International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

A Comprehensive Analysis of Therapeutic Plants and Substances to Enhance Pancreatic β-Cell Mass and Functionality in the Treatment of Diabetic Mellitus

Thakur Dinesh[1], Dr. Sangeeta Thakur[2], Thakur Gajendra Singh[3], Dr. Santram Lodhi[4]

RKDF University Bhopal M.P.

Abstract

Diabetes represents a significant financial burden at a national level and poses a global health concern. Despite the presence of numerous antidiabetic drugs in the market, there remains a demand for novel treatment options that offer enhanced effectiveness and reduced side effects. The appeal of medications derived from natural compounds surpasses that of their synthetic counterparts due to their diverse nature and minimal occurrence of adverse reactions. This review encompasses the primary effects of various naturally occurring substances obtained from plants on the functionality of pancreatic beta cells. Studies have indicated that these natural substances have the ability to alter the growth and division of pancreatic beta cells, prevent their demise, and directly enhance the production of insulin. Investigating natural compounds as potential sources for advanced medications is of utmost importance. Consequently, further exploration into the mode of action of these compounds is imperative to advance their potential as prospective anti-diabetic agents.

Keywords: Regeneration process, B-cell, therapeutic Plants

1. Introduction

Diabetes mellitus (DM) is a chronic endocrine disorder characterized by abnormalities in the metabolism of lipids, proteins, and carbohydrates. The key features of all forms of diabetes include a decrease in the levels of insulin in the bloodstream (insulin deficiency) and a reduction in the responsiveness of peripheral tissues to insulin (insulin resistance). The disease has reached pandemic proportions and presents a significant global health threat. According to the World Health Organization (WHO), approximately 285 million individuals worldwide were affected by the condition in 2010; this number is projected to increase to 438 million by 2030. India stands as the nation with the highest prevalence of diabetes cases globally, and the incidence of diabetes is steadily climbing, leading to its unfortunate designation as the "Diabetes Capital of the World." The onset and progression of diabetes-related complications are closely linked to oxidative stress. Reactive oxygen species (ROS) are continuously generated in hyperglycemic conditions, and studies have shown that diabetes impacts the function of antioxidant enzymes in various tissues. Free radicals are scavenged by antioxidants, which also shield the organism from oxidative stress. Therefore, a medication that possesses both anti-oxidant and

antidiabetic properties might be beneficial in managing diabetes mellitus. Many medicinal plants have been employed as antidiabetic medicines and have been claimed to heal diabetes globally in recent times. Given that traditional plant remedies for diabetes are well-researched, safe, and seen to be great options for oral medication, has WHO recommended looking into these therapies further?

1. Type-1 Diabetes Because of the loss of beta cells, the pancreas is unable to produce enough insulin, which leads to type 1diabetes. Earlier terms for this condition included "insulin dependent diabetes mellitus" and "juvenile diabetes". The autoimmune response is what leads to the loss of beta cells. It is unknown what is causing this autoimmune reaction. Type 1 diabetes can strike adults even though it typically first manifests in childhood or adolescence
2. Type-2 Diabetes Insulin resistance is the first stage of type 2 diabetes, a disorder in which cells do not react to insulin as they should. Lack of insulin may also develop as the disease worsens. Previously, this type of diabetes was known as "adult-onset diabetes" or "non-insulin-dependent diabetes mellitus". Although type 2 diabetes is more common in older adults, there has been a notable rise in type 2 diabetes cases in younger people due to the high prevalence of obesity among
3. children. Excessive body weight combined with inadequate exercise is the most common cause (Ma ZA, et al.2012.)

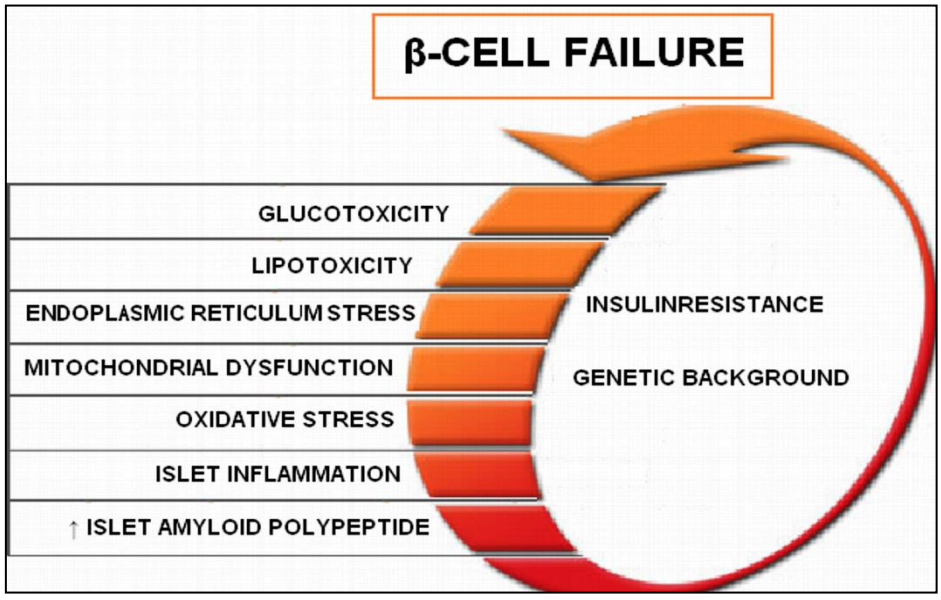

Figure: B-cell Failure

1.1 IS REGENERATION POSSIBLE?

According to Aguayo-Mazzucato and Bonner-Weir (2018), it is widely recognized that the endocrine pancreas exhibits a slower turnover rate and a lower capacity for self-renewal in comparison to tissues such as blood, skin, and gut, which possess well-defined niches for adult stem cells. Despite these characteristics, the mass of β-cells in rats can steadily increase during the initial seven months due to the infrequent occurrence of both proliferation and apoptosis (Montanya et al., 2000). The concepts of neogenesis and transdifferentiation have gained traction following a period of controversy lasting more than a decade regarding the possibility of islet regeneration through mechanisms other than the

