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Herbals and Their Compounds Targeting Pancreatic Beta Cells for the Treatment of Diabetes

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Abstract

Diabetes, the metabolic disorder can strike anyone, from any walk of life. In the last decade, The situations of people living with diabetes get jumped almost 50 percent – to more than 30 million Americans. Worldwide, diabetes afflicts more than 422 million people. The high blood sugar levels over a prolonged period is distinguishing feature of Diabetes mellitus (commonly recognized as diabetes). Diabets is a significant cause of blindness, kidney failure, amputations, heart failure and stroke. The diabetes is the global health problem and a national economic burden for any country. There are many more drugs of antidiabetic nature. Still, there is a need for novel therapeutic agents with improved efficacy and few side effects. The herbal drugs (derived from natural compounds of the plant) are more attractive than synthetic drugs. This is because of their diversity and minimal side effects. The present attempt is summarizing the most relevant effects of various herbal drugs (plant-derived natural compounds) on the functionality of pancreatic beta cells. The natural compounds through herbal drugs directly enhance insulin secretion. The herbal drugs are known to prevent pancreatic beta cell apoptosis (a process of programmed cell death), and modulate pancreatic beta cell differentiation and proliferation.

Keywords: Streptozotocin (STZ); medicinal plant; antidiabetic, antioxidant, diabetes Abbreviations: NOD: Nonobese Diabetic; HbA1c: Haemoglobin A 1 c; HOMA – β: Homestatic Model Assessment Beta; ZDF: Zuker Diabetic Fatty; NO: Nitric Oxide; ROS: Reactive Oxygen Species; NF –kB: Nuclear Factor – kB; ERK: Extracellular-*signal Regulated Kinase.*

INTRODUCTION

The number of persons with diabetes worldwide has more than doubled during the past 20 years. The emergence of type 2 diabetes in children, adolescents, and young adults is supposed to be one of the most worrying features of this rapid increase. The role of traditional risk factors for type 2 diabetes, which include: genetic, lifestyle, and behavioral risk factors. Recent studies has focused on identifying the contributions of epigenetic mechanisms and the effect of the intrauterine environment. The epidemiological data predict an inexorable and unsustainable increase in global health expenditure attributable to diabetes, so disease prevention should be given high priority. There should be integrated approach to prevent type 2 diabetes and must recognize its heterogeneity. There is a need to be directed at improved understanding of the potential role of determinants, such as the maternal environment and other early life factors, as well as changing trends in global demography, to help shape disease prevention programs.

In diabetes, there are two possibilities. In the first possibility, the pancrease is not secreting sufficient amount of insulin. In the second possibility, the cells of the body are not responding properly to the available insulin (*Shoback and Gardner, 2011).* In a normal healthy body, insulin regulates the metabolism of carbohydrates, fats and protein by promoting the absorption of, especially, glucose from the blood into liver, fat and skeletal muscle cells (*Stryer,1995). Deficiency of insulin leads to diabetic disorder. The* diabetes is characterized by hyperglycemia, condition of glucose circulation in excessive amount in the blood plasma. The diabetes can cause other complications including cardiovascular disease, nephropathy, retinopathy, and neuropathy (Russell and Cooper, 2015). Disturbance of glucose homeostasis (process by which the levels of sugar, primarily glucose in blood are maintained by the body within a narrow range) is a major factor in the development of hyperglycemia. Insulin, the peptide hormone released by pancreatic beta cells is the key hormone. This hormone is responsible for glucose metabolism homeostasis (Plum, *et al* , 2006). The diabetes is known to appear in four broad categories, which include: type 1, type 2, gestational diabetes, and other specific types. In type 1 diabetes and type 2 diabetes, there is absolute or relative insulin deficiency, which results in the development of hyperglycemia (Atkinson and Eisenbarth, 2001; . Butler, *et al* , 2003). The damage of pancreatic beta cells through immunological factors (such as cytokines and macrophages or T cells activated by autoimmune responses) is the feature of type 1 diabetes. The type 2 diabetes is the result of insulin resistance and relative insulin deficiency. This cannot compensate for the insulin resistance. The persistently high glucose or lipid levels, inflammatory mediators released from the adipose tissue and endoplasmic reticulum, or oxidative stress are responsible to damage pancreatic beta cells in type 2 diabetes. The maintenance of pancreatic beta cells in functional condition may be a strategical approach for the prevention and treatment of diabetes. The importance of research lie in the discovery of novel and cost-effective agents (antidiabetics) that can enhance pancreatic beta cell function or can increase pancreatic beta cell mass. The cells in the body of living organisms are known to produce the natural products in the form of a chemical compound or substance (https://en.wikipedia.org/wiki/Natural_product). The natural products can also be prepared by chemical synthesis (both semisynthesis and total synthesis). The natural products have played a central role in the development of the field of organic chemistry by providing challenging synthetic targets. The term natural product has also been extended for commercial purposes to refer to cosmetics, dietary supplements, and foods produced from natural sources without added artificial ingredients. The plants, animals, and microorganisms constitute various sources of the natural compounds (Lam, 2007). The novel pharmaceuticals are obtained from the natural bioactive compounds. Because of their diversity, they enable the synthesis of drugs that differ from other chemical compounds in terms of their complex structures and biological potency (Dias, *et al* , 2012). There are about fifty percent of the drugs approved

by the US Food and Drug Administration that belong to: phytogenic compounds or derivatives thereof. The best examples of natural compound-derived pharmaceuticals are: Aspirin, metformin, morphine, vinblastine, vincristine, quinine, artemisinin, etoposide, teniposide, paclitaxel, and camptothecin (Kingston, 2011). There are about 1200 plants that have been claimed to contain compounds with antidiabetic properties. There are over 400 plants and their bioactive compounds have been scientifically evaluated for type 2 diabetes treatment (Singh, *et al* , 2011). However, very little information is available about the mechanism of action of plants traditionally used as antidiabetics, preventing them from being used in diabetes care. Recently, more investigation is being focused on elucidating the mechanism of action of the plants and their active bio-compounds. The present attempt is the review to focus on plant-derived compounds and extractives that affect pancreatic beta cell function. The chemical structures and actions of natural compounds on pancreatic beta cell function in cell culture systems, animal models, and type 2 diabetic patients are also considered (Figure 2 and Table 1).

METHOD FOLLOWED FOR COLLECTION OF DATA:

Online research methods (ORMs) was followed for the purpose collection of data pertaining "Herbal Compounds Targeting Pancreatic Beta Cells for the Treatment of Diabetes". The methods of research through online (Online Research Methods: ORMs) are ways in which researchers can collect data via the internet. They are also referred to as Internet research (Reips, 2012); Internet Science (Reips & Bosnjak , 2001) or iScience, or Web-based methods (Reips, 2006). Many of the enlisted "Online Research Methods" are related to the methods already existing. It is a need to "re-invent" and "re-imagine" them in the light of new technologies and conditions associated with the available internet resources. The field of "Online Research Methods" is relatively new and evolving. With the growth of social medias a new level of complexity and opportunity of "Online Research Methods" has been created. Inclusion of social media research can provide unique insights into consumer and societal segments and gaining an "emotional" measure of a population on issues of interest. Some specific types of method include: Cyber-ethnography; Online content analysis; Online focus groups; Online interviews; Online qualitative research; Online questionnaires; Social network analysis; Web-based experiments and Online clinical trials (https://en.wikipedia.org/wiki/Online_research_methods). The "Online Research Methods" provide means of getting to know informants (also called an informer. The informants are a personalities who provides privileged information about a person or organization to an agency) as well as generating important insights that can be compared with the results of our structured techniques.

A literature survey for the present attempt was performed in "PubMed" using the keywords "anti-diabetic activity, beta cell function, beta cell proliferation, and beta cell differentiation" to evaluate the effects of each natural product. To investigate the response of diabetes to natural products, the present attempt included any articles describing the effect of natural product-derived compounds on beta cell function using cell culture and diabetic animal models. For the purpose to evaluate the compounds' effect on humans, the attempt of tried it's best to summarize all relevant reviews, such as cohort/case-control studies, randomized clinical trials, controlled clinical trials, and systemic reviews.

The first step in the present attempt for effective online search in the present was to establish the list of key words or terms (main topic of research). The search key words or terms term should be as concise as possible, while still covering the area one would like to find. Next step was to form phrases (avoid common phrases unless they are placed in quotes) and terms that describe one's topic. The search was through the of use nouns and pronouns as keywords when possible with the most important terms being placed first. Many search engines operate by Boolean operators which are set theory based and include the terms and, or and but among other terms. For example, if one would like to find the current herbal

chemical status of any plant, a search term of "Herbal Chemicals" would come up with too many responses, such as protein, lipid, carbohydrates,….. etc. many of which would be totally unusable. A good search should be stated in the terms that one is looking for. In this case "Herbal Chemicals of Specific Plant" would be a better search term. The search term was placed "Search Box" of website in quotes asking the search engine for a match ONLY based on the terms within the quotes. Unless the search engine selected can accept plain English (which a growing number of search engines can) searching a search term not placed in quotes would result in a search for EVERY term in the search box. This obviously would not lead to an efficient search. A good starting point for effective internet research is finding an effective search engine. Many different types of search engines are available such as a standard search engine such as www.google.com , an invisible web search engine such as www.incywincy.com , a Meta search engine such as www.ez2find.com , or a specialized search engine such as www.firstgov.gov .

The Plants, extractives of which are working for the regulation of cells of islets of Langerhans include**:** *Bidens pilosa (*L.*); Capsicum annuum (*L.*) ; Carica papaya (*L.*); Gymnema sylvestre (*L.*); Momordica charantia (*L.*); Nymphaea stellata (*L.*) and Panax ginseng; (*L.). Let us have a short review on these herbal sources working for the regulation of cells of islets of Langerhans.

(A). HAIRY BEGGARTICKS, *Biden pilosa* (L.):

The hairy beggarticks, *Biden pilosa* (L.) is the significant member of family: Asteraceae. It is distributed throughout the tropical and warm temperate regions of the world. Most species of biden occur in the Americas, Africa, and Polynesia, and there are some in Europe and Asia. The hairy beggarticks, *Biden pilosa* (L.) is traditionally used as an antidiabetic herb in various countries. It contains flavonoids and polyynes; the latter are reported to possess antidiabetic activity (Bartolome, 2013). The polyyne compounds have also been called oligoynes, or carbinoids after "carbyne", the hypothetical allotrope of carbon that would be the ultimate member of the series. The bioactive compounds identified in hairy beggarticks, *Biden pilosa* (L.) include three polyynes: 3-*β*-D-glucopyranosyl-1-hydroxy-6(*E*)-tetradecene-8,10,12-triyne; 2-*β*-D-glucopyranosyloxy-1-hydroxy-5(*E*)-tridecene-7,9,11-triyne and 2-*β*-D-glucopyranosyloxy-1-hydroxytrideca-5,7,9,11-tetrayne (cytopiloyne). The cytopiloyne exhibited significant effect on the glycemic control over that of the other two polyynes (Chang, 2013). Chang, 2013 demonstrated that, the cytopiloyne dose-dependently increased insulin mRNA expression and insulin secretion in rat insulinoma RIN-m5F cells, and calcium, diacylglycerol, and protein kinase C*α* were shown to be involved in increased secretion and production of the insulin.

