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Review Article

Antidiabetic Phytochemicals: A comprehensive Review on Opportunities and Challenges in Targeted Therapy for Herbal Drug Development

P PRABHAKAR[1]*, MAMONI BANERJEE[2]
[1,2]Bio-Research Laboratory, Rajendra Mishra School of Engineering Entrepreneurship, Indian Institute of Technology Kharagpur, Kharagpur, India
*Corressponding Author
Email ID: pawanprabhakar1@gmail.com
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ABSTRACT
The traditional system of medicine has shown much better improvement, less side effect, and less expensive as compared to modern synthetic drugs in the treatment of diabetes mellitus. Medicinal plants and phytochemicals have much importance in the present scenario in developing countries where resources are limited. The effectiveness and activity of a phytochemical depend upon its binding ability with the target molecules. Identification of the target molecule, its mechanism, and interaction with the specific phytochemical drug, can be proved to be an efficient therapeutic against diabetes. This review addressed different classes of molecules and enzymes involved in the pathogenesis of diabetes mellitus, antidiabetic activities of different classes of phytochemicals, its activity on antidiabetic drug targets, as well as possibilities of herbal drug development for diabetes in context with targeted therapy.

Keywords: Diabetes, synthetic drugs, side effects, herbal drugs, Phytochemicals, target molecules

INTRODUCTION

Diabetes is a chronic condition where the body fails to maintain the blood glucose level or blood sugar due to lack in production of sufficient insulin by the pancreas or the body is unable to use the produced insulin effectively (Canivell & Gomis, 2014). Diabetes is one of the major lethal epidemics in India as well as in the world. According to the International Diabetic Federation (South-East Asia) out of 425 million people suffering from diabetes in the world in which 82 million people are living in South East Asia and there were 72,946,400 cases of diabetes reported in India in the year 2017 (IDF, 2019). It has been estimated that the worldwide diabetic population will increase from 425 million people in 2017 to 629 million by 2045, while India alone will have 98 million diabetic patients by the end of 2030 (Cho et al., 2018; Forouhi & Wareham, 2019). Thus, diabetes becomes a serious health concern after cancer and AIDS worldwide (Giovannucci et al., 2010). Diabetes causes a series of metabolic disorders due to abnormality or defects in the secretion of insulin hormone. A prolonged or untreated diabetic condition may result in severe complications of liver and kidney. The glucose is delivered by the blood to all the parts of the body to perform necessary functions and all other physiological activities. The food is converted into glucose by the liver and goes into the bloodstream and insulin is responsible for controlling the blood glucose level. This endocrine hormone is produced by beta-cells of the pancreas. In diabetic conditions, blood glucose level remains high leads to a harmful effect on organs and systems in the body. Diabetes is divided into two categories- Type 1 Diabetes (T1DM) and Type 2 Diabetes (T2DM). Type 1 diabetes is characterized by the deficiency in the production of insulin hormone due to damage in the β-cell of the pancreas and such condition needs daily uptake of insulin. The tissues have a deficiency of glucose and there is an excess of glucose in the blood. In high blood sugar conditions, the lack of insulin leads to an accumulation of ketone bodies as the body is unable to metabolize the glucose. As a consequence, several abnormalities and other disorders occur like liver damage, hypertension, renal failure, coma, and in some cases death may occur eventually. In the low blood sugar condition, the cell is unable to get glucose resulting in unconsciousness, feeling of hunger, weakness, sweating, and coma. Death may occur if the brain does not get enough glucose(Canivell & Gomis, 2014; IDF, 2019). Type 2 diabetes is one of the major complex disorders that arise due to several lifestyle factors and genetics. Sedentary lifestyle, alcohol consumption, cigarette smoking, physical inactivity are the major lifestyle factors responsible for it. Such a lifestyle causes overweight and obesity leads to a reduction in

insulin sensitization and glucose tolerance. When beta-cells are remaining no longer to produce a sufficient amount of insulin then this would cause type 2 diabetes. Obesity and overweight also contribute to diabetes via many pathways such as increased in glucagon level, reduced adiponectin, increased leptin, increased concentration of interleukin 6, tumor necrosis factor-alpha, suppresser of cytokine signaling, suppressor of a retinal binding protein (Wellen & Hotamisligil, 2005; Yang et al., 2005). It has been reported that among all types of diabetes, 90%-95% of patients suffer from type 2 diabetes (Randle et al., 1963). Reports also state that a large number of patients suffering from type 2 diabetes are Africans, Indians, Americans, a native of Hawaiians, Latinos/Hispanics, which is a huge population comprises of 300 million people across the globe(Johnson & Olefsky, 2013). Diabetes mellitus causes long term complications that severely affect many organs in the body. Such complications results into blindness, cardiovascular diseases, stroke, reanal failure and even nerve damage (Ahmed et al., 1998). Thus, diabetes is really an epidemic to the world and considering the molecular mechanism, responsible factors, epidemiology, and available treatment in this review, we have focused on promising area of effective therapeutics that have already demonstrated their usefulness and their applicability for multiple target approach which seems promising for novel drug development.

MATERIALS AND METHOD

A progressive literature study was done using the database of several reputed publishing houses, databases, and platforms like Scopus, NIH, PubMed, Springer link, Mendeley, Google, Google Scholar, Researchgate, and Nature publications. The keywords involved in the research work were diabetes mellitus, synthetic drugs, side-effects, antidiabetic, herbal drugs, phytochemicals, toxicology, etc. Article published in the non-English language (German, French, Chinese, Portuguese) were excluded as no subject matter experts were available. Proper reprint permission was taken from the American Chemical Society to reproduce the figure. The review consists of three research work reported, diabetes mellitus, antidiabetic phytochemicals, and target molecule involved in the epidemiology of diabetes. Only evidence-based research and reviews were considered while unexplained views, ideas, beliefs of a community were not included in this review work.

Abnormalities and disorders associated with diabetes

Cardiovascular disease (Diabetic Cardiomyopathy)

In diabetic conditions, the heart is no more able to circulate the blood throughout the body that leads to heart attack, stroke, heart failure together with the accumulation of fluid in the lungs (pulmonary edema) and legs (peripheral edema). Heart failure is one of the high risks of complications in diabetes due to coronary artery diseases. It may be due to chronic hyperglycemia responsible for cardiomyopathy in patients (Miki et al., 2013). Disturbed or altered metabolic pathways result in the generation of reactive oxygen species (ROS) due to hyperlipidemia, hyperglycemia which results in creating oxidative stress causes contraction of the myocardial muscle and myocardiocyte fibrosis. Cellular DNA damage caused by oxidative stress leads to cell apoptosis (Fiorentino et al., 2013). Abnormalities in cellular Na^{+}-Ca^{2+} ion channel, causes decreased extrapolation and an increase in Ca^{2+} ions lead to an increase in intracellular concentration of Na^{+} ions which further increase in intracellular Ca^{2+} concentration in cardiac cells caused by diabetic hyperglycemia and it results into abnormalities of the cardiovascular system and heart failure (Liamis, 2014).

3.2 Renal Damage (Diabetic Nephropathy)

Adult renal failure is one of the diseases caused by diabetes mellitus. Abnormal physical status of the kidney such as tubular atrophy, interstitial fibrosis, increase in the glomerular basement membrane, hypertrophy of the kidney, nodular and diffused glomerulosclerosis cause abnormalities like systemic hypertension, subsequent proteinuria, increase in glomeration rate with intraglomerular hypertension and sometimes renal function loss (Ayodele & Alebiosu, 2004). Hyperglycemia induced hemodynamic change that causes renal damage and such change activates renin-angiotensin-aldosterone and endothelin system which enhances the secretion of profibrotic cytokines, responsible for an increase in interglomerular and systemic pressure. Due to increased blood glucose, it remains diluted in fluid, exceeds its osmotic pressure and more and more water is filtered out results in high volume in the urine. High dilution of NaCl in the urine suppresses macula densa to secrete high renin leads to vasoconstriction and inhibits renal functions (Tsavdaridis & Mironidou-Tzouveleki, 2011).