replication of existing cells. Depending on the species and nature of the damage, the regeneration of islets can be achieved through either proliferation or the generation of new β-cells, with varying degrees of emphasis placed on each approach (Aguayo-Mazzucato and Bonner-Weir, 2018).The majority of research on the regeneration of β-cells has been conducted with several rodent models (Kodama et al., 2003), and there is strong evidence that post-natal rodent β-cells may proliferate impressively in conditions with increased metabolic demand (Desgraz et al., 2011). Moreover, transgenic mice have demonstrated (Cano et al., 2008) that the mature pancreas may recover completely from nearly total ablation of all extant β-cells; however, it is unclear if a comparable strategy is applicable to humans. Despite decades of speculation that the human pancreas includes progenitor cells capable of islet regeneration, There is insufficient evidence to definitively prove that the human pancreas is capable of regeneration (Ku, 2008). According to research from the Diabetes Research Institute, progenitor cells in the human pancreas may be stimulated to differentiate into β-cells that respond to glucose when bone morphogenic protein-7 is present (Qadir et al., 2018). The presence of Pancreatic and Duodenal Homeobox-1 (Pdx-1), a protein necessary for β-cell growth, was another characteristic that set these cells apart. These discoveries therefore pave the way for the creation of regenerative treatments to fight the illness (Qadir et al., 2018).

Table: 1 Effect of medicinal plants on diabetes mellitus through pancreatic β–cell regeneration.

Name	Extract	Model	Reference
Cynodon dactylon	Reduced hyperglycemia by 70%, and the blood sugar level was significantly reduced by both dosages of extract, anti-hyperglycemic action,	T2D (Diet-induced rats) (GTT)	(Singh SK,.et al 2008) (Shweta Das, ,et.,al 2021) (G. Abbas et al 2019)
Triticuma estivum	decreased risk of type 2 diabetes, decreased fasting blood glucose, albumin, globulin, bilirubin, urea, creatinine,	T2D (Diet-induced rats)	(Chetna. Bogar et al2017) (Al-Numair et al 2019) (Karadag, A. et al.2019)
Gymnema sylvestre	Reduced blood glucose, increased insulin levels, and β-cell regeneration Hypoglycemic and hypolipidemic activity and significant recovery of damaged β-cells.	T1D (STZ or Alloxan)	(Chattopadhyay, 1998) (Ahmed et al., 2010) (Aralelimath et al 2012) (Fatima, 2015) (Daisy et al., 2009) (Sugihara et al., 2000)
Artemisia dracunculus	regulate insulin sensitivity, insulin production, reduced glucose tolerance significant recovery of damaged β-cells	T1D (STZ or Alloxan)	(Oltman CL et al 2007) (Drel VR et al 2008)

Hibiscus Rosa-sinensis	decrease in the increased levels of serum glucose, decreased the spermatogenic elements of testis, reduced blood glucose, urea, uric acid and.	T2D (Diet-induced rats)	(Sreenivas SA.et al 2011) (Abdur Rahman et al 2013) (Al-Snafi et al 2015)
Tinospora cordifolia	β-cell regenerative properties modulated the expression of Glut-4Regulated blood glucose, increased insulin secretion, suppressed oxidativestress marker, and TBARS levels	T2D (Diet induced rats)	(Rajalakshmi,et al 2016) (Sangeetha et al., 2011)
Costus pictus	These extracts increased insulin secretion, which amplified its effects. and β-cell regeneration Hypoglycemic and hypolipidemic activity and significant recovery of damaged β-cells.	T2D (Diet-induced rats)	(Aruna et al., 2014). (Ashwini et al. 2015) (Benny et al., 2020).
Woodfordia fruticosa	decrease in the elevated blood glucose Levels significantly β-cell renewal Hypoglycemic and hypolipidemic state together with strong β-cell recovery from injury.	T1D (STZ or Alloxan	(Ghosh S.et al 2012) (Gupta RK et al 2005)
Aloe vera	PF demonstrated defense-related actions on β-cells through the GLP-1/DPP-IV pathway. Decreased FFA and TG, improved glucose intolerance, decreased RBG, and HbA1c values, enhancing lipid metabolism and β-cell activity. Reduced abnormalities on the surface of islet cells	T2D (Diet-induced rats) STZ induced	(Misawa et al., 2008). (Deora et al., 2021)
Tamarindus indica linn.	strong antidiabetogenic effect, lowering blood sugar levels, substantial reduction in the activities of liver glucose-6-phosphatase, liver and kidney glutamate oxaloacetate transaminase (GOT),	STZ induced (Diet-induced rats)	(So Yeon Park et al 2020) (Sanchetia et al., 2011)

1.2 Methods Used for Literature Collection

A literature search was performed in "PubMed" to evaluate the effects of each natural substance using the keywords "anti-diabetic activity, beta cell function, beta cell proliferation, and beta cell differentiation." All relevant publications discussing the impact of chemicals derived from natural products on beta cell function, utilizing cell culture and diabetic animal models, were included in the analysis to investigate the response of diabetes to natural products. Cohort/case-control studies, randomized clinical trials, controlled clinical trials, and systematic reviews were all incorporated to assess the effects of the substances on individuals.