There are several studies dealing with use of hairy beggarticks, *Biden pilosa* (L.) could treat type 1 and type 2 diabetes. Chang (2007) demonstrated normal levels of glucose and insulin after 10 weeks of treatment with cytopiloyne at 25 μg/kg in non-obese diabetic (NOD) mice. The Cytopiloyne at 0.5 mg/kg was found markedly stimulating insulin production in diabetic dyslipidemia (db) mice compared with the two other polyynes administered at the same concentration. The administration of an ethanol extract of the aerial part of hairy beggar ticks, *Biden pilosa* (L.) (1 g/kg) was found lowering blood glucose in diabetic dyslipidemia (db) mice. The treatment with a mixture of two polyynes (3-β-D-glucopyranosyl-1-hydroxy-6(*E*)-tetradecene-8,10,12-triyne and 2-β-D-glucopyranosyloxy-1-hydroxy-5(*E*)-tridecene-7,9,11-triyne) was found significantly reducing blood glucose levels Ubillas (2000). Despite the advancement in phytochemistry and animal models of diabetes, there are rare reports on "Use of hairy beggar ticks, *Biden pilosa* (L.) for human diabetes". In one of the attempt, Lai, *et al* (2015), evaluated the effect of herbal formulation of hairy beggar ticks, *Biden pilosa* (L.) (400 mg/day) on fasting blood glucose (FBG), fasting serum insulin, and glycosylated hemoglobin A1c (Hb_{A1c}) in diabetic human subjects. The formulation of hairy beggar ticks, *Biden pilosa* (L.) was found reducing the level of FBG and Hb_{A1c} in diabetic human patients. At the same time, the attempt of Lai, *et al* (2015), reported increased fasting serum insulin in healthy human subjects. The attempt of Lai, *et al* (2015) further reporting combination of hairy beggar ticks, *Biden pilosa* (L.) formulation with antidiabetic drugs had better glycemic control in diabetic human patients. The homeostatic model assessment (HOMA) data suggested that the antidiabetic activity of this hairy beggar ticks, *Biden pilosa* (L.) was through the improvement of β-cell function**.** Collectively**,** hairy beggar ticks, *Biden pilosa* (L.) or cytopiloyne derivatives may be potential agents to treat type 2 diabetes by acting on pancreatic beta cells.

(B). CHILLI PEPPER, *Capsicum annuum* (L.):

Chilli Pepper, *Capsicum annuum* (L.) is a flowering plant from family Solanaceae and is widely cultivated in South- East Asian and Latin-American countries (Islam, *et al*, 2008). The fruits of Capsicums are used for extraction total phenolic contents, total flavonoid contents and antioxidant activity. The capsaicin is the major compound in red chilli, *Capsicum annuum* (L.). This compound was first extracted in impure form in 1816 by Christian Friedrich Bucholz (1770–1818) (Russell and Cooper,

2015). John Clough Thresh (1850–1932), who had isolated capsaicin in almost pure form, gave it the name "capsaicin" in 1876. Karl Micko isolated capsaicin in its pure form in 1898. Capsaicin's chemical composition was first determined by E. K. Nelson in 1919, who also partially elucidated capsaicin's chemical structure. Capsaicin was first synthesized in 1930 by Ernst Spath and Stephen F. Darling. In 1961, similar substances were isolated from chili peppers by the Japanese chemists S. Kosuge and Y. Inagaki, who named them capsaicinoids. In 1873 German pharmacologist Rudolf Buchheim (1820–1879) and in 1878 the Hungarian doctor Endre Hőgyes stated that "capsicol" (partially purified capsaicin) caused the burning feeling when in contact with mucous membranes and increased secretion of gastric acid (https://en.wikipedia.org/wiki/Chili_pepper).

Treatment of cells in "Rat Insulinoma cell line: RIN-m5F" with capsaicin (10 pM–10 nM) was reported increased insulin secretion in a dose-dependent manner. This effect was mediated by the capsaicin-sensitive afferent neuron transient receptor potential vanilloid receptor 1 calcium channel (Akiba, 2004). Provision of capsaicin to Zucker Diabetic Fatty (ZDF) rats was found reduced blood glucose levels and increased plasma insulin levels compared with those of control mice (Gram, *et al*, 2007). Dietary provision of chili pepper powder for two weeks to streptozotocin- (STZ-) induced diabetic rats fed a high-fat diet was found no change in the blood glucose level, but the plasma insulin level was higher in these rats than that in the control group. This attempt is suggesting that capsaicin possesses an insulinotropic activity rather than hypoglycemic effect (Islam, *et al* , 2008).However, the effects of capsaicin in diabetic patients are non-significant.

(C). PAPAYA, *Carica papaya* (L.):

Papaya, *Carica papaya* (L.) significant member of the family: Caricaceae. The tropics of the Americas, perhaps from southern Mexico and neighboring Central America are the native regions of Papaya, *Carica papaya* (L.). It is cultivated in most of the tropical countries. The diabetes, obesity, infection, such and other human diseases are cured through the use of Papaya, *Carica papaya* (L.). Therefore, it is listed in "Traditional medicine for the treatment of various human diseases". The leaves of Papaya, *Carica papaya* (L.) in particular, show antidiabetic actions. The bioactive phytochemicals of Papaya, *Carica papaya* (L.) include: flavonoids, alkaloids, saponins, and tannins. It may have other compounds is

said that, have not yet been identified. Juárez-Rojop, *et al* (2012) reported significantly reduced plasma blood glucose levels, serum cholesterol, and serum triacylglycerol in STZ-induced and alloxan-induced diabetic rats through treating with aqueous extract of *C. papaya* leaves (0.75 g and 1.5 g/100 mL). Sasidharan, *et al* (2011) reported antihyperglycaemic effects of ethanol extracts of Papaya, *Carica papaya* (L.) and leaves of pandanus palms, *Pandanus amaryfollius* (L.) in streptozotocin-induced diabetic mice. Histological studies on the pancreas of the treated groups revealed significant regeneration of the β-cells in comparison with the diabetic control. The hepatic cells of the treated group exhibited significant reduction in fatty changes and pyknotic nucleus. The kidney tissues of the treated groups indicated significant recovery in the cuboidal tissue. The studies from the phytochemical screening demonstrated the presence of flavonoids, alkaloids, saponin and tannin in C. papaya and P. amaryfollius. Histological staining of the pancreatic islets of Langerhans showed that these extracts significantly induced the regeneration of pancreatic beta cells (Sasidharan, *et al* , 2011). Recently, Isela Esther, et al (2017) reported decreased blood glucose levels ($p<0.05$); decreased cholesterol, triacylglycerol and amino-transferases blood levels in the streptozotocin (STZ) (60 mg/kg) induced diabetic rats treated with aqueous extract of Carica papaya (0.75 g and 1.5 g/100 mL). Further, this attempt reported "No change in low plasma insulin levels after treatment in diabetic rats and significant increase in plasma insulin levels in non-diabetic experimental individuals". Papaya, *Carica papaya* (L.) could help islet regeneration manifested as preservation of cell size. Papaya, *Carica papaya* (L.) exert a hypoglycemic influence.

(D). GURMAR, *Gymnema sylvestre* (L.):

The GURMAR, *Gymnema sylvestre* (L.) is a perennial woody vine (plant that climbs or grows along the ground and has twisting stems). It grows in tropical areas of India, Africa, and Australia. It has been used for medicinal purposes in Ayurvedic medicine. Common names include gymnema, (*Duke, 2002). The common Indian name for* the *Gymnema sylvestre* (L.) is GURMAR. Meaning of this Hindi word "Gurmar" is "Sugar Destroyer" (*Quattrocchi, 1999; Ulbricht, et al , 2011 and Tiwari, et al , 2014).* The extractives of leaves of GURMAR, *Gymnema sylvestre* (L.) contain gymnemic acids as major bioactive constituents. This gymnemic acid is known to interact with taste receptors on the tongue to temporarily suppress the taste of sweetness *(Kurihara,1969; Brala and Hagen, 1983; Gent, et al, 1999 Gardner and McGuffin M , 2013; Sanematsu, et al , 2014).*

It has traditionally been used to treat diabetes in India for centuries. Triterpenoid saponins known as gymnemic acids are the main chemical constituents of *G. sylvestre* and are considered to be the active compounds responsible for the antidiabetic effects of the extracts (Kanetkar, *et al* , 2007). *G. sylvestre* extract is known to stimulate insulin secretion in various pancreatic beta cell lines, such as HIT-T15 (hamster pancreatic beta cell line) and RIN-m5F cells (Persaud, *et al* , 1999). In addition, treatment of MIN6 (mouse insulinoma cell line) and isolated human islets of Langerhans with Om Santal Adivasi

extract (OSA), a high-molecular-weight leaf extract, stimulated insulin secretion (Liu, *et al* , 2009; Al-Romaiyan, *et al* , 2012).

The insulinotropic (that stimulates or affects the production of insulin) action of extractive GURMAR, *Gymnema sylvestre* (L.) was mediated via permeabilization of the plasma membrane resulting from the high saponin glycoside content of the extract and increased Ca^{2+} influx through voltage-dependent Ca^{2+} channels (Persaud, *et al* , 1999). There was significant increase in the levels of plasma insulin in diabetic Wistar rats and Sprague-Dawley rats through administration of leaf extractives of GURMAR, *Gymnema sylvestre* (L.) at a dose of 13.4 mg/kg, 20 mg/kg, and 100 mg/kg, respectively. This attempt , further reporting concomitant with decreased glucose levels (Kang, et al , 2012; Sugihara, et al , 2000 and Daisy, et al , 2009).