Eye Damage (Diabetic Retinopathy)

In diabetic retinopathy, retinal damage becomes the common factor for blindness. The development of soft and coarse blood capillaries in the retina is one of the major problems

associated with diabetic retinopathy. An increase in blood sugar level causes blood flow change, thickening of the basement membrane, change in blood flow to the retina, and retinal vascular permeability due to activation of protein kinase C enzyme. Advanced glycation Ends (AGEs) produced due to activation of glycation that from pericyte loss and microaneurysm causes damage to the retina (Duh et al., 2017).

3.3 Neural Disorder (Diabetes Neuropathy)

In this state of neural disorder, the blood capillaries supply blood to the nerves that are damaged. Diabetic neuropathy leads to complex abnormalities such as polyneuropathy, thoraco-abdominal neuropathy, third nerve palsy, diabetic amyotrophy, etc. Accumulation of polyols also damages nerve fibers. In the state of hypoglycemia, neuron mitochondrion produces free radical species that damage DNA and other cell membranes, inhibits the normal activity of cell and degeneration of nerve cells (Rolim et al., 2017).

Molecular Biology of Diabetes and identification of therapeutic target molecules:

By definition, a molecular entity or macromolecule whose property and function is modulated by a particular drug or chemical compound is known as 'drug target'. In a diseased condition, a drug target is crucial for proper diagnosis and treatment. Finding a drug target is the most important step in drug design and discovery. An ideal drug target must have a valid role in the pathophysiology of the disease, must not express its distribution throughout the body and must be responsive towards drug interaction(Schenone et al., 2013). If the target is known and valid, the process of drug development is highly facilitated by the rational design of a new drug molecule with high efficacy and no adverse effect. In the case of diabetes mellitus, many drug targets have been identified but it is still a big challenge to treat diabetes with high efficacy (Huggins et al., 2012). Researchers have done a lot of work to improve the work of insulin on targeted sites and also tried to identify the lead to successfully improve the secretion of insulin by pancreatic islet cells. Hence, in the last 20 years, researchers have concluded the following target molecules that can be modified by natural and synthetic drugs in diabetes mellitus(Sperling et al., 2003).

Therapeutic Targets for Type 1 Diabetes

Type 1 diabetes accounts for 5%-10% of the total diabetic population and can be characterized by the high blood sugar level and no insulin production by pancreatic β-cells. The actual cause of type I diabetes is known but certain risk factors have been identified involving autoimmunity, genetic susceptibility, and environmental factors. Type I diabetes is genetically associated with some variations of HLA (Human Leukocyte Antigen) class II alleles such as HLA-DQA1, HLA-DRB1and HLA-DQB1. Such genes are involved in the translation of proteins that distinguishes and identifies the body's protein from pathogen or invader's protein (virus and bacteria). Type 1 diabetes is an autoimmune disorder in which the bodies sometimes attack their organ and tissues. Hence, the immune system damages pancreatic β-cells for unknown reasons and secretion of insulin is inhibited and symptoms of Type I diabetes appears (Redondo et al., 2018).

Glutamic Acid Decarboxylase (GAD)

Glutamic Acid Decarboxylase (GAD) is an enzyme with a molecular weight of 65-67 KDa that works as a catalyst in the conversion of glutamate to Gamma-Immunobutyric Acid (GABA) and carbon dioxide. Two isoforms of GAD are GAD65 (MW 65 KDa) and GAD67 (MW 67 KDa). It is a neurotransmitter, expressed in the insulin-producing β-cells in the pancreas. GAD is the chief candidate in auto-antigen involved in the auto-immunity of β-cells (Ludvigsson, 2009). Menard et al (1999) reported that when non-obese diabetic (NOD) mouse was administered with GAD inhibition in disease growth was observed.

DiaPep277

Diapep277 is a new molecular drug target that belongs to the class of heat-shock proteins made up of 24 amino acid peptides having a molecular weight of 60kDa. Heat shock proteins are the family of proteins, produced by the cells, releases during stress conditions, and other external stimuli such as wound healing, cold, tissue-regeneration, UV light, etc (Morimoto, 1993). The human variant of pep277 was administered in diabetic female mice inoculated with T-cells. When T-cells were vaccinated specifically for p277 peptide; it prevented pancreatic β-cells from destruction in NOD diabetic mice for 7 months; reduction in both anti-human hsp65 and antibodies was reported. In another experiment, the administration of pep277 also prevented one-month-old mice from hyperglycemia(Dana Elias et al., 1991). When pep277 was administered to the 12, 15, and 17 weeks old mice at a dose of 50μg and after 40 days, only one of the mice was died due to hyperglycemia, it was concluded that p277 can arrest the autoimmune response (Elias & Cohen, 1994). In the human trial, it was demonstrated that diapep277 is effective in the maintenance of c-peptide production for a short

duration and reduces the need for insulin but there is a need for long term trial and follow-up data. Daipep277 was also proved to be efficient in curing patients with LADA as the destruction of β-cells takes time as compared to type I diabetes. It can be highly susceptible to the intervention in the autoimmune process so, favors its efficacy in LADA patients(Raz et al., 2001).

The therapeutic target for Type 2 diabetes:

Type 2 diabetes is also referred to as Non-Insulin Dependent Diabetes Mellitus (NIDDM) because there is no need for insulin administration externally as compared to Type 1 diabetes. As reported earlier, 90%-95% of the patients are suffering from type 2 diabetes. Type 2 diabetes can be treated by a change in diet, proper medication, and exercise (Li et al., 2010). However, despite high efficacy drugs diabetes is still a crucial challenge and researchers are continuously working in search of a safer and high potential natural and synthetic derivatives on many target molecules with the strong evaluation of the mechanism of drug action leads to concrete validation of a target molecule (Prabhakar & Doble, 2008).

α-glucosidase Inhibitors

α-glucosidase is one of the main active enzymes that have a vital role in carbohydrate absorption. α-glucosidase inhibitors are the class of enzymes that slows or retard the rate of d-glucose as a byproduct of the carbohydrates metabolism. This inhibitory action results in a postprandial reduction in blood glucose levels hence reduce the chances of hyperglycemia (Lebovitz, 1997; Kumar et al., 2011).

Peroxisome Proliferator-Activated Receptor-Gamma ($PPAR_\gamma$)

Peroxisome Proliferator-Activated Receptor-Gamma ($PPAR_\gamma$) is a nuclear receptor that is expressed in adipose and fat tissues. $PPAR_\gamma$ is responsible for regulating glucose metabolism and fatty acid storage. $PPAR_\gamma$ activates the genes that are involved in adipogenesis and lipid metabolism by adipose tissues (Rieusset et al., 1999). It has been reported that complex formation takes place when some ligand or agonist are attached to $PPAR_\gamma$ that activate it and bind with another transcriptional factor. It again binds to DNA motif specifically in promotor part of the targeted gene. A drug like glitazones activates $PPAR_\gamma$ which in turn activates sensitivity of insulin (Balasubramanyam & Mohan, 2000).

G-Protein coupled Receptor (GPR)

G-Protein coupled receptor is transmembrane receptors that identify or detect molecules at the surface of the cells. It helps in internal signal transduction and cellular responses. GPR120 belongs to rhodopsin G protein-coupled receptor groups that are preferably expressed in the intestinal epithelium and adipose tissue(Trzaskowski et al., 2012). Activation and secretion of glucagon are done by GPR120 which is responsible for the level of insulin secretion. Hence, GPR120 is found to be a potential therapeutic target for diabetes mellitus. Besides, GPR120; GPR140, and GPR119 are also suitable targets in developing drug molecules. GPR is significant in stimulating insulin secretion together with suppressing the secretion of glucagon (Milligan et al., 2014; Fredriksson et al., 2003).