Table :2 Pharmacological agent that aid in the regeneration and function of β –cells.

S.No.	Molecules	Salient feature	Mechanism of action	Reference
1	Gamma-aminobutyric acid (GABA)	Immune protective and regenerative effects on islet beta cells play a crucial role in the prevention of Type 1 Diabetes (T1D) in Non-Obese Diabetic (NOD) mice	Activation of PI3-K/Akt-dependent growth and survival pathways	(Soltani et al., 2011) (Hayder M. Al-Kuraishy et al 2021)
2	GLP-1	Enhanced glucose-stimulated insulin secretion (GSIS) is observed alongside elevated β-cell replication and a reduction in the rate of beta-cell programmed cell death	Pancreas-specific mediator of incretin response in islet beta cells operates via a cyclic AMP (cAMP)/Ca(2+)-dependent pathway.	(Nie et al., 2013) (Zinman B et al., 2009)
3	Combined treatment of GABA and Sitagliptin	protects beta cells from harm and encourages β-cell regeneration	suppression of the bulk of alpha cells, elevation of Pdx-1+ cells, and decrease in Tunel+ beta cells.	(Wenjuan Liu et al 2021)
4	Aminopyrazine compound	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)
5	Thiadiazine	β-cell proliferation	Inhibition of DYRK1A	(Belgardt and Lammert, 2016)

1.3 Plant Extracts for the Control of Beta Cell Function in the Pancreas

Extract from the following families: Cornus officinalis Sieb. et Zucc. (Family: Cornaceae), Centaurium erythraea Rafn (Family: Gentianaceae), Artemisia dracunculus L. (Family: Compositae), and Gynura divaricata (L.) DC (Family: Asteraceae), Uncaria tomentosa (Willd.) DC (Family: Rubiaceae), Panax ginseng C.A. Meyer (Family: Araliaceae), Tamarindus indica Linn. (Family: Fabaceae), Teucrium polium L. (Family: Lamiaceae), Thymus praecox subsp. skorpilii var. skorpilii (Family: Lamiaceae), and Woodfordia fruticosa (L.) Kurz (Family: Lythraceae) have all demonstrated improvements in β-cell regeneration and function. The research on herbal remedies that may enhance β-cell activity and regeneration is the main topic of the sections that follow.

1.3.1 CYNODON DACTYLON

Numerous reports have confirmed that C. dactylon possesses hypoglycemic qualities that effectively regulate blood sugar levels and lessen tiredness. This plant's juice, when combined with neem juice, is particularly beneficial to health since it helps to control blood sugar (Shweta Das, Sonia Morya**,**et.,al 2021) The anti-diabetic impact of C. dactylon's roots and stems reduced hyperglycemia by 70%. A combination of 10 mg/kg xylazine and 60 mg/kg ketamine was discovered to have an anti-diabetic effect on diabetics. 50 mg/kg and 100 mg/kg of this extract were utilized to treat the mice, and the blood sugar level was significantly reduced by both dosages of extract. Since the initial dose's effects were similar to those of insulin, it was seen that the mice responded to it more effectively. (Singh SK, Kesari AN.et al 2008) Furthermore, the non-polysaccharide and aqueous extract of C. dactylon significantly reduced the levels of triglycerides, glucose, cholesterol, low-density lipoprotein, and urea in the diabetic rats. The effects of the aqueous extract at 250 mg/kg, 500 mg/kg, and 1000 mg/kg were investigated in diabetic rats. The study came to the conclusion that the oral dosage of 500 mg/kg was more efficient. Within four hours of administering it, the blood sugar level in normal rats was reduced by thirty-one percent. The ethanolic mixture of C. dactylon root stalks was used to treat diabetic rats administered streptozotocin in order to counteract the effects of diabetes. According to the analysis, the extract at 500 mg/kg demonstrated anti-hyperglycemic action and was clearly comparable to the conventional medication tolbutamide. (G. Abbas et al 2019*)*