Obesity is health condition in which excess body fat has accumulated to the extent that it may exert a negative influence. The major peripheral hyperinsulinemia, resulting from both higher insulin secretion and reduced insulin clearance, as well as by marked insulin resistance are the distinguishing features of obesity. The abnormalities or impaired glucose tolerance seen in severely obese individuals can be explained away by the presence of major insulin resistance that cannot be fully compensated for by adequate insulin secretion. With further intolerance to glucose, fasting hyperglycemia and diabetes occur (Olefsky, *et al*, 1982; Zuniga-Guajardo, *et al* , 1986; Jahr, *et al* , 1983 and Felber, 1992). These abnormalities in the metabolism of glucose–insulin may be improved after calorie restriction and weight loss in obese diabetic patients (Wing, *et al* , 1987; Henry, *et al* , 1985 and Hughes, *et al* , 1984). The listed treatments are associated with improved insulin sensitivity; decreased glucose production, and increased insulin secretion. The exercise, often added to calorie restriction in treatment programs for obesity. This also has preventive effects on the development of diabetes (Eriksson, 1991 and Knowler, *et al* , 1995). Although weight reduction can improve hyperglycemia, especially when treatment is initiated soon after diagnosis, normal glucose tolerance may be difficult to achieve or maintain. The ob / ob mouse is genetically deficient in leptin and displays metabolic abnormalities similar to those seen in obese humans with non-insulin-dependent diabetes mellitus. These abnormalities include obesity, hyperglycemia, glucose intolerance, and hyperinsulinemia (Herberg, *et al* , 1977; Bray, et al , 1979; Bailey and Flatt, 1986).The excess of body weight in ob / ob mice can be reduced by repeated injections of recombinant leptin (Pelleymounter, *et al* , 1995; Halaas, *et al* , 1995 and Campfield, 1995). Treating the diabetic obese mice with capsules of Orthosilicic Acid (OSA) (500 mg/kg) was reported to decrease plasma glucose levels and significant induction in insulin secretion compared with that in control mice (Ahmed, et al , 2010). ; Al-Romaiyan, *et al* , 2013). Ahmed, *et al* (2010) demonstrated lowered blood glucose levels through the regeneration of pancreatic beta cells in alloxan-induced diabetic Wistar rats through administration of leaf extractives of GURMAR, *Gymnema sylvestre* (L.) (200 mg/kg). Baskaran, *et al* , (1990) demonstrated antidiabetic efficacy in clinical trials on the use of leaf extractives of GURMAR, *Gymnema sylvestre* (L.) for the control of type 2 diabetes. In a cohort attempt of study with type 2 diabetes patients, oral administration of Orthosilicic Acid (OSA) (1 g/day, 60 days) was found inducing significant increase in circulating insulin and C-peptide concomitant with a significant reduction in blood glucose levels (Al-Romaiyan, *et al* , 2010). The extractives of GURMAR, *Gymnema sylvestre* (L.) showed hypoglycemic effects via the increase in pancreatic beta cell regeneration and insulin secretion.


(E). BITTER GOURD, ***Momordica charantia*** **(L.):**

The *Momordica charantia* (L.) is known as bitter melon, bitter gourd, bitter squash, or balsam-pear. It is a tropical and subtropical vine belong to the family : Cucurbitaceae. It is widely grown in Asia, Africa, and the Caribbean for its edible fruit. It appears in many varieties differ substantially in the shape and bitterness of the fruit. In Kerala (State of India), the fruits of *Momordica charantia* (L.) are recognized as bitter guard, karela, or balsam pear (Geil and Shane-McWhorter 2008) and referred to as "vegetable insulin". The biochemical constituents of extractives of fruits of BITTER GOURD, *Momordica charantia* (L.) share structural similarities with animal insulin (Geil, *et al* 2004). The fruit and the whole plant are believed to possess antidiabetic properties (Grover, 2004). The biochemistry and bioactivity underlying the antidiabetic effect of the extractives of BITTER GOURD, *Momordica charantia* (L.) have been extensively studied. Treatment with aqueous extractive of BITTER GOURD, *Momordica charantia* (L.) *was found* preventing alloxan-induced pancreatic beta cell apoptosis and increasing insulin secretion in HIT-T15 cells (Xiang, et al , 2007). The fruit pulp extractive, seeds extractive, leaf extractive and whole plant extractive of BITTER GOURD, *Momordica charantia* (L.) were confirmed to have a hypoglycemic influence in diabetic animal models. A daily oral administration fruit juice of BITTER GOURD, *Momordica charantia* (L) was significantly increased pancreatic beta cell numbers compared to untreated diabetic rats Ahmed, et al (2004). The extractives of BITTER GOURD, *Momordica charantia* (L) in water, ethanol and acetone extracts exhibited anti-hyperglycemic effect in STZ- and alloxan-induced diabetic rats (Bailey, *et al* , 1985; Shibib, *et al* , 1993; Singh, *et al* , 2007). The seed extractives of BITTER GOURD, *Momordica charantia* (L.) also showed a glucose-lowering influence in diabetic mice (Kedar, *et al*, 1982). These attempts are the proofs for the antidiabetic action of BITTER GOURD, *Momordica charantia* (L.). The contents of BITTER GOURD, *Momordica charantia* (L.) may either repair damaged pancreatic beta cells or prevent their death. The results of randomized, double-blind controlled trials and case studies of the hypoglycemic property of BITTER GOURD, *Momordica charantia* (L.) were evaluated, and most of them demonstrated that fasting and postprandial blood glucose levels were significantly reduced by *M. charantia* administration (Grover and Yadav,2004; Tongia, *et al*, 2004; Srivastava, *et al*, 1993). Although several clinical studies have been performed, their sample sizes were very small. Therefore, clinical trials with sufficient sample size should be performed to evaluate *M. charantia* as a potential treatment for diabetes.

(F). BLUE WATER LILY EGYPTIAN LOTUS**,** *Nymphaea stellata* (L.):

BLUE WATER LILY EGYPTIAN LOTUS, *Nymphaea stellata* (L.) is a tropical and subtropical plant belong to the family: Cucurbitaceae. It is widely grown in Asia, Africa, and the Caribbean for its edible fruit. Many varieties of BLUE WATER LILY EGYPTIAN LOTUS, *Nymphaea stellata* (L.) differ substantially in the shape and bitterness of the fruit. It is a well popular and recognized medicinal plant. It is widely used for the treatment of diabetes, inflammation, and liver disorders. The bioactive content of this BLUE WATER LILY EGYPTIAN LOTUS, *Nymphaea stellata* (L.) is a plant sterol: nymphayol (25,26-dinorcholest-5-en-3b-ol). This plant sterol was initially isolated from the chloroform extractive of the flowers of BLUE WATER LILY EGYPTIAN LOTUS, *Nymphaea stellata* (L.) (Subash-Babu, *et al*, 2009). Oral administration of extractives of flower and leaf of extracts of *N. stellata* lowered blood glucose levels and increased insulin levels in STZ-induced diabetic rats and alloxan-induced Wistar rats (Subash-Babu, *et al*, 2009; Dhanabal, *et al* , 2007; Rajagopal, *et al* , 2008). Immuno-staining of pancreatic sections from nymphayol-treated diabetic rats exhibited increased numbers of insulin-positive cells in the islets of Langerhans (Subash-Babu, *et al*, 2009). This attempt is suggesting that stimulation of pancreatic beta cell regeneration and the subsequent release of insulin are one of the potential mechanisms underlying nymphayol's antidiabetic influence. However, the influence of nymphayol in type 2 diabetic patients is largely unknown. Water lilies have many edible parts. The young leaves and unopened flower buds of water lilies can be boiled and served as a vegetable. The seeds water lilies are with contents of high starch, protein, and oil. Therefore, the seeds water lilies may be popped, parched, or ground into flour.

(G). ASIAN GINSENG, *Panax ginseng* (L.):

The ASIAN GINSENG, *Panax ginseng* (L.) is a species of plant whose root is the original source of medicinal ginseng. It is a perennial plant that grows in the mountains of Eastern Asia. The ASIAN GINSENG, *Panax ginseng* (L.) is native to mountainous regions of Russian Far East, Manchuria, and the Korean Peninsula. It is a protected plant in Russia and China, and most commercial ginseng is now sourced from plants cultivated in China, Korea and Russia. The plant is a slow-growing perennial and the roots are usually harvested when the plants are five or six years old (*Mahady, et al , 2001***).** This plant has received attention for its antidiabetic and antiobesity effects in diabetic patients and in animal models of type 2 diabetes. Ginsenosides are the significant chemicals extracted from roots of the ASIAN GINSENG, *Panax ginseng* (L.). The ginsenosides are known to be responsible for the antidiabetic and antiobesity effects. The ginsenosides are reported to protect pancreatic beta cells from apoptosis. Ginsenoside Rb1 and Rg1 are reported to promote glucose-stimulated insulin secretion in MIN6 cells (Park, *et al* , 2008) and to protect RIN-m5F cells from high glucose/cytokine-induced apoptosis via a decrease in nitric oxide (NO) production and the down regulation of FAS (Fetal alcohol syndrome is a condition that causes physical and mental disorders in children whose mothers drank alcohol heavily during pregnancy. FAS is characterized by abnormal facial features, growth retardation, and central nervous system problems. Individuals with FAS may have difficulties with learning, memory, attention

span, problem solving, speech, and hearing. They can also have problems in school and problems getting along with others. FAS is an *irreversible, lifelong* condition that affects every aspect of an individual's life and the lives of his or her family) and caspase-3 gene expression (Cysteine-Aspartic Proteases, Cysteine Aspartases or Cysteine-dependent aspartate-directed proteases are a family of protease enzymes playing essential roles in programmed cell death (including apoptosis, pyroptosis and necroptosis) (Chen, *et al* , 2012). Root extractives of the ASIAN GINSENG, *Panax ginseng* (L.) have also been shown to protect against cytokine-induced apoptosis of MIN6 cells (Kim and Kim, 2007). Another study proposed that American ginseng root (25 μg/mL) stimulated insulin production and prevented cytokine-induced apoptosis via regulation of uncoupling protein-2 in INS-1 cells, a rat insulinoma cell line (Luo and Luo, 2006).

Extractives from roots, berries, or leaves of the ASIAN GINSENG, *Panax ginseng* (L.) were found to be effective against type 2 diabetes in rodents. Administration of red or green ginseng berry extractives at the rate of 150 mg/kg was found significantly reducing blood glucose levels and improving glucose tolerance in STZ-induced diabetic mice. Moreover, insulin secretion was increased in in the mice treated with extractives of berries of the ASIAN GINSENG, *Panax ginseng* (L.). This possibly may be due to increased pancreatic beta cell proliferation (Park, *et al* , 2012). In ob/ob and db/db mice, oral administration of extractives of berries of the ASIAN GINSENG, *Panax ginseng* (L.) also found reducing blood glucose levels (Dey, *et al* , 2003; Xie, *et al* , 2002). The Ginsenosides from leaves and roots of the ASIAN GINSENG, *Panax ginseng* (L.) also showed glucose-lowering effects in db/db mice (Dey, *et al* , 2003; Xie, *et al* , 2002).