Glucose Transporter Type 4 (GLUT 4)

Glucose Transporter 4 or GLUT 4 is a polypeptide made up of 509 amino acids in the cell membrane, has an efficient role in blood glucose reduction. It has a crucial role in insulin resistivity and regulates body glucose balance. It helps in the movement of glucose into the cells with a responding mechanism associated with insulin. Gene alteration or mutation in this receptor causes Type 2 diabetes. This can be a potential target for the development of antidiabetic drugs(Huang & Czech, 2007; Thunell et al., 1988).

Nuclear Factor Kappa Light Chain Enhancer of Activated B-cells (NFKB)

Nuclear Factor Kappa Light Chain Enhancer of B cells (NFKB) is a polypeptide complex that has a significant role in cytokine production, cell signal as well as the transcription of DNA. It has been demonstrated that NKFB has a significant role in the conduction of immune response. When the bovine cell line is studied, it was found that when the plasma glucose level is high, free radical species activation is generated which activates NFKB. Free Fatty Acid (FFA) and pro-inflammatory cytokines are also responsible for the activation of NFKB. Such pathways have an important role in oxidative stress (ROS) induced-insulin resistance. Such stress-induced pathways are proved to be a potential molecular target for the researchers to develop drug molecules that can inhibit the function of NFKB pathways(Benzler et al., 2016; Oeckinghaus & Ghosh, 2009).

P38 Mitogen-Activated Protein Kinase (P38MAPK)

P38 Mitogen-Activated Protein Kinase belongs to Mitogen-Activated Protein Kinase enzyme families that are susceptible to adverse and stressful conditions such as UV-irradiation, heat shock, cytokines, and osmotic shock. They have a significant role in programmed cell death and autophagy (Segalés et al., 2016). P38MAPK

genes are activated during hyperglycemic conditions. P38MAPK pathway is also responsible for several cellular mechanisms viz. cell growths, apoptosis, immunity and inflammation, and other pathways. It has been reported that activation of P38MAPK is predominant while treating insulin and hyperglycemia (Igarashi et al., 1999).

Sodium-Glucose Transporter 2 (SGLT 2)

Sodium-Glucose Transporter is the class of membrane proteins that are involved in the transport of many macromolecules such as amino acids, glucose, vitamins, ions in the membrane of intestinal epithelium as well as proximal renal tubule (Chao, 2014). SGLT2 is mainly involved in transporting 90% of glucose reabsorbed by the kidneys. Inhibition of SGLT2 leads to stopping the reabsorption of filtered glucose and thus hyperglycemia is controlled. Glycosuria formed in this process coupled with SLGT2 reduction calorie and weight. Hence, SLGT2 inhibitors can be an efficient drug molecule in the drug development process against diabetes mellitus(Gerich and Bastien, 2011).

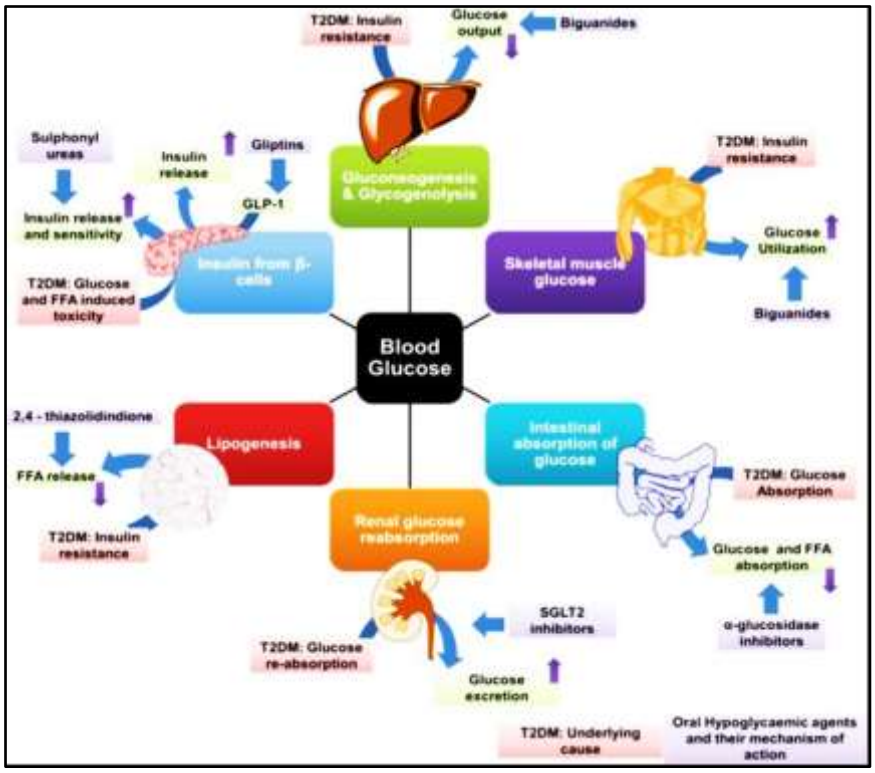

Fig.1: Pathways by which commonly prescribed oral hypoglycemic agents achieve glucose homeostasis.

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Stress Activated Protein Kinase/c-Jun NH (2) terminal Kinase (SAPK/JNK)

Stress Activated Protein Kinase/ c-Jun NH (2) terminal Kinase (SAPK/JNK) plays an essential role in the development of organs. They belong to the class of Mitogen-Activated Protein Kinase and susceptible to heat shock, UV, cytokines, osmotic shock. They are activated by hyperglycemia, free radical species, oxidative stress, cytokines, and most crucially apoptosis. SAPK-JNK pathway performs a significant pathway and direct inhibition of phosphorylation leads to insulin resistance (Hassanin et al., 2018).

Dipeptidyl Peptidase-4 (DPP4)

Dipeptidyl Peptidase-4 is a protein associated with signal transduction, apoptosis, and immune regulation. It involves in glucose metabolism and degradation of GLP-1 like incretins. GLP-1 are the peptide-1 glucagon when combined with glucose-dependent insulinotropic peptide, they stimulate the secretion of insulin and decrease the secretion of insulin and decrease the secretion of glucagon. Hence DPP-4 inhibitors are the class of drugs that can inhibit the function of incretin (Deacon et al., 2004; Mentlein, 1999).