Figure: Cynodon dactylon

1.3.2 TRITICUM AESTIVUM

A 12-week intervention trial using wheat bran extract of Arabinoxylan-Oligosaccharide (AXOS) results in a lower postprandial glucose concentration as compared to the placebo, according to recent research. **(**Sanjeevini A.Hattarki, Chetna. Bogar et al 2017) Furthermore, frequent consumption of whole grains has been consistently linked to a decreased risk of type 2 diabetes, according to three meta-analyses of research Furthermore, eleven prospective studies published by Priebe consistently shown that consuming more whole grains (27–30%) or cereal fiber (28–37%) was associated with a lower risk of type 2 diabetes. %). These findings demonstrate that consuming whole grains may lower the incidence of type 2 diabetes. A diet based on T.A. seeds significantly decreased fasting blood glucose, albumin, globulin, bilirubin, urea, creatinine, Na, and K levels, according to research by Ajiboye investigating the antidiabetic action and mechanism of wheat seeds. Moreover, T.A. seed-rich diet for diabetic rats resulted in noticeably greater insulin and glycogen levels. Furthermore, there was an increase in the antioxidant levels of hexokinase, catalase, superoxide dismutase, and glutathione peroxidase. In the same study, compared to the control group, diabetic rats fed T.A. seed had significantly lower concentrations of malondialdehyde, activities of glucose-6-phosphatase and fructose 1,6-diphosphatase, and reversed the activities of liver function such as alanine transferase, gamma-glutamyl transferase, alkaline phosphatase, and liver, kidney, and pancreas tissue regeneration. groupFlavonoids' capacity to scavenge free radicals and potential antioxidant properties have been connected to hypoglycemic effects and protection against oxidative stress. Notably, wheatgrass is utilized for its health benefits, and wheat is a major food crop that is cultivated all over the world. Coadministration of a polyphenol-rich wheatgrass meal "9 days after germination" has been shown to decrease hyperglycemia, glycosuria, and body weight increase in streptozotocin-induced diabetic rats It has been demonstrated that flavonoids, such apigenin, improve liver function in diabetic rats given a high-fat diet. Moreover, lipase is rendered inactive by insulin deficiency, increasing blood phospholipid levels. By increasing glucokinase activity and consequently reducing adipogenesis and gluconeogenesis, polyphenols like flavones and hydroxycinnamic acids reduced these processes in a variety of animal models . Oxidative stress in diabetes pathogenesis produces reactive oxygen species, which in turn triggers glucose auto-oxidation, alterations in antioxidant enzymes, and the creation of lipid peroxides. Lipid peroxide damage results in cellular deformability, increased membrane stiffness, and impaired membrane function—all characteristics that are common in the development of diabetes. When kaempferol was given to diabetic rats, as demonstrated by (Al-Numair et al 2019) plasma glucose, insulin, lipid peroxidation products, and enzymatic and non-enzymatic antioxidants returned to almost normal levels. It also demonstrated that kaempferol significantly decreased the quantity of lipid peroxidative markers in their tissues and plasma. Likewise, ferulic acid administration led to decreased levels of glucose, TBARS, hydroperoxides, free fatty acids, and glutathione in the diabetic rats. (Karadag, A. et al.2019)

Figure: Triticum Aestivum

1.3.3 GYMNEMA SYLVESTRE

Gymnemic acids, gymnemasaponins, and gurmarin are three triterpene saponins that provide the plant its sweetinactivation effect.The hypoglycemic effect of G. sylvestre on rats treated with streptozotocin and beryllium nitrate was validated by experimental trials. There was a modest rise in body weight andprotein and a considerable drop in fasting blood glucose indiabetic rats treated with G. sylvestre, C. auriculata, E. jambolanum, andS. reticulata and the effectswerequite comparable to insulin and glibenclamide treated mice (A. Haleem, M. Javaid at al 2023)

Gymnema sylvestre is most well-known for its anti-diabetic properties. This plant's ethanol extract is said to lower glucose levels by 46%, while the water and methanol extracts lower glucose levels by 26% and 12%, respectively. (Shah et al.2011). Aqueous extract of this plant was reported to be correcting the altered lipid profile, insulin, and glucose in rats with insulin resistance caused by dexamethasone (Kumar S, et al., 2015). When this plant was given to an animal model of diabetes, blood levels of insulin, protein, triglycerides, cholesterol, and glucose were all reduced. Additionally, body weight was decreased, and liver histology was observed to improve (Sujin,et al 2008). This plant extract was found to significantly ($p < 0.05$) lower fasting blood glucose, total cholesterol, serum triglycerides, and increase HDL-cholesterol levels in another study using alloxan-induced diabetic rats. It was also shown to significantly ($p < 0.05$) lower elevated levels of urea, uric acid, and creatinine in diabetic rats to nearly normal levels (Sathya et al., 2008). Following both acute and long-term treatment of this plant's methanolic extract to Wister rats, Gymnema sylvestre decreased blood glucose levels (Dholi et al,2014). It has been demonstrated that treating Streptozotocin-induced diabetic rats with this plant significantly ($p < 0.05$) reduced the elevated levels of triglycerides, blood glucose, ALT, AST, total cholesterol, LDL-cholesterol, and malondialdehyde; additionally, it significantly ($p < 0.05$) increased the levels of insulin, HDL-cholesterol, and erythrocyte superoxide dismutase in diabetic rats; furthermore, it is capable of regenerating insulin-producing β-cells (Kumar et al., 2017) .The active ingredients that have been separated from Gymnema sylvestre belong to the class of triterpene saponin chemicals, or gymnemic acids. In comparison to glibenclamide, it was discovered that administering 3.4/13.4 mg/kg of gymnemic acid intravenously over the course of six hours reduced blood glucose levels by 14.0–60.0%. Additionally, when given at a dose of 13.4 mg/kg, gymnemic acid IV raised plasma insulin levels in STZ-diabetic mice (Sugihara et al., 2000). In a trial, the raised blood sugar levels brought on by sucrose were reduced when this plant was taken orally in tiny doses (0.2 g/kg) (Kang et al., 1990). also reported that Gymnema sylvestre did not exhibit any anti-diabetic effects in an animal model treated with alloxan.