Clinical studies have demonstrated that ingestion of *P. ginseng* (6 g/day) for 12 weeks improved glycemic control in type 2 diabetes patients (Vuksan, *et al* , 2000; Vuksan, *et al* , 2008). However, one study reported that ginseng had no antidiabetic effect in these specific diabetes patients **(**Kim**,** *et al* , 2011). Since differences in the concentrations of the various ginsenosides may have been the cause of the outcome variability, standardization of the types of ginsenoside and their ratios are needed to obtain consistent efficacy.

(H). MULBERRY, *Morus alba* (L.):

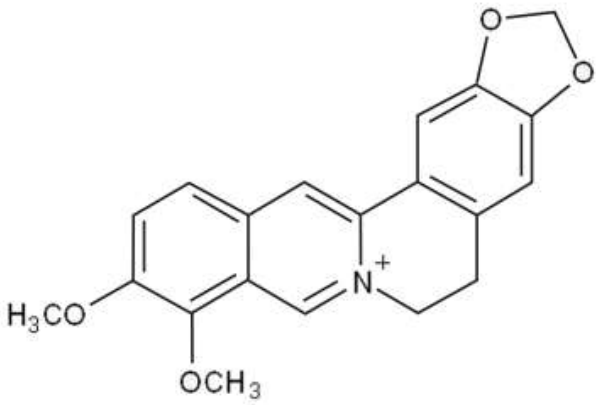
Hypolipidemic and antioxidant effects from freeze-dried powder of mulberry (*Morus alba* L.) fruit (Yang, *et al*, 2010).Neuroprotective effects in *in vitro* and *in vivo* (fruit) (Kim, et al, 2010). Albanol A, isolated from the root bark extract of *M. alba*, may be a promising lead compound for developing an effective drug for treatment of leukemia (Kikuchi, *et al*, 2010). Moracin M, steppogenin-4′-O-β-D-glucoside and mulberroside A were isolated from the root bark of Morus alba L. and all produced hypoglycemic effects

(Zhang, et al, 2009). Mulberroside A, a glycosylated stilbenoid, can be useful in the treatment of hyperuricemia and gout (Wang, *et al*, 2010 ; Kim, *et al*, 2010). A methanol extract of Morus alba roots showed adaptogenic activity, indicating its possible clinical utility as an antistress agent (Kawale, *et al*, 2009). *Morus alba* leaf extract help restore the vascular reactivity of diabetic rats. Free radical-induced vascular dysfunction plays a key role in the pathogenesis of vascular disease found in chronic diabetic patients (Naowaboot, 2009). An ethanolic extract of mulberry leaf had antihyperglycemic, antioxidant and antiglycation effects in chronic diabetic rats, which may suggest its use as food supplement for diabetics (Naowaboot, 2009). In the literature it has been reported as a digestive, astringent, blood purifier and anthelmintic. It is reported as antibacterial, analgesic, anti-inflammatory, antioxidant, as well as gastro protective agents. It is also reported for the treatment of bronchitis, asthma, thirst, biliousness, dysentery, ulcers, diabetes. Several studies using modern techniques have authenticated its use in diabetes and shown promising results (Brahmachari and Augusti, 1961 ; Ajit Kar, et al, 2003 ; Pepato, et al, 2005). Therefore in the present study the hypoglycemic activity of the different extracts of mulberry, *Morus alba* (L) leaves were evaluated in order to isolate the component responsible for the antidiabetic activity of the plant. Study is further carried out to evaluate the antidiabetic, hypolipidemic and hepatoprotective effect of active component (Mulberroside) from mulberry, *Morus alba* (L) leaf extracts on normal and NIDDM rats. Gtibenctamide, a commonly used hypoglycemic agent for diabetes was used as a standard drug. Results were compared with the diabetic control.

The hypoglycemic and hypolipidernic activity of leaves of mulberry, *Morus alba* (L) was studied in normal and non insulin dependent diabetes mellitus (NIDDM) rats. Diabetes was induced by streptozotocin in neonates. Administration of petroleum ether, chloroform, acetone, methanol and water extracts of *Morus alba* (L) leaves (100 mg/kg, p.o.) for 21 days caused a decrease in fasting blood sugar in diabetic rats (FBS). Among all the extracts methanol extract was found to lower the FBS significantly in diabetic rats. Glibenclamide at a dose of 5 mg/kg p.o was used for comparison. Methanol extract was subjected to column chromatography which led to the isolation of an active principle, which was given trivial name Mulberroside. The mulberroside (50 mg/kg, p.o.) caused significant reduction in fasting blood sugar in diabetic rats. Further it also caused a significant reduction in cholesterol, triglycerides, low density lipoprotein (LDL), hepatic enzymes such as aspartate-amino-transferase (AST), alanine-amino-transferase (ALT), lactate dehydrogenase (LDH) level and improvement in the level of high density lipoproteins (HDL) in diabetic rats. Reduction in the fasting blood sugar, normalization of liver enzymes level and improvement in the lipid profile by indicates that Mulberroside has cardio protective potential with antidiabetic activity and provides a scientific rationale for the use of Mulberroside as an antidiabetic agent. Efficient utilization of Mulberroside compound of mulberry, *Morus alba* (L) may open a new avenue in for the prevention and treatment of diabetes.

(I) Herbal Bioactive Compounds for the Regulation of Pancreatic Beta Cell Function: Natural products and its derived active compounds are serving a lot as achievable alternatives for the treatment of type 2 diabetes and its complications without any adverse effects. There are a huge number of active medicinal plants and its natural bioactive molecules that have already reported the therapeutic nature against diabetes (Patel, *et al* , 2012). Several medicinal plants have been used since ancient times to manage and prevent diabetes and associated conditions (Arulselvan, *et al* , 2014). Looking into the list of drugs approved within the last decades demonstrates that, plant ingredients are still of importance in drug discovery. Plant bioactive compounds have been shown to confer some protection against the pathology of diabetes mellitus through the attenuation of inflammatory mediators. This is the list of Herbal Bioactive Compounds for the Regulation of Pancreatic Beta Cell Function, considered here in this attempt of review: Berberine, Conophylline, Curcumin, Epigallocatechin-3-gallate, Genistein, Kinsenoside, Quercetin , Resveratrol and Silymarin.

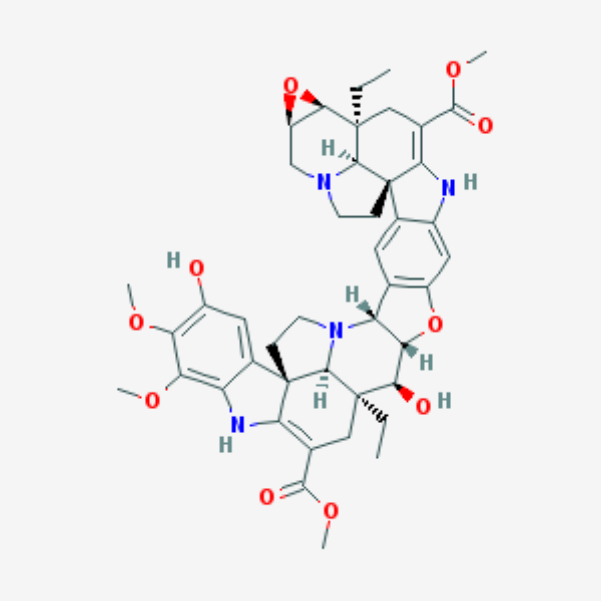
(i). Berberine :



Berberine is an isoquinoline derivative alkaloid isolated from rhizoma coptidis, which is used to treat diabetes in China (Vuddanda, *et al* , 2010). Rhizoma Coptidis is the dried rhizome of *Coptis chinensis* Franch, *Coptis deltoides* C.Y. Cheng et Hsiao, *Coptis japonica* Makino (Ranunculaceae), or other berberine-containing species of the same genus(http://apps.who.int/medicinedocs/en/d/Js2200e/13.html). The effect of berberine on insulin secretion is controversial. Chronic treatment with berberine increased insulin secretion in a dose-dependent manner (1–10 μM) in HIT-T15, MIN6, and mouse islets of Langerhans (Leng, *et al* , 2004; Zhou, *et al*, 2008). However, acute treatment with high concentrations (50 μM for 1 h) of berberine was found reducing insulin secretion (Zhou, *et al*, 2008). The reduction in the secretion of insulin in barberene treated instance might have been largely owing to the different cell types and experimental conditions used. Although controversial effects on insulin secretion *in vitro* were reported, berberine lowered hyperglycemia, improved insulin resistance, and stimulated pancreatic beta cell regeneration in type 2 diabetic animals. Feeding of db/db mice with berberine (380 mg/kg) resulted in weight loss and a significant improvement in glucose tolerance (Lee, *et al* , 2006). Daily administration of berberine for four weeks to STZ-induced diabetic rats significantly reduced oral glucose tolerance compared with that in the control group (Leng, *et al* , 2004). In a randomized, double-blind, and placebo-controlled (RDBPC) trial, decreased fasting and postprandial plasma glucose with body weight reduction were observed in type 2 diabetic patients after three months of treatment with berberine (Yin, *et al* , 2006). A meta-analysis study involving 1068 participants showed that berberine *per se* did not have a glucose-lowering effect in type 2 diabetes patients compared with metformin, glipizide, or rosiglitazone treatment (Dong, *et al* 2012).but that the combination treatment with antidiabetic agents showed improved glycemic control over that of either treatment alone (Dong, *et al* 2012). Berberine is an alkaloid extracted from various plants used in traditional Chinese medicine. Berberine is supplemented for its anti-inflammatory and anti-diabetic effects. It can also improve intestinal health and lower cholesterol. Berberine is able to reduce glucose production in the liver. Human and animal research demonstrates that 1500mg of berberine, taken in three doses of 500mg each, is equally effective as taking 1500mg of metformin or 4mg glibenclamide, two pharmaceuticals for treating type II diabetes. Effectiveness was measured by how well the drugs reduced biomarkers of type II diabetes. Berberine may also synergize with anti-depressant medication and help with body fat loss. Both of these benefits need additional evidence behind them before berberine can be recommended specifically for these reasons. Berberine's main mechanism is partly responsible for its anti-diabetic and anti-inflammatory effects. Berberine is able to activate an enzyme called Adenosine Monophosphate-Activated Protein Kinase (AMPK) while

inhibiting Protein-Tyrosine Phosphatase 1B (PTP1B). Berberine has a high potential to interact with a medications, and some interactions may be serious. Berberine is one of the few supplements in the Examine.com database with human evidence that establishes it to be as effective as pharmaceuticals (https://examine.com/supplements/berberine/).