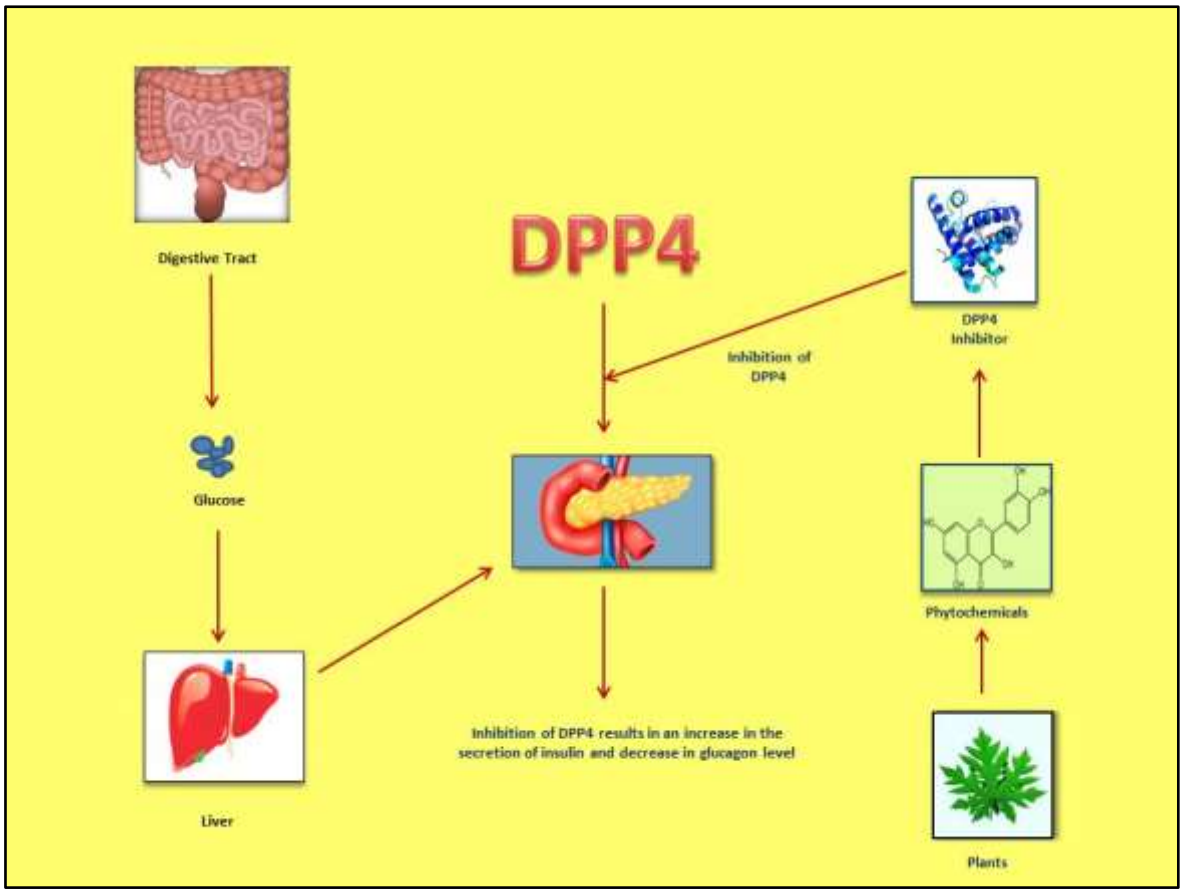

Fig.2: Inhibition of Dipeptidyl Peptidase-4 (DPP4) results in the secretion of insulin together with a decrease in glucagon level.

11β Hydroxysteroid Dehydrogenase (11β-HSD)

11β Hydroxy-Steroid Dehydrogenase (11β-HSD) is an enzyme of oxidoreductase class, responsible for the conversion of cortisone to cortisol. It is an NADP/NADPH dependent enzyme and hence a much important role in liver, CNS, and adipose tissue metabolism. The conversion of cortisone to cortisol leads to increase blood sugar levels and hyperglycemia. Hence, 11β Hydroxy-Steroid Dehydrogenase inhibitor can be a potential target in drug development for diabetes mellitus (Davani et al., 2004; Walker, 1999).

Glucose Fructose-6-Phosphatase Amidotransferase (GFAT)

Glucose Fructose-6-Phosphatase Amidotransferase (GFAT) is responsible for controlling the glucose flux into the hexosamine pathway. Synthesis of glucosamine from HBP (Hexosamine Biosynthetic Pathway) can lead to the movement of glucose into the cell. GFAT catalyzes the conversion of fructose-6-phosphate into glucosamine-6-phosphate and responsible for glucose-induced insulin resistance by the action on the hexosamine biosynthetic pathway (HBP), it can be a novel drug target for diabetes mellitus(Buse, 2006; Chou, 2004).

17β-Hydroxysteroid dehydrogenase Type 1

It belongs to the group of alcohol oxidoreductase enzyme that has a vital function in the synthesis of estrogen estradiol. It is a potential biomarker for the identification of breast cancer and diabetes. It has been reported that increase insulin resistivity. Hence, it is one of the preferred molecular targets for drug discovery (Nguyen & Le, 2012; Strong & Study, 2002).

Solute Carrier Family 16 Member 11 (SLC16A11)

Rusu et al., 2017 reported a new target molecule, Solute Carrier Family 16 Member 11 (SLC16A11) which is a monocarboxylate, proton couples transporter, and subsequent inhibition of SLCA11 changes lipid and the fatty acid metabolic mechanism that can increase the chances of Type 2 diabetes.

Role of Phytochemicals in Diabetes

Drugs available for the treatment of diabetes mellitus comprise many drugs like biguanides, sulfonylureas, α-glucosidase inhibitors, and glinides, either used alone or in the composition to get a better result. Still the side effects of drugs are the major challenges associated with it (Prabhakar & Banerjee, 2020). Drugs like

chlorpropamide, tolazamide, glibenclamide, help in reducing the glucose absorption from the intestine(Chaudhury et al., 2017). Carbohydrates that are digested fastly leads to a rapid increase in blood glucose level after a meal. Routine intakes of rapidly metabolized carbohydrate-containing diets cause hyperglycemia-induced chronic disease. Such chronic postprandial hyperglycemia results trigger the generation of free radicals leading to oxidative stress affects protein and DNA when excessive free radicals interact with it. Hyperglycemia induces glycosylation of protein, an increase in the level of lipid and plasma insulin together with the risk of cardiovascular diseases. A controlled diet is also one of the very important things to treat diabetic patients as without proper and controlled diet drugs will not work (ADA, 2003).

Phytochemicals are the chemical compounds obtained from the plant by various extraction procedures. They are considered as non-nutritive plant biomolecules having preventive properties against disease (Altemimi et al., 2017). They are generally not required by the normal function of the body. It has been reported that plant produces these phytochemicals to protect them but they can also protect human against a range of diseases (David et al., 2011). Due to the known biological activity, plant phytochemicals are one of the effective methods for the treatment of diabetes mellitus. Formulations like pancreatic tonic 180 cp, diabecon, diasulin, bitter gourd powder, chakrapani, dia-care, epinsulin, diabeta, and syndrex are effective and well known remedies available in the market(Modak et al., 2007). As per the world health organization report, about 20000 medicinal plants found in 91 countries including 12 mega biodiversities of the world located in these countries. Many extraction procedures are used from ancient days for collecting bioactive compounds in which maceration; infusion, percolation, and decoction are the important methods (Sasidharan et al., 2011). Medicinal plants are the source of therapeutics from the early days with the development of civilization on the earth. Early civilizations of Sumerian, Akkadian, Indus-valley were well aware of plant extract for the treatment of diseases. The use of the herbal plant was in practice because more and more sophisticated techniques and practices of writing text and documents were started in China, India, Egypt, and Middle East (Sofowora et al., 2013). The herbal drug used as in the form of tincture, poultices, powders, teas followed by formulations, and with the advent of new extraction techniques pure compounds were identified. Several texts and manuscripts have been written in many languages based on plant medicines and treatment procedures. By definition, according to the World Health Organisation (WHO), a medicinal plant is any plant or plant part of which one or more plant organs can be used to cure diseases. The World Health Organization has also reported that about 3.4 billion people around the globe are directly dependent on the medicinal plant which comprises 88 percent of the total world's population. Medicinally active compounds can be obtained by various extraction methods. An extraction is a method of separation of medicinally active compounds from plants or plants part by selective solvents through standard protocols and procedures (Handa et al., 2008). The plant produces both primary and secondary metabolites. Primary metabolites are produced by the plants. Metabolites are the chemical compounds synthesized by all the living organisms by their enzyme-mediated pathways so-called metabolic pathways.