Figure 3. Triticum Aestivum

1.3.4 ARTEMISIA DRACUNCULUS

A dracunculus plant ethanolic extract's ability to regulate insulin sensitivity, insulin production, and blood sugar levels was examined. A randomized, double-blind clinical study including 24 individuals with reduced glucose tolerance was carried out for this reason. For ninety days, a 1000 mg twice-daily dose of the encapsulated ethanolic extract of A. dracunculus was given. Systolic blood pressure (120 mm Hg in the control group, 113 mm Hg in the test group) decreased significantly, as did the concentration of glycosylated hemoglobin (5.8% in the test group, 5.6% in the control group), the area under the curve for insulin levels (56.136–27.426 pmol/L in the control group, 44.472 to 23.370 pmol/L in the test group), and the insulinogenic index (0.45–0.23 in the control group, 0.35 to 0.18 in the test group). Overall, these findings are documented. Levels of HDL cholesterol rose. the study's findings suggested that A. dracunculus herb extracts may be employed as a medicinal agent in the future to treat impaired glucose tolerance. (Méndez-Del Villar et al.2016),

Figure 4. artemisia dracunculus

1.3.5 HIBISCUS ROSA-SINENSIS

At a concentration of 25 mg/kg bw, the ethyl acetate fraction of Hibiscus rosa-sinensis petals (EHRS) was tested in experimental diabetes to determine its antidiabetic efficacy in comparison to metformin.

The treatment of EHRS resulted in a considerable decrease in the increased levels of serum glucose (398.56 ± 35.78) and glycated haemoglobin (12.89 ± 1.89) in diabetic rats (156.89 ± 14.45 and 6.12 ± 0.49, respectively). Serum hepatotoxicity marker enzyme levels returned to normal, and by controlling the activity of the enzymes that break down glycogen, the amount of glycogen was replenished**.** The expression of marker genes linked to the glucose homeostasis signaling pathway was markedly altered by it. The pancreatic and liver histopathological analyses corroborated the chemistry results Rats with streptozotocin-induced diabetes were used to study the anti-diabetic properties of Hibiscus rosa-sinensis aqueous ethanolic extract. For four weeks, diabetic rats receiving an oral dose of 500 mg/kg of Hibiscus rosa-sinensis aqueous extract had a significant reduction in blood glucose, urea, uric acid, and creatinine. However, the administration also increased the activities of insulin, C-peptide, albumin, and the albumin/globulin ratio, and all marker enzymes were restored to nearly control levels. Hibiscus rosa-sinensis extract, therefore, has an antihyperglycaemic action and reduces hepatic and kidney damage linked to diabetes mellitus produced by streptozotocin in rats. Rats were used to test the ethanol extract of Hibiscus rosa-sinensis for its hypoglycemic properties. An extract dosage resulted in a mildly hypoglycemia impact at 30 and 90 minutes, and a mildly significant hypoglycemic effect at 120 minutes. Following seven days of daily administration of the extract, there was a statistically significant ($P<0.001$) drop in blood glucose levels at 30, 90, and 120 minutes. after glucose loading. Following several doses of 250 mg/kg leaf extract, the average hypoglycemic activity was 81%; under comparable circumstances, tolbutamide's average activity was 96%. The extract's effectiveness was determined to be 84% that of tolbutamide (100 mg/kg) at 250 mg/kg. Animals treated repeatedly with Hibiscus rosa-sinensis or tolbutamide, a sulphonylurea, showed improvements in glucose tolerance of 2-3 times when compared to those treated only once. Hibiscus rosa-sinensis flower powder's antidiabetic potential was investigated in individuals with type II diabetes. Hibiscus rosa-sinensis flower powder (2 grams) was taken orally for 60 days, which resulted in a substantial reduction in mean blood glucose levels, postprandial blood glucose levels, glycosylated hemoglobin levels, mean total cholesterol, triglyceride levels, total LDL, and total VLDL cholesterol levels. The ethanolic extract of Hibiscus rosa-sinensis leaves yielded 5 fractions. Of these, fractions 3 (F3) and 5 (F5) were shown to be more efficient than the other 4 fractions, therefore their anti-diabetic effects were investigated in non-obese diabetic mice. Estimates were made for blood urea, insulin, triglycerides, cholesterol, glucose, glycosylated hemoglobin, LDL, VLDL, and HDL. In non-obese diabetic mice, fractions F3 and F5 (100 and 200 mg/kg bw) both showed an insulinotropic nature and a protective effect When oral administration of an ethanol floral extract of Hibiscus rosa-sinensis was given to streptozotocin-induced diabetic rats, blood glucose and total lipid levels were assessed. Following oral treatment of the extract for 7 and 21 days, ethanol flower extract exhibited a hypoglycemic effect. After 21 days, the blood glucose level decreased to its maximum (41-46%). The extract reduced blood triglycerides by 30% and total cholesterol by 22%, respectively. Compared to glibenclamide (1%), the extract significantly raised HDL-cholesterol (12%). This extract's hypoglycemic action was similar to glibenclamide's, but it wasn't caused by insulin release Hibiscus rosa-sinensis root extract was investigated for its hypolipidemic effects in rats with hyperlipidemia caused by a high-fat diet (HFD) that was high in cholesterol and triton. In the triton model, root extract (500 mg/kg bw/day) was shown to have a lipid-lowering effect based on the reversal of plasma levels of triglycerides (TG), phospholipids (PL), and total cholesterol (TC), as well as the reactivation of plasma's post-heparin lipolytic activity (PHLA). In a cholesterol-rich, high-fat diet

paradigm, the root extract (500 mg/kg bw/day orally) for 30 days also reduced the lipid levels in plasma and liver homogenate and reactivated plasma PHLA and hepatic total lipoprotein lipase activity.