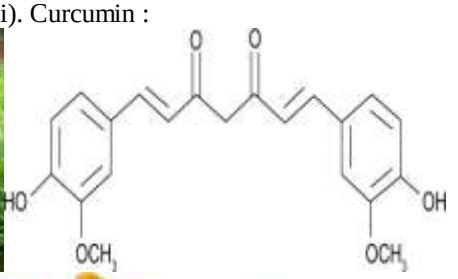
(ii). Conophylline :



The conophylline (CnP) is a vinca alkaloid extracted from the tropical plant *Tabernaemontana bufalina* (L.) and *Ervatamia microphylla* (L.) species of plant in the Apocynaceae family. *Tabernaemontana bufalina* (L.) and *Ervatamia microphylla* (L.) are found in southern China, Indochina, and western Malaysia. These plant species are known to mimic the differentiation-inducing activity of activin A (Umezawa, et al , 1996). The conophylline (CnP) was found to induce the differentiation of pancreatic progenitor cells to insulin-producing cells. Treatment of acinar carcinoma cells (AR42J) with CnP (0.1 mg/mL) induced the expression of neurogenin-3 by activation of p38 mitogen-activated protein kinase (Kawakami, *et al* , 2010), and a combination treatment of CnP (0.4 mg/mL) and betacellulin (1 nM) in ductal cells obtained from neonatal rats stimulated their differentiation into insulin-producing cells (Ogata, *et al* , 2004). Although activin A has shown effects on beta cell differentiation similar to those of CnP, it also induced apoptosis (Umezawa, *et al* , 2003). Therefore, CnP is preferred in clinical applications because of the lack of apoptosis-inducing activity. The conophylline (CnP) is effective in reversing hyperglycemia in diabetic animal models. A subcutaneous injection of 5 mg/kg CnP reduced blood glucose levels and improved glucose tolerance in neonatal STZ-induced diabetic mice. The number of insulin-positive ductal cells and the pancreatic beta cell mass increased after CnP treatment, suggesting a role for CnP in the differentiation and regeneration of pancreatic beta cells *in vivo* (Ogata, *et al* , 2004). A combination of CnP (2 μg/g) and betacellulin (200 pmol/g) administered for one week reduced glucose tolerance in neonatal STZ-induced diabetic rats (Kodera, *et al* , 2009). In addition, The conophylline (CnP) administration (9 mg/kg, orally) reduced blood glucose levels and increased plasma insulin levels

in Goto-Kakizaki rats after four weeks of treatment (Saito, *et al* , 2011). However, only little is known about conophylline rich diets and the incidence of diabetes, warranting further studies.

(iii). Curcumin :



The Curcumin is a major chemical constituent of the rhizomatous powder of *Curcuma longa* (L.), the herbaceous perennial flowering plant of the ginger family, Zingiberaceae. *Curcuma longa* (L.) is native to the Indian subcontinent and Southeast Asia, and requires temperatures between 20 and 30 °C (68 and 86 °F) and a considerable amount of annual rainfall to thrive. Plants are gathered annually for their rhizomes and propagated from some of those rhizomes in the following season. The rhizomatous powder of *Curcuma longa* (L.) is commonly used as a food product and medicine in Southern Asia (Meng, *et al* , 2013). The rhizomatous powder Curcumin showed a stimulatory effect on insulin secretion by the islets of Langerhans (Best, *et al* , 2007). The Curcumin pretreatment of pancreatic islets of Langerhans protected the islets against STZ-induced oxidative stress by scavenging of free radicals and significantly increased cell viability and insulin secretion (Meghana, *et al* , 2007). Oral administration of curcumin or the extractives of rhizome powder of *Curcuma longa* (L.) (150–300 mg/kg) significantly reduced blood glucose levels in STZ-induced diabetic rats (Hussain, et al , 2002; Na L.-X., et al , 2011). Daily intake of curcumin for 70 days along with a high-fat diet also showed a glucose-lowering effect in Sprague-Dawley rats (El-Moselhy, *et al* , 2011). Curcumin treatment for nine months in a prediabetic population resulted in increased pancreatic beta cell function with high HOMA-β (Chuengsamarn, *et al*, 2012). These data suggest that curcumin ameliorates type 2 diabetes via regulation of pancreatic beta cell function. In one of the attempt, curcumin decreased glucose levels in less than 2 weeks of treatment, lowering HbA1c levels in diabetic mice without affecting HbA1c levels in lean mice.[6] (Weisberg, *et al* , 2008). HbA1c tests show the average levels of blood sugar and are a way to gauge the control of diabetes. Here again, there were significant weight differences between curcumin-fed lean groups, diabetic/obese curcumin-fed groups, and diabetic/obese control groups as well. Curcumin was associated with less body fat and more lean mass in both the curcumin groups, and the curcumin-fed groups actually *lost* weight 2 weeks into the study (Weisberg, *et al* , 2008). The curcumin moderates the inflammation that would normally be caused by a high-fat diet, inhibiting NF-kB expression and JNK signaling. This, in turn, prevents the creation of fat cells that would normally be one of the results of systemic inflammation. Plus, curcumin has been shown to inhibit macrophage infiltration into adipocytes, which ramps up fat cell production as well.

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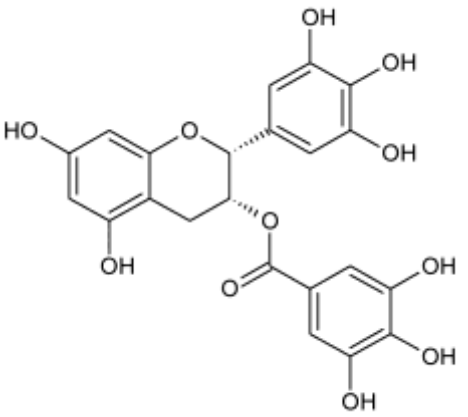
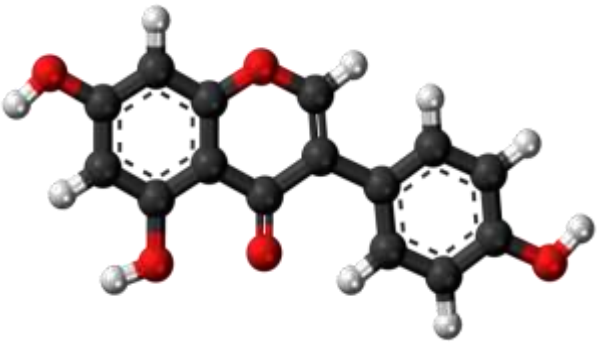


The epigallocatechin gallate (EGCG) is type of Catechin. It is also known as epigallocatechin-3-gallate. Chemically, it is the ester of epigallocatechin and gallic acid, and is a type of catechin. It is in most abundant quantity in catechin form in the tea leaves. It is a polyphenol and used in many dietary supplements. It is phytochemical constituent of green tea, *Camellia sinensis (L*). The Epigallocatechin-3-gallate (EGCG) is a polyphenolic bioactive compound found in green tea (*Camellia sinensis*). EGCG is known to be beneficial as a nutritional supplement against various diseases, including diabetes (Fu and Koo, 2006; Landis-Piwowar, *et al* , 2007). The EGCG protects against cytokine-, reactive oxygen species- (ROS-), and glucose-induced toxicity. EGCG dose-dependently protected against cytokine-induced cell death in RIN-m5F cells. This effect was mediated by the down-regulation of inducible Nitric Oxide (NO) synthase expression through the inhibition of nuclear factor-κB (NF-κB) activation (Han, 2003). EGCG also protected RIN-m5F cells against high glucose-induced impairment of insulin secretion (Cai and Lin, 2009). A diet supplemented with EGCG ingested for seven weeks was recorded to improve the oral glucose tolerance in ZDF rats and db/db mice (Wolfram, *et al* , 2006). However, contradictory results have been reported in one study: when administrated for four days (5 mg/kg/day) to STZ-induced diabetic rats, EGCG impaired insulin secretion stimulated by high glucose loading (Yun, *et al* , 2006). Similarly, it was found that treatment of HIT-T15 cells with EGCG (5–100 μM) decreased cell viability and increased apoptotic cell death concomitant with the production of hydrogen peroxide (H_2O_2) and ROS (Suh, *et al* , 2010). These results suggest that controlling the EGCG concentration is difficult under experimental conditions.

Several studies demonstrated a potential antidiabetic effect of green tea in healthy subjects but found no significant effect in diabetic patients. Tsuneki et al., for example, found that in healthy Japanese subjects acute and high doses of EGCG-concentrated green tea supplement controlled postprandial hyperglycemia, thus potentially reducing the risk for diabetes (Tsuneki, *et al* , 2004). However, in a long-term study performed by Mackenzie *et al*. (2007), no hypoglycemic effect was observed in type 2 diabetic adults who consumed green tea extract.



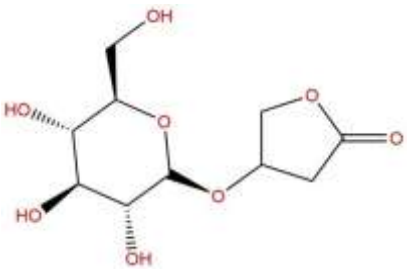
(v). Genistein

Genistein is an isoflavone that is described as an angiogenesis inhibitor and a phytoestrogen. It was first isolated in 1899 from the dyer's broom, *Genista tinctoria*; hence, the chemical name. The compound structure was established in 1926, when it was found to be identical with that of prunetol. It was chemically synthesized in 1928 *(Walter, 1941).* Isoflavones of nutritional interest are substituted derivatives of isoflavone, being related to the parent by the replacement of two or three hydrogen atoms with hydroxyl groups. The parent isoflavone is of no nutritional interest. Isoflavones such as genistein and daidzein are found in a number of plants including lupin, fava beans, soybeans, kudzu, and psoralea being the primary food source, *(Coward, et al , 1993; Kaufman, et al , 1997)* also in the medicinal plants, Flemingia vestita *(Rao and Reddy, 1991)* and F. macrophylla, *(Rao, et al , 1983 ; Wang, et al , 2012)* and coffee *(Alve, et al , 2010).* It can also be found in Maackia amurensis cell cultures (*Fedoreyev, et al , 2000).* The soybean, *Glycine max* (L.) is an important protein source. soybean Isoflavones of the soybean, *Glycine max* (L.) have been reported to prevent diabetes (Gilbert and Liu, 2013). Genistein is also major isoflavone present in *Glycine max*.It is known to have several beneficial effects in pancreatic beta cells, such as increased insulin secretion and cell proliferation and the prevention of pancreatic beta cell apoptosis. Genistein treatment increased glucose-stimulated insulin secretion in MIN6 cells and in isolated mouse and rat islets of Langerhans, *et al* (1993). However, discrepant effects on insulin secretion were observed depending on the concentrations of genistein used: high concentrations (100 μmol/L) of genistein inhibited insulin secretion in isolated rat islets of Langerhans (Persaud, *et al* , 1999). While physiological concentrations (5 μmol/L) potentiated glucose-stimulated insulin secretion in both pancreatic beta cell lines and isolated mouse islets of Langerhans (Liu, *et al* , 2006). In addition, although pancreatic beta cell proliferation reduced and apoptosis increased after treatment with high genistein concentrations, proliferation was inhibited at low genistein concentrations. Acute treatment (24 h) with a low concentration (5 μmol/L) of genistein was found induced proliferation in INS-1 cell and human islets (Sorenson, *et al* , 1994). Moreover, low doses of genistein reduced sodium fluoride-induced pancreatic beta cell apoptosis (Elliott, *et al* , 2002). The insulin-secreting activity and proliferative effects in pancreatic beta cells and mouse islets of Langerhans required the activation of protein kinase A and extracellular signal regulated kinase (ERK) (Liu, *et al* , 2006; Fu, *et al* 2010).