Metabolites are divided into mainly two groups-primary metabolites and secondary metabolites. Primary metabolites constitute different organic compounds such as lipids, carbohydrates, and proteins and are regarded as basic compounds formed in any metabolic pathways like photosynthesis, glycolysis, Krebs's cycle, etc. Primary metabolites are essential for the growth and development of the plants whereas secondary metabolites are distributed to all the plants and have a specific function associated with that plant. Secondary metabolites do not have any direct role in plant growth and development. They play an important role in species interaction and protection in plants and are highly specific to them. Secondary metabolites are colored, flavored, and aromatic compounds having economic importance to mankind. Secondary metabolites fall into three major categories named alkaloids, phenols, and terpenoids (Hussain & EI-Anssary,2019; Ibrahim et al., 2012).

High generation of reactive oxygen species and its ineffective scavenging is one of the major roles in diabetes mellitus. Such weak antioxidant defense systems make diabetes one of the major health killers after cancer and cardiovascular diseases(Giugliano et al., 1995). Several remedies are available in the market for the prevention of diabetes including synthetic as well as herbal drugs. The big challenges related to the time taking treatment and side effects of the available synthetic drugs. Herbal medicines have been practiced for a very long time as compared to modern synthetic drugs and are always preferred. Plants are always recommended as a novel source of drugs. It has been reported that

about 800 plants have been identified that may cure diabetes(Singh, 2011). A recommendation made by the World Health Organization to evaluate the traditional plants for the treatment of diabetes considering their efficacy, non-toxic effect, less or no side effect (Modak et al., 2007). While going through the enzymes and molecules involved in the molecular mechanism of diabetes mellitus, the majority of them are acting upon rapid absorption of carbohydrates that cause an increase in the level of blood glucose. Hence, one of the important therapeutic approaches is to inhibit their carbohydrate absorption activity and keeping the postprandial plasma glucose level in control.

The efficiency of phytochemicals extracted from several plants in reducing blood glucose levels has gained a scientific validation that highlights their role in curing diabetes. Further research is essential in exploring their potential for new drug formulation development and bioactive compound from plants. It has been reported that the treatment of a patient having insulin-dependent or non-insulin-dependent with herbal formulations has shown an effective remedy but many herbal formulations used today have not gone under precise evaluation and cytotoxicities and their drug-to-drug interaction not have been assessed. In the past few years, many phytochemicals have been extracted, purified, and isolated from plants that have a remarkable effect against diabetes. Some of the important phytochemical compounds such as polyphenols, alkaloids, glycosides, amino acids, terpenoids, peptidoglycans, glycolipids, saponins and other compounds obtained from many plant sources that are reported and discussed as a potential agent for antidiabetic effect. Such phytochemicals can improve metabolic disorders by regulating them and can delay complications related to diabetes (Choudhury et al., 2018). Here, recent research reports and discussions on various classes of phytochemicals that are playing a crucial role in the treatment of diabetes mellitus are given below:

Polyphenols

Polyphenols are the secondary metabolites obtained from plants, primarily involved in protection against UV-rays and aggression by pathogens (Aryaeian et al., 2017). Poly phenols are proved to be protective against many diseases such as diabetes, cancer, osteoporosis, cardiovascular diseases, and neurodegenerative disorders. Polyphenols are categorized based on the number of phenol rings and structural elements that bind these rings to each other. Polyphenols are divided into four classes: phenolic acids, flavonoids, stilbenes, and lignans. All the polyphenols have shown an antihyperglycemic effect (Pandey & Rizvi, 2009).

Phenolic Acids

Phenolic acids are widely derived distributed polyphenols that are derived from the derivetization of benzoic acid with a peak absorbance at 280 nm C6-C1 derivative and C6-C3 derivative cinnamic acid. Important phenolic acids that are reported to be antioxidant and antidiabetic include gallic acid, salicylic acid, ferulic acid, caffeic acid, ellagic acid, protocatechuic acid, p-coumaric acid, rosamic acid and elgol (Coryet et al., 2018). The antioxidant property of phenolic acid is due to the stabilization and delocalization of unpaired electrons of the phenolic ring (Verma & Srivastav, 2020). Jain et al (2010) reported that ethanolic extract of gallic acid extracted from Paspalum scrobiculatum (Linn.) with a dose of 500mg/kg when administered to alloxan-induced diabetic rats showed a decrease in plasma glucose level from 181.67 ± 1.12 to 119.17±1.9 mg/dl on 15th day of administration. Ramesh et al, 2011 reported a significant reduction in the serum glucose, triglyceride, total cholesterol, LDL-cholesterol, VLDL cholesterol levels at a dose of 50mg/kg, and 100mg/kg (Patel & Goyal, 2011). Ramkumar et al (2014) reported that administration of gallic acid to alloxan-induced diabetic rats reduced the blood glucose level to 150 mg/dl at a dose of 20mg/kg. There was also a significant improvement in hemolysis in gallic acid administered mouse compared to glibenclamide one and a reduction in lipid peroxidation. Gallic acid is also reported to be synergistically important in drug-herb interactions leads to ti improved therapeutic effect together with reduced side effects. (Oboh et al., 2016) reported that acarbose, an antidiabetic drug together with gallic acid (75:25) have shown a mild inhibitory effect on α-amylase and a high inhibitory effect on α-glucosidase as excessive inhibition of α-amylase could result in abnormal bacterial fermentation. Rena et al, 2015 reported the antihyperglycemic activities of salicylic acid and anti-inflammatory effect by directly linked to NF-κB signaling. A recent report suggests direct activation of AMPK contributes to antihyperglycemic activities of salicylic acids with proper drug action-mechanism(Rena & Sakamoto, 2014). The synergistic effect of salicylic acid was observed when Figueroa-Pérez et al (2015) reported the enhancement of antidiabetic property of Mentha piperba was done using 2mM of salicylic acids leads to decrease in glucose level up to 25%. Furthermore,

a concentration of 0.5 and 2 mM salicylic acid-treated Mentha reduced the LDL level to 24 and 27 % respectively, and increased HDL levels upto18 and 37%, respectively. Chowdhury et al (2019) showed a single dose of ferulic acid of 50 mg/kg was administered to STZ-induced diabetic rat leads to significant hypoglycemic, antioxidant, anti-inflammatory, anti-apoptotic activities. Thus, ferulic acid has ability to ameliorate renal tissue impairment and apoptosis by inhibiting ROS generation oxidative stress-induced, signaling pathway (p38, JNK, ERK 1/2) activation, activation of NF-kB pathway and promoting autophagy as well. Matboli et al (2017) reported the effective results of caffeic acid in the treatment of diabetic nephropathy in STZ induced diabetic rats at a dose of 40 mg/kg bodyweight for 12 weeks. Significant improvement was observed in albumin excretion, reduction in renal mesangial matrix extension together with high vacuolation, and reappearance of autophagosomes that lead to conceptualize that caffeic acid is efficient in modulating autophagy pathway via inhibition of autophagy regulatory miRNAs hence proved to be protective against diabetic nephrotoxicity. The Transmission Electron Microscope (TEM) analysis has shown the presence of rare autophagic vacuoles in the tubular cells of the control and diabetic rats. There was an increased autophagy level observed in rat groups treated with caffeic acid and prophylactic caffeic acid. Subsequent increase autophagosomes and autophagolysosomes together with autophagic was observed in proximal tubular cells. In tubule, double membrane vacuoles consist of degenerating cytoplasmic organelles, electron-dense material, and mitochondria with loss of visible crista. Adedara et al (2019) reported neuroprotective, prevention in oxidative stress; control acetylcholinesterase activity leads to an improvement in pancreatic, cerebral and cerebellar structure when streptozotocin-induced type 1 diabetic rat was treated with protocatechuic acid at a dose of 50mg/kg. The structurally and functionally normal pancreatic sections are observed from control as well as the protocatechuic acid group. Pathological lesions were identified in untreated diabetic rats that showed infiltration of the acini by inflammatory cells.