Figure 5. hibiscus rosa-sinensis

1.3.6 TINOSPORA CORDIFOLIA

Alkaloids, cardiac glycosides, saponins, flavonoids, tannins, and steroids are among the substances that have been extracted from guduchi that have anti-diabetic properties. Therefore, it enables broad applicability in both clinical and experimental research Alkaloids from guduchi are said to have effects mediated by insulin and to have an impact similar to that of insulin hormone. Increases in GSH and other reactive species can pose a risk to both the mother and the fetus in cases of gestational diabetes (Sharma *et al*., 2015). Nonetheless, a study found that T. cordifolia had a protective effect by lowering the oxidative load and avoiding the relative occurrence of illnesses and birth defects when administered as part of a daily meal to a diabetic-pregnant rat (streptozocin induced diabetes). Guduchi root extracts have been shown to have anti-diabetic and lipid-lowering properties in a diabetic rat model by attenuating the brain-mediated lipid level and downregulating blood glucose and urine glucose levels.63 In an alloxan-induced diabetes model, guduchi root extract exhibits antihyperglycemic action by bringing blood and urine glucose levels down to normal ranges.64 herbal formulations, including guduchi, are used in medicinal herbal preparations such Ilogen-Excel, Hyponidd, and Dihar. Testing these formulations on diabetic rat models revealed that T. cordifolia alone is responsible for the preparations' anti-diabetic effects. Ilogen Excel is said to have the ability to lower blood glucose levels and improve insulin utilisation by boosting the quantity of the hormone in the bloodstream. According to reports, hyponidd lowers the glucose-mediated hemoglobin count and reactive species to sustain the oxidative load. "Dihar" in the test reduced blood levels of urea and creatinine for 1.5 months in a streptozotocin-induced diabetic mouse, which was followed by an increase in enzyme activity (Rajalakshmi,Anita,et al 2016). According to reports, T. cordifolia stem extract has the ability to prevent diabetes by improving insulin release from beta pancreatic cells and stimulating a number of anti-diabetic pathways, including reducing the amount of endogenous glucose by promoting glycogenesis and other processes that restrict the production of glucose.According to a clinical investigation, 68 guduchi extract inhibits the glucosidase enzyme, lowering the elevated glucose levels that occur after meals.