Soy protein containing genistein and daidzein suppressed blood glucose levels in NOD mice by increasing plasma insulin levels (Choi, *et al* 2008). Chronic consumption of a genistein-supplemented diet (250 mg/kg) prevented STZ-induced rises in fasting blood glucose and improved glucose tolerance and circulating insulin levels (Suzuma *et al* , 2007). Administration of genistein at 10 mg/kg for 10 weeks in STZ-induced diabetic mice significantly reduced fasting blood glucose levels (Yatoh, *et al* , 2007).

The effect of genistein in type 2 diabetic patients is largely unknown. However, data from a recent human study investigating the effect of genistein administration in postmenopausal women showed that genistein administration at 54 mg/day decreased fasting glucose levels and increased glucose tolerance and insulin sensitivity (Kaneto, *et al* , 2007).

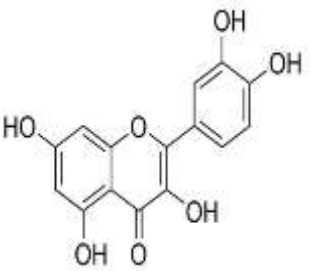
(vi). Kinsenoside:

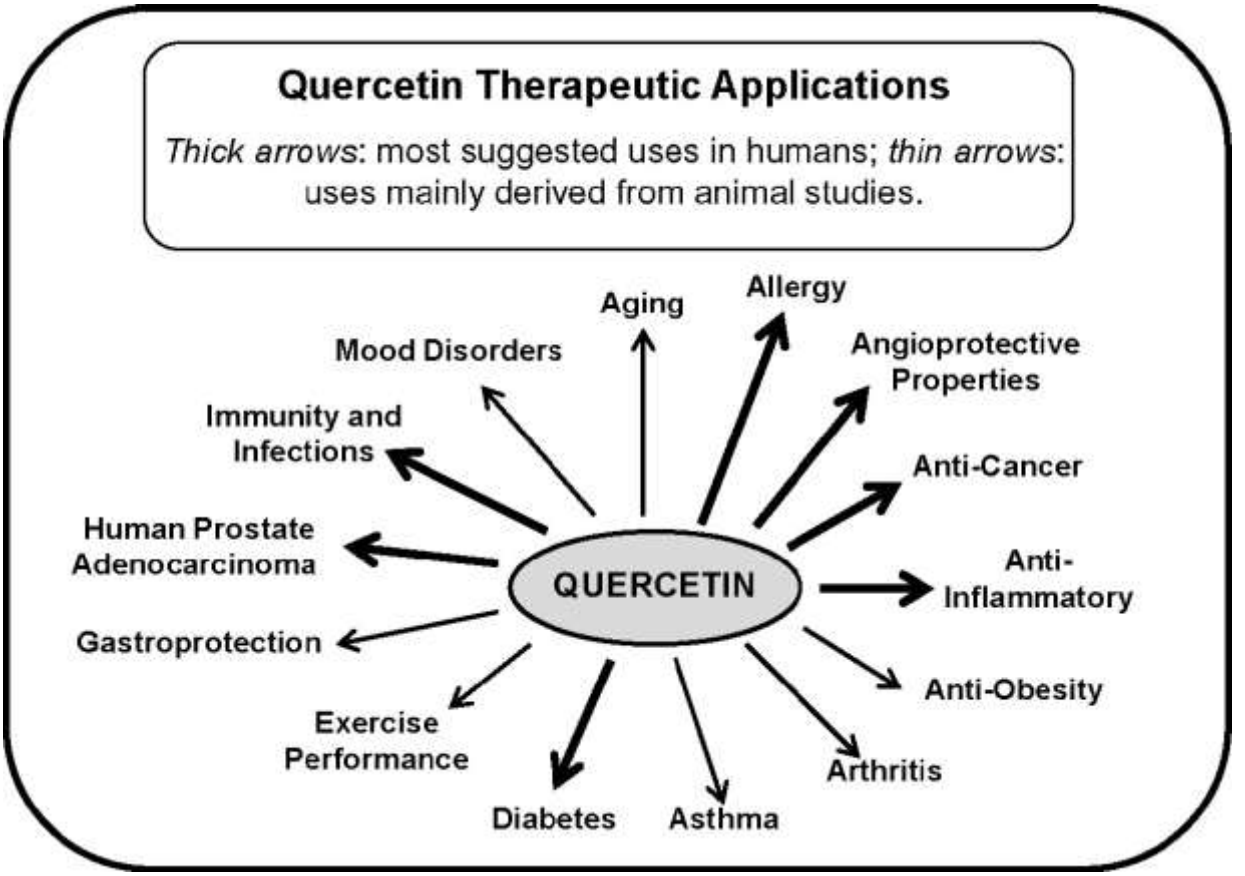


The kinsenoside is a major chemical constituent of *Anoectochilus roxburghii* (L.) (Family: Orchidaceae). *Anoectochilus roxburghii* (L.) is one of the original plants used for diabetes. Kinsenoside is isolated from *Anoectochilus roxburghii* (L.) through the use of n – butanol as solvent. Kinsenoside exhibited antihyperglycemic activity in STZ-treated rats at dose of 15 mg/kg. More intact pancreatic beta cells were observed in the islets of Langerhans in the kinsenoside-treated group, and glucose tolerance was improved in both diabetic and normal rats (Zhang, *et al* , 2007), suggesting that the hypoglycemic effect could be partially attributed to pancreatic beta cell regeneration. In view of its protective property and hypoglycemic and antioxidant activity, kinsenoside may be a promising candidate as an antidiabetic agent for humans. A variety of dosage forms of kinsenoside from *Anoectochilus roxburghii* (L.) are currently being applied to patients suffering from hyperuricemia, type 2 diabetes mellitus, chronic hepatitis B, Helicobacter pylori infection, cough-variant asthma, and other conditions. Nevertheless, further research

is needed to clarify absorption, distribution, metabolic, and excretion pathways in the animal models treated with kinsenoside from *Anoectochilus roxburghii* (L.). Moreover, the toxicology in *Anoectochilus roxburghii* also in urgent need of research, especially long-term in vivo chronic toxicity tests need to be carried out.

(vii). Quercetin(QE):





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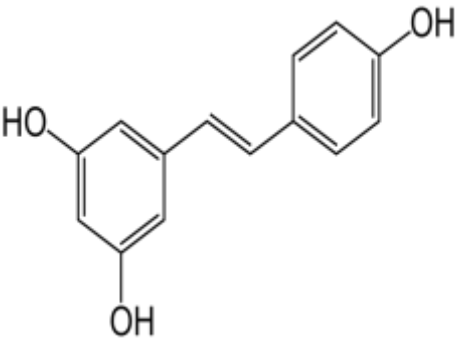
Quercetin, a herbal flavonol from the flavonoid group of polyphenols, is found in many fruits, vegetables, leaves, and grains; red onions and kale are common foods containing appreciable content of quercetin *(Fischer, et al , 1997).* Quercetin has a bitter flavor and is used as an ingredient in dietary supplements, beverages, and foods. Quercetin is a natural polyphenolic biflavonoid found in a wide variety of plants, vegetables, and fruits and displays antidiabetic properties *in vivo*. Quercetin has been shown to increase insulin secretion and protect against cell death from apoptotic stimuli. Quercetin is a polyphenol, which is a derivative of plants, and has been shown in vitro as well as in a few animal models to have several potential anti-inflammatory as well as anticarcinogenic applications. The substance has also been shown to aid in the attenuation of lipid peroxidation, platelet aggregation, and capillary permeability. However, further research is called for to gain a better understanding of how quercetin is able to provide these beneficial effects. This manuscript reviewed quercetin's anti-inflammatory properties in relation to obesity and type 2 diabetes. Quercetin treatment (20 μmol/L) potentiated insulin secretion in INS-1 cells exposed to various secretagogues such as glucose, glibenclamide, or KCl (Youl, et al , 2010) and stimulated insulin release via enhanced Ca^{2+} uptake from isolated islet of Langerhans cells (Hii , *et al* , 1985). Quercetin treatment protected pancreatic beta cells from H_2O_2-induced damage and interleukin 1β-induced nitrite production (Cho, *et al* , 2012). Coskun, *et al* (2005) carried out the experimentation on, "Quercetin, a flavonoid antioxidant, prevents and protects streptozotocin (STZ) -induced oxidative stress and beta-cell damage in rat pancreas". The aim of this attempt by Coskun, *et al* (2005) was the evaluation of possible protective influence of quercetin (QE) against beta-cell damage in experimental