Flavonoids

Flavonoids are one of the important secondary metabolites which come under polyphenols, widely distributed in the plant kingdom. They have remarkable antioxidant, anticancerous, anti-Alzheimer, and antidiabetic properties. Such compounds are classified into several phenolic compounds such as flavones, flavonols, anthocyanins, catechins etc. (Ayodele & Alebiosu, 2004; Sarian et al., 2017; Sarraf, 2017; Babaei, & Naji-Tabasi, 2019). A number of flavonoids have been reported which have shown anti-diabetic properties. Kaempferol, quercetin, naringenin, and baicalein are the flavonoids derived from Ficus racemosa (gular) that have shown hypoglycemic effect results in reducing blood glucose level from 300 to 185 mg/dL by 1-week administration in vivo models. Streptozocin induced diabetic rats were given the flavonoid extracts at a dose of 2.0 Ml/kg body weight, 1.0mL/kg body weight, 10mg/kg body weight, and 100mg/kg body weight into seven groups including normal control. Such an administration also resulted in a balanced glycogen level in the liver (Keshari et al., 2016). Wu et al (2013) and Rukmini et al (2004) reported Glabrin flavonoid from Glycyrrhiza glabra that showed a reduction in glucose level, SOD (Super Oxide Dismutase)activity of kidney and liver. In addition to this, the reduction in FBG (Fast Blood Glucose) and MDA (Malondialdehyde) was also observed which was high in diabetic cases. In SOD activity, superoxide dismutase enzyme catalyzes the dimutation of superoxides (O_2^-) radical into either or oxygen molecules or peroxides (H_2O_2). In oxygen metabolism, superoxide is produced which is regulated by several metabolic pathways to reduce its toxic effect. Cell damage occurs when a superoxide molecule is not disintegrated by these pathways. Enzymes like catalases are responsible for the metabolism of harmful peroxides produced during metabolic processes. Hence, SOD has an important role in superoxide metabolism in all living cells and tissues having interaction with oxygen molecules. Tsuda et al (2006) demonstrated that when anthocyanins a flavonoid when treated with human adipocyte cells shown a change in gene expression for adipocytokine secreted from adipocytes. Adipocyte dysfunction causes the irregular secretion of adipocytokine that is responsible for obesity as well as a reduction in insulin sensitivity. (Sarian et al (2017) reported the extraction of flavonoids in a large quantity from Tetracera indica Merr. and Tetracera scadens (L.). Isolation of T.indica leaves yield isoscutellarein and hypolectin, kaempferol, and quercetin respectively. The -glucosidase inhibitory activity was done and an IC_{50} test indicated the sample concentration needed to inhibit the activity of the α-glucosidase enzyme by linear regression analysis. Again, the inhibitory action of dipeptidyl peptidase IV enzyme was tested, responsible for insulin secretion and blood glucose level. It has been revealed that quercetin and isoquercetin

have shown high IC_{50} value of 21.75±8.81 and 22.33±1.52 μg/ml followed by hypolaetin and kaempferol at 34.89±7.44 and 45.93±8.6 μg/ml whereas wogonin, techtochysirin, 8-hyrdo-7-methoxyflavone, norwogenin and acetate showed the least activity which was less than100μg/ml. Li et al (2015) reported grape seed having proanthocyanindin flavonoids have significant role in reducing reducing FBG, HbA1C serum insulin, and systolic blood pressure. Such flavonoids are also helpful in improving kidney functions. Falvonoids like Galbridin, luteolin, eurycarpin A, licochalconetin, glabrone, 4'-7 Dihydroxyflavone, formonetin, glabrol, licoflavone, A-C liquiritigenin and glabrol were isolated from species Glycyrrhiza, family Fabacae. A significant activity was reported against alpha-glycosidase (upto 95%) at a concentration of 5 μg/mL (Z. Guo et al., 2015). Granados et al (2015) reported that isolation of flavonoids such as 5,7,4'-trihydroxy-3-5'-Dimethoxyflavone from Jatropha gossypifolia from the family Euphorbiacae shown as significant increase in glucose uptaking in C2C12 myotubes. There was also a reduction in under the curve of glucose tolerance, which was found to be 32 percent. Chakravarthy et al (1981) reported an important flavonoid epicatechin isolated from the bark of Indian medicinal plant Pterocarpus marsupium Roxb. A dose of 30mg/kg was significantly effective in protection against alloxan induced diabetic albino rats.

Another flavonoid epigallocatechin gallate isolated from Camellia sinensis of family Theaceae has been significantly effective in protecting β-cells from streptozotocin-induced diabetic rats(Gomes et al., 1995). Mezei et al (2003) reported that soy contains flavonoids like High Isoflavone (HIS) that activates $PPAR_{\gamma}$ (Peroxisome Proliferator-Activated Receptor-gamma) that is responsible for transcription of many genes involved in lipid metabolism and insulin sensitization results in a significant hypolipidemic and lowering blood glucose level. In another research report, flavonoid, hesperetin has shown lower glucose level and an improvement in glucokinase activity results in lower hepatic gluconeogenesis in diabetic rats (Jayaraman et al., 2018). Gao et al (2007) reported chebulin, chebulinic acid, and chebulagic acid were isolated from the Terminalia chebula using 70% methanol as solvent and shown inhibiting activity against α-glucosidase. It has been reported that these three compounds showed intestinal maltase inhibitory activity with IC_{50} of 670μm, 30μm, 97μm respectively. While two phenolics compound, 3-O-galloylepicatechin, and 3-O-galloycatechin was isolated from the Bergenia ciliate using 50% aqueous methanol and demonstrated significant inhibitory action against α-glucosidase activity (Bhandari et al., 2008). Minaiyan et al (2014) reported that fruits of Prunnus varicata contain phenolic compound pruning that has the potential to inhibit the activity against α-glucosidase activity. Geetha et al (1994) isolated a phenolic derivative leucodelphinidin from the bark of Ficus benghalensis and a dose of 200 mg/kg was highly effective on alloxan induced diabetic rats and was found to be hypoglycemic. In other experiment, Manickam et al (1997) reported that marsupin and pterostilbene phenolic compound from heartwood; Pterocarpus marsupium significantly helpful in reducing the blood pressure level of hyperglycemic rats. Yang et al (2017) reported that total flavonoid extract of Oxytropis falcata Bunge results in lowering of blood glucose level. (Hui et al., 2015) reported that the dried root of Radix puerariae contains isoflavone that has hypoglycemic effect and help in lipid peroxide reduction. Huang et al (2018) reported antidiabetic activity of four flavonoids-apigenin, maackiain; leachianone A and leachianone B isolated from Sophora davidi (French.) and invitro and invivo models suggested that Sophora davidi (French.) promoted GLUT4 expression and activated AMPK (Adenosine Monophosphate-activated Protein Kinase) phosphorylation in insulin target tissues of KKAy mice, leads to ameliorate insulin resistance in type 2 diabetes mellitus. Simultaneously, activation of $PPAR_{\gamma}$ and inhibiting activity of ACC (Acetyl-CoA carboxylase) was also observed.