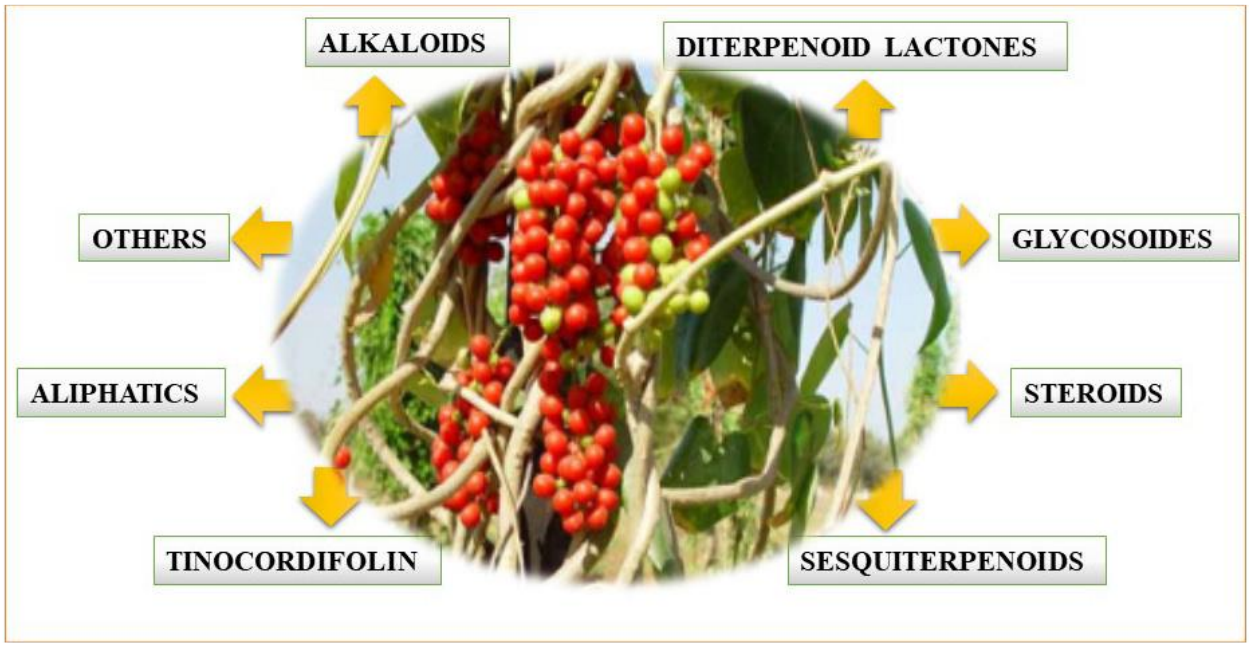

Figure 6. Tinospora cordifolia

1.3.7 COSTUS PICTUS

Chronic hyperglycemia affects how people generally metabolize fat, protein, and carbohydrates. It results in the development of "Diabetes mellitus." Insulin malfunction, aberrant insulin production, or both may be the cause of hyperglycemia**.** Because there are no functioning beta cells, type I diabetes is entirely insulin-dependent and is characterized by insulin insufficiency. Insulin resistance is a disease associated with type 2 diabetes. In humans, type 2 diabetes is more common. Diabetes has emerged as the main medical issue due to its rising incidence. Despite the numerous glucose-lowering medications, Human blood glucose levels were shown to decrease when Costus pictus leaves were given at dosages of 500–2000 mg daily. On rats given diabetes, the methanolic leaf extracts of C. pictus also showed anti-diabetic properties. These extracts increased insulin secretion, which amplified its effects. An increase in the amount of insulin in the bloodstream has an antihyperglycemic effect. Furthermore, the liver's ability to use glucose is restricted under diabetes circumstances, which lowers the amount of glycogen stored in the liver. According to (Ashwini et al. 2015), the C. pictus extracts enhanced the voltage-gated calcium channels' ability to let calcium ions (Ca 2 +) enter the □-cells of the pancreatic islets. Patients with diabetes had an increase in insulin release from their glucose-unresponsive □-cells as a result. Additionally, they investigated the molecular mechanism behind the C. pictus extracts' induction of insulin sensitivity. These extracts increased insulin sensitivity by inhibiting the phosphorylation of protein kinase C (PKC) and extracellular signal-regulated kinase (ERK). This, in turn, downregulated inflammatory cytokines. These demonstrated that, in contrast to manufactured medications, it may be a useful herbal cure. The extracts were also shown to be non-toxic. By preventing muscle tissue damage brought on by a hyperglycemic state and by having anti-diabetic properties in their methanolic extract, C. pictus extracts also increased body weight. They discovered an active substance called methyl tetra-cosanoate, which inhibited the PTP1B enzyme and increased the expression of GLUT4 mRNA. These led to an increase in PI3K and IR □ protein expression, which in turn affected insulin sensitivity. High quantities of flavonoids, including isoquercetin, astragalin, kaempferol, and quercetin, were found in the

leaves of C. pictus. Quercetin generally promoted the anti-diabetic effects by stimulating the release of insulin and regenerating pancreatic □-cells. Isolated from Costus pictus leaves, daucosterol (□-sitosterol-3 -O-□-D-glucoside) shown anti-hyperglycemic properties (Benny et al., 2020). One steroidal sapogenin that is abundant in the rhizomes of C. pictus is called diosgenin

Figure 7. costus pictus

1.3.8 WOODFORDIA FRUTICOSA

Water-based extract of Woodfordia fruticosa leaves and stem barks in both control and alloxan-induced diabetic rats. Albino rats were given a single intraperitoneal injection of 200 mg/kg alloxan**.** Five sets of albino rats were created: standard, test, diabetic, and normal controls. For testing the antidiabetic effect, test groups were given individual doses of 200 mg/kg of aqueous extracts of Woodfordia fruticosa leaves and stem bark (Ghosh S.et al 2012) **.** The usual dosage of glibepenclamide (500 ug/kg) was administered. Rats given alloxan were given a one-touch blood glucose monitoring device, and their blood glucose levels were recorded on days 0, 2, 4, 6, 8, 10, and 12 as well as their body weight. In diabetic rats, it was revealed that all aqueous extracts substantially (P›0.05) suppressed raised blood glucose levels and increased body weight Aqueous extracts of the leaves and bark of Woodfordia fruticosa include phytoconstituents such as tannin, terpenoids, saponins, and flavonoids, according to preliminary phytochemical screening. The phytoconstituents saponins and flavonoids found in Woodfordia fruticosa may be responsible for its antidiabetic properties. These components have been shown to enhance insulin sensitivity or stimulate insulin secretory cells, as well as to lower elevated blood glucose levels in diabetic rats caused by alloxan**.** According to the research, in alloxan-induced diabetic rats, Woodfordia fruticosa leaves and stem bark aqueous extracts demonstrated statistically significant antidiabetic efficacy**.** (Gupta RK et al 2005)

Figure 8. Woodfordia fruticosa

1.3.9 ALOE VERA

Aloe vera, a plant with succulent leaves, holds a substantial historical significance across numerous cultures due to its therapeutic attributes (Sahu et al., 2013). The anti-diabetic capacity of A. vera has been examined by several researchers (Rajasekaran et al., 2004; Tanaka et al., 2006), where the administration of various formulations leads to a notable reduction in plasma glucose levels in diverse experimental models (Beppu et al., 2006).