streptozotocin (STZ)-induced diabetes in rats. The streptozotocin (STZ) was administered intraperitoneally at a single dose of 50 mg per kg of animal body weight. The streptozotocin (STZ) is known for diabetes induction. After confirmation of diabetes, provision of Quercetin (QE) through intraperitoneal (i.p.) injection, at the rate of 15 mg per kg body weight of experimental animal per day was made. These injections of querectin were continued for 4 weeks. It has been believed that oxidative stress plays a role in the pathogenesis of diabetes mellitus (DM). For the purpose to determine the changes of cellular antioxidant defense system, the bioassay of antioxidant enzymes such as glutathione peroxidase (GSHPx), superoxide dismutase (SOD) and catalase (CAT) activities were measured in pancreatic homogenates. Moreover this attempt of Coskun, *et al* (2005) also measured serum nitric oxide (NO) and erythrocyte and pancreatic tissue malondialdehyde (MDA) levels, a marker of lipid peroxidation, if there is an imbalance between oxidant and antioxidant status. Pancreatic beta-cells were examined by immunohistochemical methods. The streptozotocin STZ induced a significant increase lipid peroxidation, serum NO concentrations and decreased the antioxidant enzyme activity. Erythrocyte MDA, serum nitric oxide (NO) and pancreatic tissue malondialdehyde (MDA) were found significantly increased ($P < 0.05$) in diabetic group of individuals. The antioxidant level was found significantly decreased ($P < 0.05$) in diabetic group of individuals. The quercetin (QE) treatment was reported significantly decreased the elevated MDA and NO ($P < 0.05$), and also increased the antioxidant enzyme activities ($P < 0.05$). The quercetin (QE) treatment has shown protective effect possibly through decreasing lipid peroxidation, nitric oxide (NO) production and increasing antioxidant enzyme activity. Islet cells degeneration and weak insulin immune-histochemical staining was observed in streptozotocin (STZ) induced diabetic rats. Increased staining of insulin and preservation of islet cells were apparent in the quercetin (QE) -treated diabetic rats. These findings suggest that, the quercetin QE treatment has protective effect in diabetes by decreasing oxidative stress and preservation of pancreatic beta-cell integrity. Quercetin has beneficial effects in animal models of type 1 and type 2 diabetes. Quercetin (15 mg/kg) for three days induced the regeneration of pancreatic islets of Langerhans and increased insulin release in STZ-induced diabetic rats (Coskun, *et al* , 2005). Rutin (100 mg/kg), a glycosidic form of quercetin, decreased glucose levels and increased insulin levels in STZ-induced diabetic rats after 45 days of treatment (Mainzen, *et al* , 2006). It also lowered fasting and postprandial blood glucose levels in db/db mice (0.08% diet for seven weeks) (Kim, et al , 2011). In a randomized, blinded, crossover study, a single oral dose of quercetin (400 mg) effectively suppressed postprandial hyperglycemia in patients with type 2 diabetes (Brown, *et al* , 1996). Proponents of quercetin claim it can help treat a variety of human ailments including atherosclerosis, coronary heart disease, diabetes, and rheumatoid arthritis. It may also act as a performance enhancer for athletes by increasing exercise endurance.

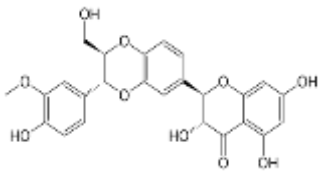
Resveratrol:



The resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) is a stilbenoid, a type of natural phenol, and a phytoalexin produced by several plants in response to injury or, when the plant is under attack by pathogens such as bacteria or fungi (*Fremont Lucie, 2000); Higdon, et al , 2016).* Sources of resveratrol in food include the skin of grapes, peanuts, pistachios, blueberries, raspberries, mulberries, cranberries, and even cocoa and dark chocolate *(Jasiński, et al , 2013).* Although it is used as a dietary supplement, there is no good evidence that consuming resveratrol affects life expectancy or human health (*Vang, et al , 2011; Sahebkar, et al , 2015).* It is a polyphenolic compound found in plants. It has anti-inflammatory, antiaging, and antidiabetic effects (Borra, *et al* , 2005). Anti-diabetic action of resveratrol has been extensively studied in animal models and in diabetic humans. In animal models with experimental diabetes, resveratrol has been demonstrated to induce beneficial effects that ameliorate diabetes. Resveratrol, among others, improves glucose homeostasis, decreases insulin resistance, protects pancreatic β-cells, improves insulin secretion and ameliorates metabolic disorders. Effects induced by resveratrol are strongly related to the capability of this compound to increase expression/activity of AMPK and SIRT1 in various tissues of diabetic subjects. Moreover, anti-oxidant and anti-inflammatory effects of resveratrol were shown to be also involved in its action in diabetic animals. Preliminary clinical trials show that resveratrol is also effective in type 2 diabetic patients. Resveratrol may, among others, improve glycemic control and decrease insulin resistance. These results show that resveratrol holds great potential to treat diabetes and would be useful to support conventional therapy (Tomasz Szkudelski and Katarzyna Szkudelska, 2015). It shows beneficial effects for the prevention of diabetes and diabetic complications, but its effect on insulin secretion *in vitro* is controversial. Resveratrol's effect on insulin secretion was found to be concentration-dependent and to depend on the cell lines and experimental design used. Although a wide range of resveratrol concentrations (3–100 μmol/L) had no effect on the insulin secretion by RIN-m5F cells (Zhang, *et al* , 2004), resveratrol (10–100 μmol/L) induced insulin secretion in other cell lines (HIT-T15 and INS-1) (Chen, *et al* , 2007). Furthermore, resveratrol treatment suppressed cytokine-induced NF-κB activation and, consequently, reduced damage to isolated rat islets of Langerhans cells (Lee, *et al* , 2009). Consistent with *in vitro* reports, the effect of resveratrol on insulin secretion differed depending on the animal model used. In normal control mice and rats, resveratrol (3 mg/kg) increased the plasma insulin levels and reduced blood glucose levels (Chen, *et al* , 2007). However, in STZ/nicotinamide-treated diabetic mice, resveratrol treatment (0.5 mg/kg) reduced the plasma insulin levels (Su, *et al* , 2006). Most studies in humans demonstrated that resveratrol improved glucose tolerance. A pilot trial in obese insulin-resistant adults showed decreased glucose tolerance after four weeks of treatment (1-2 g/day) (Crandall, *et al* , 2012). Bhatt et al. conducted a randomized trial with

type 2 diabetic subjects and found that the fasting blood glucose, HbA1c, total cholesterol, triglyceride, and low density lipoprotein concentrations were significantly reduced in the resveratrol group (250 mg/day for three months) compared with those in the control group (Bhatt, *et al* , 2012). Available literature indicate that, resveratrol is a compound exerting numerous beneficial effects in organisms. The rodent studies, for example, have demonstrated that resveratrol decreases blood glucose in animals with hyperglycemia. This effect seems to predominantly result from increased intracellular transport of glucose. Resveratrol was also demonstrated to induce effects that may contribute to the protection of β cells in diabetes. In experiments on pancreatic islets, the ability of resveratrol to reduce insulin secretion was demonstrated; this effect was confirmed in animals with hyperinsulinemia, in which resveratrol decreased blood insulin levels. Moreover, inhibition of cytokine action and attenuation of the oxidative damage of the pancreatic tissue by resveratrol were recently shown. Studies of animals with insulin resistance indicate that resveratrol may also improve insulin action. The mechanism through which resveratrol improves insulin action is complex and involves reduced adiposity, changes in gene expression, and changes in the activities of some enzymes. These data indicate that resveratrol may be useful in preventing and treating diabetes.

(viii). Silymarin:



Silymarin is a flavonoid mixture composed of silybin, silydianin, and silychristin. The silybin, silydianin, and silychristin are active components of the milk thistle plant (*Silybum marianum*) (Rui, 1991). Silymarin is antiapoptotic in cytokine-induced MIN6 cell death. Treatment with 50 μg/mL of silymarin reduced cytokine mixture-induced NF-κB-activated NO production; the effect was mediated by ERK-1 and ERK-2 phosphorylation (Kim, *et al* , 2014). It has been reported that silymarin rescued pancreatic beta cell function in diabetic animals. Soto *et al* (2004), for example, demonstrated that silymarin (150 mg/kg) rescued the expression levels of insulin and pancreatic and duodenal homeobox 1 in islets of Langerhans from alloxan-induced diabetic rats. In a pancreatectomy model, silymarin treatment (200 mg/kg) upregulated the expression level of Nkx6.1 and insulin in the pancreas, thereby increasing and decreasing the serum insulin and glucose levels, respectively (Soto, *et al* , 2014). Cotreatment of diabetic patients with insulin and silymarin (200 mg/day) reduced the blood glucose levels after three months of treatment (Jose, *et al* , 2011). A randomized double-blind clinical trial also demonstrated a beneficial effect of silymarin (200 mg/day) on hyperglycemia as shown by a significant decrease in HbA1c at four months after treatment (Huseini, *et al* , 2006).

CONCLUSION

Natural products, such as plant extractives and their bioactive compounds, are the most safe drug candidates. More attention must be paid to their potential use in the treatment and prevention of type 2 diabetes. Given a reasonable likelihood that medicinal plants with a long history of human use will

ultimately yield novel drug prototypes, systematic and intensive search in plants for new drugs to treat Type 2 diabetes mellitus seem to be of a great utility. This approach seems likely to increase the chances for discovering new drugs for the management of Type 2 diabetes mellitus. Herbal drugs individually or in combination have been recommended in various medical treatises for the cure of different diseases. It can be said that, the decrease in the fasting blood sugar level, improvement in the lipid profile and decrease in the liver enzymes level by herbal extractives and biocompounds are responsible for antidiabetic, cardio protective and hepato protective activity of the plant. Further study will give complete structure of herbal biocompounds will be a lead compound, on which structure activity relationship would be carried out, so that it could be an alternative cure for oral hypoglycemics. Given a reasonable likelihood that medicinal plants with a long history of human use will ultimately yield novel drug prototypes, systematic and intensive search in plants for new drugs to treat Type 2 diabetes mellitus seem to be of a great utility. This approach seems likely to increase the chances for discovering new drugs for the management of Type 2 diabetes mellitus.

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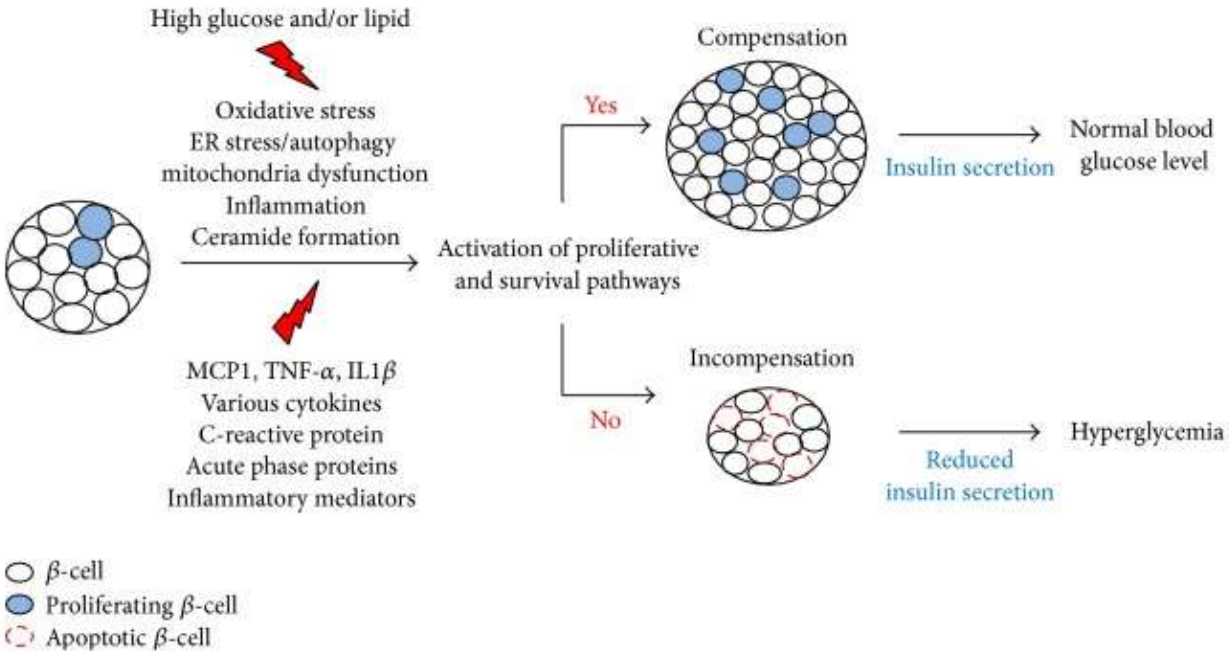

Fig. 1: Mechanisms of failure of pancreatic beta cell in type 2 diabetes. Environmental factors such as lipids (lipotoxicity), glucose (glucotoxicity), and inflammatory mediators secreted by the adipose tissue are responsible for progressive pancreatic beta cell loss in type 2 diabetes. Decompensation of pancreatic beta cell mass induces pancreatic beta cell apoptosis and decreases insulin secretion, thereby accelerating the hyperglycemic state.