Table 1: Antidiabetic flavonoids and their therapeutic effect

S.No	Plant Name	Phytochemicals	Therapeutic Effects	Part Used	References
1.	Ficus racemosa	Kaempferol, quercetin, naringenin, baiclain	Singnifying diabetic action, reduced blood glucose level, restored body weight	Stem bark	(Keshari et al., 2016)
2.	Glycyrrhiza glabra	Glabrin	Reduction in FBG (Fast Blood Glucose) and MDA (Melanodialdehyde),	root and stolon	(Wu et al., 2013)

			SOD (Super Oxide Dismutase) activity of kidney and liver, Reduction in glucose level		
3.	Tetracera indica Merr. and Tetracera scadens (L)	isocutellarein and hypolaetin, kaemferol and quercetin	inhibits the activity of alpha-glucosidase enzyme	leaves	(Sarian et al., 2017)
4.	Grape seed	proanthocyanindin	reducing FBG, HbA1C serum insulin, systolic blood pressure and kideney functions	seed	(Y. Li et al., 2015)
5.	Glycyrrhiza	Glabridin, luteolin, eurycarpin A, licochalaconetin, glabrone, 4'-7' dihydrooxyflavone, formonetin, glabrol, licoflavone, A-C liquiritigenin and glabrol	inhibit the activity of alpha-glucosidase enzyme	root and stolon	(Z. Guo et al., 2015)
6.	Jatropha gossypifolia	5,7,4'-trihydroxy-3-5'-dimethoxyflavone	increase in glucose upataking in C2C12 myotubes	Leaves	(Granados et al., 2015)
7.	Pterocarpus marsupium Roxb	epicatechin	Reduction in glucose level	Bark	(Chakravarthy et al., 1981)
8.	Camellia sinensis (L.) Kuntze	epigallocatechin gallate	protecting beta-cells from streptozotocin induced diabetic rats	Leaves	(Gomes et al., 1995)
9.	Soybeans	High Isoflavone (HIS)	in lipid metabolism and insulin sensitization	Seed	(Mezei et al., 2003)
10.	Prunus varicata	Prunin	inhibits the activity of alpha-glucosidase	stem	(Minaiyan et al., 2014)
11.	Garcinia kola	kolaviron	Reduction in glucose level	seed	(Iwu et al., 1990)
12.	Ficus benghalensis	Leucodelphinidin	antihypoglycemic	bark	(Geetha et al., 1994)
13.	Pterocarpus marsupium	marsupsin and pterostilbene	Reduction in glucose level	Heartwood	(Manickam et al., 1997)
14.	Oxytropis falcata	Total flavonoid	Reduction in glucose level	Bunge	(Yang et al., 2017)
15.	Radix puerariae	Total flavonoid	antihypoglycemic	root	(Hui et al., 2015)

Stilbenes

Stilbenes are polyphenols having 1, 2-Diphenylethylene nucleus, have a C6–C2–C6 carbon skeleton. They are produced by plants in response to any stress conditions (Huang et al., 2018; Panel et al., 2014). Stilbenes compound occur in many plant species including pean (Arachis hypogaea), grape wine (Vitis vinifera), sorghum (Sorghum bicolor) and Pinus and Picea species (Hammerbacher et al., 2011). Zhang et al (2019) isolated and identified one paeonilactiflorol and 14 other stilbenes compound from Peony Seeds and reported their antidiabetic properties. They showed inhibitory activities on PTP1B and α-glucosidase, superior to the monoterpenes glycosides. Compounds like

stilbenes tetramers and trimers have highly inhibiting properties against PTB1B with IC_{50} values of 27.23 and 27.81 Mm respectively and α-glucosidase with IC_{50} values of 13.57 and 14.39 μM respectively together with this two Trans-dimers were also reported to be DPPIV inhibiting activity (55.35% and 61.26%, 500 μM). Takizawa et al (2015) reported that resveratrol is one of the highly investigated stilbenes that was found too high potent in activating PPARα due to the presence of 40-hydroxyl groups having a critical role in direct activation of PPARα.

Lignans

Lignans are the polyphenols made up of C6-C3 carbon units of n-propylbenzene skeleton. They are cinnamic derived units. Entrolactone and Entradiole Secoisolariciresinaol (SDG) Diglucosided Secoisolariciresinaol (SDG) are the major lignans isolate from Linum usitatissimum (flaxseed) was reported to show antioxidant and active in controlling the generation of free radicals in diabetes mellitus (Maghsoudi, 2016). Xu et al (2008) reported that the ethanol extraction of total lignan from Fructus arctii which was given to alloxan-induced diabetic mice and rats at a dose of 2.0, 1.0, 0.5 gm /kg body weight and 1.38, 0.69, 0.35 gm/kg bodyweight for 10 days. There was a notable reduction in the blood glucose level, cholesterol, total cholesterol, and triglycerides while using glibenclamide as standard drugs. While Xu et al (2014) reported total lignin extract from Fructus arctii which showed invitro α-glucosidase inhibitory activity and promotes better hypoglycemic activity than the standard drug nateglinide, together with the release of Glucagon-Like Peptide (GLP-1) and Glucose-dependent-Insulinotropic-Polypeptide (GIP) in the GK (Goto-Kakizaki) mice. The histopathological study of pancreatic islets cells revealed that there were irregularities in structure and volume and number reduction was observed compared to normal GK (Goto-Kakizaki) mice cells. Shrunken unusual cellular changes such as coarse chromatin, mild hyperchromasia, and pyknosis were the characteristics of abnormal islets cells. Later on, treatment with Nateglinide with total lignans was able to regenerate the structure to the normal control cells.

Alkaloids

Alkaloids are the lower molecular weight nitrogenous compound derived from amino acids like tryptophan, lysine, tyrosine etc. They are a structurally diverse group of over 12, 000 cyclic nitrogen-containing compounds which are found in about 20% of plant species (Kennedy and Wightman, 2011) Alkaloids are very popular and widely used in the daily life to stay alert; caffeine and tannin are among alkaloids compounds widely used by the people (Kim et al., 2011). A number of alkaloids have been extracted that are focused to show the significant hypoglycemic properties. Tiong et al (2013) reported that four alkaloids- Four alkaloids-vindoline I, vindolidine II, vindolicine III and vindolinine IV were extracted, isolated and purified from the leaves of Catharanthus roseus (L.) G.Don and MTT Assay for cytotoxicity evaluation, ORAC Assay for antioxidant activity, and DPPH Assay for cell scavenging activity were performed and vindoline I, vindolidine II, vindolicine III have no cytotoxic activity towards pancreatic β-TC6 cells at a concentration 25μg/ml. The compound vindolidine II, vindolicine III, and vindolinine IV have high inhibition activity towards protein tyrosine phosphatase-1B (PTP-1B) proved to them to be antidiabetic compounds. In another experiment, Agrawal et al (2013) reported that alkaloids isolated from the roots of Aerva lanata Juss. and methanol extract was given at a dose of 10 and 20 mg/kg to streptozotocin-nicotinamide induced diabetic rats and a reduction in serum glucose level (>180±8mg/dl) was observed. Herbs like Berberis thunbergii, Berberis vulgaris, Berberis patiolari and Berberis aquafolium contain important alkaloid berberine that has potential antihyperglycemic activity because it inhibits the activity of α-glucosidase leads to a decrease in transport of glucose through intestinal epithelium (Pan et al., 2003). The wild variety of Tinospora cordifolia has been recognized as the potential source of berberine as reported by(Singh et al., 2003). There was a significant reduction in the level of HbA1C, total cholesterol, and triglyceride and increased the secretion of insulin in diabetic mice when they were treated with berberine at a dose of 150mg and 350 mg/kg for 12 weeks consecutively Dong et al (2016). Whereas in another experiment Lan et al, 2015 reported that when a dose of 500mg was given post-meal for 12 weeks to patients suffering from diabetes mellitus, there is a reduction in Fast Blood Glucose (FBG) level, HbA1C level and post prandial blood glucose together with significant change in lipid profile (Lan et al., 2015; Dong et al., 2016). Down-regulating the function of glucose-6-phosphate and phosphoenolpyruvate carboxykinase was observed when treated with berberine in diabetic mice (Jiang et al., 2015). Berberine is considered to be a high potential alkaloid drug having the capacity to treat cardiac dysfunction, nephropathy and endothelial dysfunction complications observed in diabetic mouse (Chang et al., 2016; Tao et al., 2017).Constantino et al, 2003, reported the isolation of three alkaloids, 5-β-