The potential antihyperglycemic effects of Aloe vera were proposed to be facilitated through the enhancement of insulin production and release, mitigation of oxidative stress, and the prevention of pancreatic β-cell deterioration (Boudreau and Beland, 2006). Additionally, the administration of the ethanolic extract (300 mg/kg body weight) to rats induced with STZ led to a 50% decrease in fasting blood glucose (FBG) levels. This also resulted in the prevention of damage to the pancreatic β-cells or the regeneration of partially damaged β-cells as documented by Noor et al. in 2017 and 2008. Numerous medicinal attributes are attributed to the polysaccharides found in the inner leaf gel, along with anthraquinone derivatives and phenolic compounds that undergo metabolism in the intestine before entering the circulatory system to exhibit physiological effects. These effects include safeguarding against damage to β-cells, as highlighted by Beppu et al. in 2006.

Dyslipidemia is widely recognized for its significant role in the impairment of β–cell function, which ultimately contributes to the initiation of Type 2 Diabetes (von Eckardstein and Sibler, 2011). The oral administration of a phytosterols-rich fraction derived from Aloe vera to Zucker diabetic fatty rats led to a notable enhancement in random blood glucose, levels of glycated hemoglobin (HbA1c), serum free fatty acids (FFA), and triglycerides (TG). These improvements indicated an increase in both insulin sensitivity and secretion. However, it was observed that the total cholesterol (TC) levels remained unaffected by this treatment (Misawa et al., 2008). The insignificant impact of the fraction on TC levels

is believed to be due to the relatively low dosage of phytosterols that was administered (Misawa et al., 2008).

In the treatment of diabetic patients, the utilization of Aloe vera in combination with metformin may serve to prevent dyslipidemia associated with diabetes, enhance cellular integrity, and elevate levels of high-density lipoprotein (HDL), consequently reducing the risks of cardiovascular disease and renal failure. Findings from histopathology examinations of the pancreas and kidney indicated indications of recovery, which stood in stark contrast to the diabetic cohort displaying necrotic pancreatic cells and complete erosion of glomeruli in the kidney (Atanu et al., 2018).

A clinical study lasting five years and involving 5,000 patients diagnosed with coronary artery disease has validated that the incorporation of Aloe vera gel into the dietary regimen led to a notable decrease in fasting and post-prandial blood glucose levels among individuals with diabetes, alongside a reduction in total serum cholesterol, triglycerides, and an elevation in HDL levels as documented by Agarwal in 1985. It is noteworthy to mention that a significant proportion of the beneficiaries were diabetic patients who were not utilizing any anti-diabetic medications, and no adverse reactions were reported throughout the duration of the research, as highlighted by Agarwal in 1985. An additional research study has uncovered the anti-diabetic properties of Aloe vera in newly diagnosed cases of diabetes mellitus, resulting in enhanced triglyceride levels.

Figure 9. Aloe vera

4.1.10 TAMARINDUS INDICA LINN.

Herbal treatments, including diabetes mellitus, are recommended in the traditional medical system of India. Plants have been successfully tested in a range of pathophysiological conditions in recent years. Among them is Tamarindus indica Linn. In the current study, it was shown that an aqueous extract of Tamarindus indica Linn. (So Yeon Park et al 2020) seeds had strong antidiabetogenic effect, lowering blood sugar levels in male rats with streptozotocin (STZ)-induced diabetes. When this aqueous extract was given to STZ-induced diabetic rats by gavage at a dosage of 80 mg/0.5 ml distilled water/100 g body weight per day, the fasting blood sugar level was significantly reduced after 7 days. After 14 days of continuous supplementation, there was no discernible change in this parameter from the control level. Furthermore, compared to the diabetic group, this supplementation resulted in a considerable increase in the glycogen content of the liver and skeletal muscles as well as the activity of liver glucose-6-phosphate

dehydrogenase. The aqueous extract supplemented group exhibited a substantial reduction in the activities of liver glucose-6-phosphatase, liver and kidney glutamate oxaloacetate transaminase (GOT), and glutamate pyruvate transaminase (GPT) in comparison to the diabetes group. After taking this extract supplementation for seven days, none of the aforementioned parameters returned to the regulated level; however, after fourteen days, all of the aforementioned parameters did. (Sanchetia et al., 2011)

Figure 10. Tamarindus indica Linn

CONCLUSION

Because β-cell mortality reduces β-cell mass and hence endogenous insulin production, it plays a role in the development of T1D and T2D. There is an urgent need for therapies that can stop or even reverse the malfunction and death of β-cells. Numerous investigations have indicated that the mean shares of β-cell division, neogenesis, and apoptosis in the total β-cell mass differ according to age and stress levels. We examined a few therapeutic plants and substances generated from plants that were modeled like conventional medical systems. Numerous scientific studies have indicated that certain phytochemicals and/or plant extracts have hypoglycemic effects.certain substances, such geniposide, baicalein, and apigenin, showed extremely encouraging results. The phytochemicals and extracts discussed in this study are thought to reduce the symptoms of diabetes by a variety of mechanisms, such as extending the half-life of GLP-1 and blocking DPP-IV, reducing β-cell apoptosis by blocking caspase 9 and upregulating Bcl-2 expression, boosting the expression of genes related to islet inflammation reduction, β-cell proliferation, and insulin production and secretion. Still, the lack of controlled clinical studies is the biggest drawback. The brief period of these investigations, limited sample size, absence of randomization, and fluctuation in dosage. Therefore, more research and clinical studies are required to better understand the processes by which these extracts transmit their therapeutic effects and to establish the appropriate dosage for the prevention of diabetes and its complications. To guarantee that potential anti-diabetic plants are safe and effective phytomedicines, it is crucial to assess their toxicity.