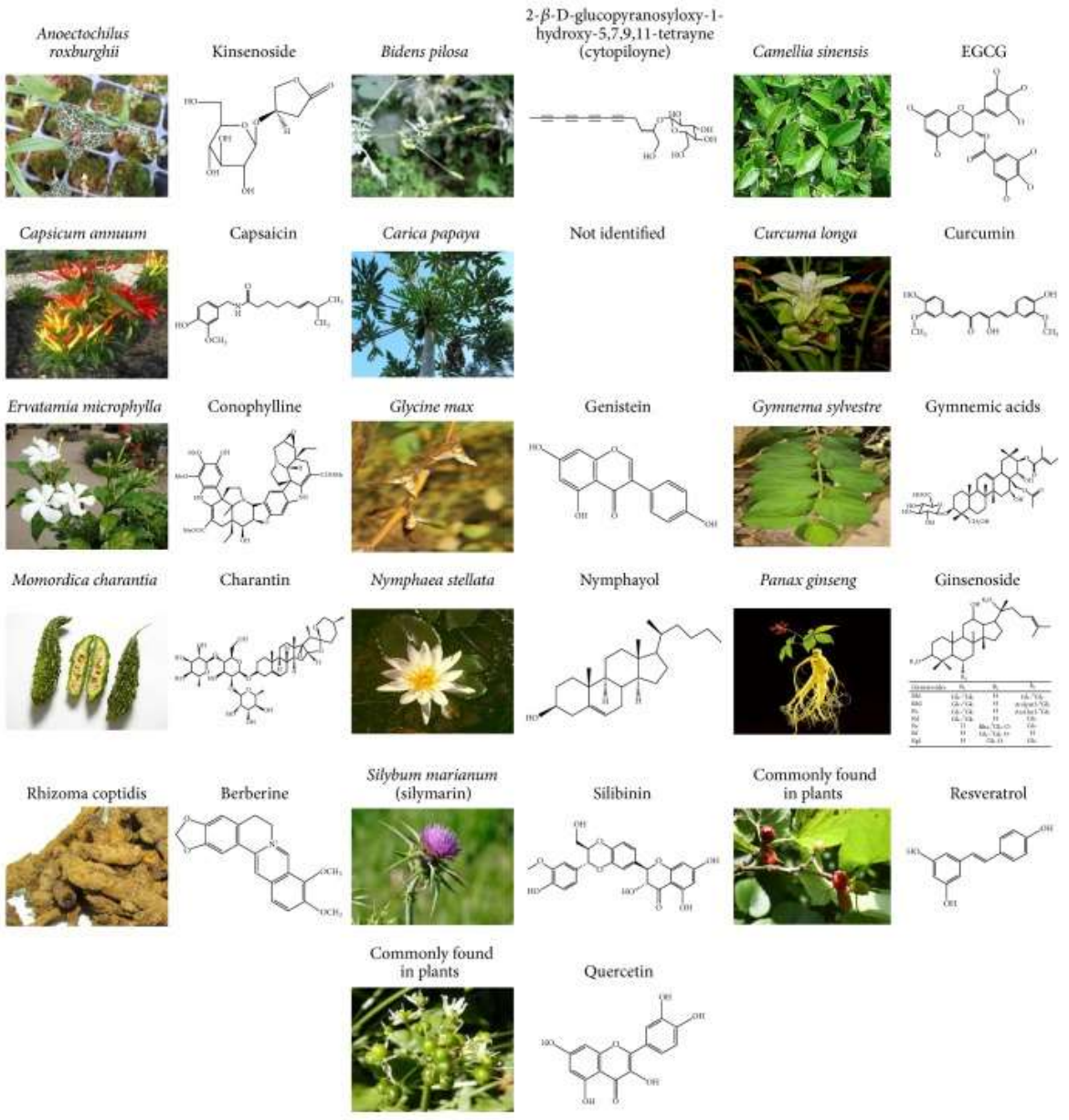

Fig. 2: Structural features of plants and bioactive compounds that affect pancreatic beta cells function and diabetes.

Table 1: Biological functions of bioactive herbal compounds with confirmed antidiabetic properties.

Serial No.	Herbal Source	Bioactive Compound	Effects of Bioactive Compound	Source Reference
1.	*Anoectochilus roxburghii* (L.)	Kinsenoside	Increase pancreatic beta cell.	Zhang, *et al* (2007).
2.	*Biden pilosa* (L.)	3-*β*-D-Glucopyranosyl-1-hydroxy-6(*E*)-tetradecene-8,10,12-triyne 2-*β*-D-Glucopyranosyloxy-1-hydroxy-5(*E*)-tridecene-7,9,11-triyne 2-*β*-D-Glucopyranosyloxy-1-hydroxy-5,7,9,11-tetrayne (cytopiloyne)	Increase and enhance insulin production and secretion of insulin.	Bartolome, *et al* (2013); Chang, *et al* (2007 and 2013); Ubillas (2000) and Lai, *et al* (2015).
3.	*Camellia sinensis* (L.)	Epigallocatechin-3-gallate	Enhances insulin secretion Inhibits pancreatic beta cell apoptosis	Fu and Koo (2006); Landis-Piwowar, *et al* (2007); Han (2003); Cai and Lin (2009); Wolfram, *et al* (2006); Yun, *et al* (2006); Suh, *et al* (2010); Tsuneki, *et al* (2004) and MacKenzie, *et al* (2007).
4.	*Capsicum annuum* (L.)	Capsaicin	Enhances insulin secretion	Islam an Choi (2008); Akiba, *et al* (2008) and Gram, *et al* (2007).
5.	*Carica papaya* (L.)	Flavonoids/alkaloids/saponin/tannins	Enhances insulin secretion	Juárez-Rojop, *et al* (2012) and Sasidharan, *et al* (2011).
6.	*Curcuma longa* (L.)	Curcumin	Enhances insulin secretion	Meng, *et al* (2013); Best, *et al*

				(2007); Meghana, *et al* (2007); Hussain (2002); Na, *et al* (2011); El-Moselhy, *et al* (2011); and Chuengsamarn, *et al* (2012).
7.	*Ervatamia microphylla* (L.)	Conophylline	Induces differentiation into insulin producing cells	Umezawa, *et al* (1996); Kawakami, *et al* (2010); Ogata, *et al* (2004); Umezawa, *et al* (2003); Ogata, *et al* (2004); Kodera, *et al* (2009) and Saito, *et al* (2012).
8.	*Glycine max* (L.)	Genistein	Enhances insulin secretion Inhibits pancreatic beta cell apoptosis	Gilbert, *et al* (2013); Ohno, *et al* (1993); Persaud, *et al* (1999); Liu, *et al* (2006); Sorenson, *et al* (1994); Elliott, *et al* (2002); Fu, *et al* (2010); Choi, *et al* (2008); Suzuma, *et al* (2007) Yatoh, *et al* (2007) and Kaneto, *et al* (2007).
9.	*Gymnema sylvestre* (L.)	Gymnemic acids	Enhances insulin secretion	Kanetkar, *et al* (2007); Persaud, *et al* (1999);

				Liu, *et al* (2009); Al-Romaiyan, *et al* (2012); Kang, *et al* (2012); Sugihara, *et al* (2000); Daisy, *et al* (2009); Al-Romaiyan, *et al* (2013); Ahmed, *et al* (2010); Baskaran, *et al* (1990); Al-Romaiyan, *et al* (2008).
10.	*Momordica charantia* (L.)	Momordicin	Increases pancreatic beta cell regeneration	Geil, *et al* (2008); Geil, *et al* (2004); Grover, *et al* (2004); Xiang, *et al* (2007); Ahmed, *et al* (2004); Bailey, *et al* (1985); Shibib, *et al* (1993); Kedar, *et al* (1982); Tongia Choi, *et al* (2004); Srivastava, *et al* (1993); Subash-Babu, *et al* (2009).
11.	*Nymphaea stellate* (L.)	Nymphayol	Enhances insulin secretion	Subash-Babu, *et al* (2009); Dhanabal, *et al* (2010); Rajagopal, *et al* (2008).
12.	*Panax ginseng* (L.)	Ginsenoside	Enhances insulin	Park, *et al* (2008);

			secretion Increases proliferation	Chen, *et al* (2012); Kim and Kim (2007); Luo, *et al* (2006); Park, *et al* (2012); Dey, *et al* (2003); Xie, *et al* (2002); Xie, *et al* (2005); Vuksan, *et al* (2000); Vuksan, *et al* (2008); And Kim, *et al* (2011).
13.	*Rhizoma coptidis* (L.)	Berberine	Enhances insulin secretion	Vuddanda, *et al* (2010); Leng, *et al* (2004); Zhou, *et al* (2008); Lee, *et al* (2006); Yin, *et al* (2008); And Dong, *et al* (2012).
14.	*Silybum marianum* (L.)	Silymarin	Inhibits pancreatic beta cell apoptosis	Rui (1991); Kim, *et al* (2014); Soto, *et al* (2004); Soto, *et al* (2014); Jose , *et al* (2011); And Huseini, *et al* (2006).
15.	Common plants	Resveratrol	Inhibits pancreatic beta	Borra, *et al* (2005);

			cell apoptosis	Zhang, *et al* (2004); Chen, *et al* (2007); Lee, *et al* (2009); Su, *et al* (2006); Crandall, *et al* (2012); And Bhatt, *et al* (2012).
16.	Common plants	Quercetin	Enhances insulin secretion Inhibits pancreatic beta cell apoptosis	Youl, *et al* (2012); Hii, *et al* (1985); Cho, *et al* (2012); Coskun, *et al* (2005); Mainzen, *et al* (2006); Kim, *et al* (2011); And Brown, *et al* (1996).