamdi B, Ghorat F, Asadollahi K, Sayehmiri K, Peyghambari R, Abangah G. *J Pharm Bioallied Sci*, 2016; **8(2):**130-134.
45. Amin A, Tahir M, Lone KP. *JPMA*, 2017; **67(5):**715-721
46. Kumar V, Mahdi F, Singh R , Mahdi AA, Singh R K. *Journal of Pharmaceutical Sciences and Research*, 2016; **7:**757-764.
47. Rajalakshmi M, Anita Roy. *Chem Biol Interact*, 2016; **243:**45-53.
48. Kumari DJ. *Bioscan*, 2010; **5:**211-214.
49. Abd El Latif A, El Bialy BES, Mahboub HD, Abd Eldaim MA. *Biochem Cell Biol*, 2014; **92(5):**413-419.
50. Xiu LM, Miura AB, Yamamoto K, Kobayashi T, Song QH, Kitamura H. et al. *Am J Chin Med*, 2001; **29(3-4):**493-500.
51. Ansarullah BB, Umarani M, Dwivedi M, Laddha NC, Begum R, Hardikar AA, Ramachandran AV. *Evid Based Complementary Altern Med*, 2012; **2012**. 13.
52. Upadhyay UM, Goyal RK. *Phytother Res*, 2004; **18(3):**233-235.
53. Sathishkumar R, Lakshmi PTV, Annamalai A. *Res J Med Plant*, 2009; **3(3):**93-101.
54. Maroo J, Vasu TV, Gupta S. *Phytomedicine*, 2003; **10(2-3):**196-199.
55. Vasu VT, Modi H, Thaikoottathil JV, Gupta S. *J Ethnopharmacol*, 2005; **101(1-3):**277-282.
56. Vijayvargia R, Kumar M, Gupta S. *Indian J Exp Biol*, 2000; **38(8):**781-784.
57. Maroo J, Vasu VT, Aalinkeel R, Gupta S. *J Ethnopharmacol*, 2002; **81(3):**317-320.
58. Bhatt N, Barua S, Gupta S. *Am J Infect Dis*, 2009; **5:**106-112.
59. Bhatt N, Chauhan K, Gupta S, Pillai P, Pandya C, Thaikoottathil J, Gupta S. *Am J Infect Dis*, 2011; **7(4):**83-90.
60. Bhatt N, Chavda M, Desai D, Zalawadia R, Patel V, Burade V, et al. *Can J Physiol Pharmacol*, 2012; **90(8):**1065-1073.
61. Vishwakarma S, Bagul M, Rajani M, Goyal R. *J Planar Chromat*, 2004; **17:**128-131.
62. Srivastava A, Bhatt N, Patel T, Dadheech N, Singh A, Gupta S. *Pharm Biol*, 2016; **54(10):**2061-2072.
63. Vasu VT, C Ashwinikumar, Maroo J, Gupta S, Gupta S. *Orient Pharm Exp Med*, 2003; **3(2):**84-49.
64. Yao DD, Yang L, Wang Y, Liu C, Wei YJ, Jia X B. et al. *Cell Death Dis*, 2015; **6:**e1746.
65. Zhang Y, Cai J, Ruan H, Pi H, Wu J. *J Ethnopharmacol*, 2007; **114(2):**141-145.
66. Soto C, Raya L, Juárez J, Pérez J, González I. *Phytomedicine*, 2014; **21(3):**233-239.
67. Voroneanu L, Nistor I, Dumea R, Apetrii M, Covic A. *J Diabetes Res*, 2016; **2016:**10.
68. Gilbert ER, Liu D. *Food Funct*, 2013; **4(2):**200-212.
69. Squadrito F, Marini H, Bitto A, Altavilla D, Polito F, Adamo EB. et al. *J Clin Endocrinol Metab*, 2013; **98(8):**3366-3374.
70. Youl E, Bardy G, Magous R, Cros G, Sejalon F, Virsolvy A. et al. *Br J Pharmacol*, 2010; **161(4):**799-814.
71. Zhou JY, Zhou SW, Zhang KB, Tang JL, Guang LX, Ying Y. et al. *Biol Pharm Bull*, 2008; **31(6):**1169-1176.
72. Yin J, Xing H, Ye J. *Metab Clin Exp*, 2008; **57(5):**712- 717.

73. Subash-Babu P, Ignacimuthu S, Agastian P, Varghese B. *Bioorg Med Chem*, 2009; **17(7):**2864-2870.
74. Park MW, Ha J, Chung S H. *Biol Pharm Bull*, 2008; **31(4):**748-751.
75. Ogata T, Li L, Yamada S, Yamamoto Y, Tanaka Y, Takei I. *Diabetes*, 2004; **53(10):**2596-2602.
76. Kojima I, Umezawa K. *Int J Biochem Cell Biol*, 2006; **38(5-6):**923-930.
77. Pezzolla D, López-Beas J, Lachaud CC, Domínguez-Rodríguez A, Smani T, Hmadcha A. et al. *PloS one*, 2015; **10(3):**e0119904.
78. Bhatt JK, Thomas S, Nanjan MJ. *Nutr Res*, 2012; **32(7):**537-540.
79. Abdul-Hamid M, Moustafa N. *JOBAZ*, 2013; **66(4):**169-179.
80. Aziz M, El-Asmar M, Rezq A, Mahfouz S, Wassef M, Fouad H. et al. *Diabetol metab syndr*, 2013; **5(1):**75.
81. Chuengsamarn S, Rattanamongkolgul S, Luechapudiporn R, Phisalaphong C, Jirawatnotai S. *Diabetes Care*, 2012; **35(11):**2121-2127.
82. Natarajan PN, Prasad S. *Planta Med*, 1972; **(22):**42-46.
83. Ghosal S, Jaiswal DK. *Verd J Pharm Sci*, 1980; **69(1):**53-56.
84. Desai PD, Ganguly AK, Govindachari TR, Joshi BS, Kamat VN, Manmade AH. et al. *Indian J Chem*, 1966; **(4):**457-459.
85. Patel TP, Soni S, Parikh P, Gosai J, Chruvattil R, Gupta S, *Evid Based Complement Alternat Med*, 2013; **2013**. 11.
86. Patel TP, Rawal K, Soni S, Gupta S. *Biomed Pharmacother*, 2016; **83:**785-791.
87. Gupta S, Dadheech N, Singh A, Soni S, Bhonde R R. *Int J Integr Biol*, 2010; **9(1):**49-53.
88. Dadheech N, Srivastava A, Paranjape N, Gupta S, Dave A, Shah G M. *PloS one*, 2015; **10(6):**e0128244.
89. Srivastava A, Dadheech N, Vakani M, Gupta S. *Biomed Pharmacother*, 2018; **100:**221-225.