hydroxyskitanthine, boschinakine and tacomine from Tecoma stans (L.) Juss. ex Kunth has shown a significant effect on the glucose uptake rate in mice adipocytes as compared haemoglycemic mice whereas the other two alkaloids have shown no activity up to 100μm (Costantino et al., 2003). Isolation of casuarine-6-α-glucoside from the bark of Syzygium malaccense family Myrtaceae has shown inhibiting activity against α-glucosidase(B. Gaikwad, Krishna Mohan, & Rani, 2014). A new type of nortropone polyhydroxylated alkaloids of a calystegine which was isolated from the fruit of Morus alba L, family Moraceae, and the structure was found to be similar to the structure of 3-O-D-glucopyranosylcalystegine and have antidiabetic property by reducing glycosidase activity (Bourebaba et al., 2016). Seeds of Nigella gladilifera family Ranunculaceae have three norditerpenoid alkaloids, nigelladines-A-C and a parrolyquinadine alkaloid, nigellaquinomine isolated by Chen et al, 2014 and it was proved to be potent PTT1B inhibitory activity and cytotoxic to A431 cell line at a concentration of 100μm (Chenet al., 2014). An increase in glucose consumption, glycogen content, and hexokinase activity was observed when nigelladines A-C was exposed to L6 myotubes that improved metabolism (Zheng et al., 2020). Liu et al (2007) provided the information that the seeds of Nigella glandulifera have shown strong α-glycosidase inhibitory activity. SZ-A, an alkaloid found in Ramulus mori and total alkaloids are fifty percent by weight and another alkaloid, 1-deoxynojirimycin is thirty or more by weight in total alkaloid has found to be a strong α-glycosidase inhibitory activity and such treatment with SZ-A had a potential significant inhibitor of maltase as well as sucrose(Li et al., 2016). Cryptoleipine an indoloquinolone alkaloid isolated from Cryptolepis sanguinolenta helps lower glucose when administered orally to diabetic rats (Gaikwad et al., 2014). Jambosine, an important alkaloid which inhibits the diastatic conservation of starch was isolated from Syzygium cumini (L.) Skeels also is known as Eugenia jambolana (Swami et al., 2012). Zhou & Zhou (2012) reported that trigonelline an alkaloid isolated from Trigonella foenum-graecum L. fenugreek acts on β-cell generation, increases insulin secretion promotes activities of enzymes related to glucose metabolism. López et al (2004) reported that quinolizidine alkaloid isolated from the Lupinus species has a significant role in the treatment of Type II diabetes. Leaves of Murray koenigii contains carbazole alkaloid that reduces elevated fasting blood glucose, low-density lipoprotein, triglycerides and increases high density lipoprotein at a dose of 50 and 100mg/kg (Dinesh kumar et al., 2010).(Asthana & Sharrna, 1990) reported that isolation of swerchirin alkaloid from the bark of S. chirayita is significant in the stimulation of insulin as well as its enhancement in its action. Alkaloids like piperumbellactum-A to C was isolated from Piperumbellactum and a moderate inhibition of α-glucosidase was observed with IC_{50} value 98.07 ±0.44, 43.80 ±0.56 and 29.64 ±0.46 respectivey as reported by Tabopda et al (2008). Gao et al (2008) reported the isolation of two major alkaloid ascinol and vasicine by assay guided fractionantion from Justicia adhatoda. L. and showed a potential high sucrose inhibitory activity with an IC_{50} value of 125 and 250 μm respectively.

Table 2: MTT Assay of β-TC6 cell [Tiong et al (2013)]

Cytotoxicity(IC_{50})	Vindolidine	Vindoline	Vindolicine	Vindolinine
μG/mL	76.7±8.1	82.1±9.8	68.0±10.4	20.5±3.6
μM	180.1±19.0	180.1±21.5	73.5±11.3	57.6±10.7

Table 3: Antidiabetic alkaloids and their therapeutic effect

S.No	Plant Name	Phytochemicals	Therapeutic Effect	Part of the Plant	References
1.	Catharanthus roseseous	Vindolidine , Vindoline Vindolicine, Vindolinine	Lowering blood glucose level	Leaves	(Tiong et al., 2013)
2.	Aerva lanata Juss.	canthin-6-one	Reduction of serum glucose level	Root	(Agrawal et al., 2013)
3.	Berberis thunbergi	Berberine	Inhibition of α-glucosidase activity	Root, stem-bark	(Pan et al., 2003)

5.	Berberis patiolaris	Berberine	Inhibition of α-glucosidase activity	Root, stem-bark	(Pan et al., 2003)
6.	Berberis aquafolium	Berberine	Inhibition of α-glucosidase activity	Root, stem-bark	(Pan et al., 2003)
7.	Tinospora cordifolia	Berberine	Inhibition of α-glucosidase activity	Root and stem	(Singh et al., 2003)
8.	Morus alba L.	calystegine	Inhibition of the α-glucosidase activity	Fruit	(Bourebaba et al., 2016)
9.	Nigella gladilifera	nigelladines-A-C parrolyquinadine	PTT1B inhibitory activity and cytotoxic to A431 cell line	Seed	(Liu et al., 2007)
10.	Ramulus Mori	SZ-A 1-deoxynojirimycin	α-glycosidase inhibitory activity	Root and stem	(M. Li et al., 2016)
13.	Cryptolepis sanguinolenta	cryptoleipine	helpful in lowering glucose	Root	(J. Luo et al., 1998)
14.	Lupinus arcticus	quinolizidine	Stimulate insulin secretion		(López et al., 2004)
15.	Murraya koenigii	carbazole	reduces elevated fasting blood glucose, low-density lipoprotein, triglycerides and increases high-density lipoprotein	Leaves	(Dineshkumar et al., 2010)
16.	Swertia chirayita	swerchirin	inhibition of α-glucosidase activity	Bark	(Kar et al., 2003)

Terpenoids

Terpenes are the largest class of phytochemicals produced by a number of floral families. Terpenes are oxidized or reduced to a specific chemical compound known as Terpenoids. Terpenes are synthesized by polymerization of their monomer known as isoperene having formula (C_5H_8). Terpenes have a basic formula $(C_5H_8)_n$ where n is the number of repeating units and consists of dreivatives like polyterpenes, tertraterpenes, triterpenes, sesterpenes, diterpenes, monoterpenes, hemiterpenes(Putta et al., 2016). Li et al, 2013 reported that a large number of terpenoids like oleanolic acid, ursolic acid acid, botulin, glycyrrhizin, glycyrrhetinic acid, betulinic acid, and lupeol were extracted from a number of plant species like Glycyrrhiza sp., Centella asiatica, Camellia sinensis, crataegus sp. and olea europaea. Such phytochemicals fall under sub-category of triterpenoids and they have a significant role in treating diabetic vascular abnormalities, neuropathy, retinopathy via a number of biological processes like glucose absorption, glucose uptake and insulin secretion (Alqahtani et al., 2013). Terpenoids like cycloartane, dammarane and protostane having a significant role in reducing blood glucose level, were isolated from Astragalus membranaceus, Gynostemma pentaphyllum, Panax quinquefolium, Panax notoginseng as reported by Alqahtani et al (2013). Lai et al (2012) reported the isolation of terpenoid 2-3-seco-2-O-(29)lapene-2,3 dioic acid from the twigs and leaf of Fagus hayate, family fagacae that acts as an inhibitor of α-glucosidase of Bacillus stearothermophillus bacterial species with a cytotoxic IC_{50} of 62.1μm. While Uddin et al (2012) demonstrated that triperpene dammarane, pistagrenine acid isolated from Pistia stratiotes family anarcadacae showed a significant inhibition of α-glycosidase activity. Twelve triterpenoids saponins were isolated from the plant Aralia chinensis and their antidiabetic effect was demonstrated by inhibition of lipid

peroxidation in rat liver as well as the evaluation of its inhibitory effect was done by haemoglobin-δ-gluconolactone(δ-glue) assay, N-acetyl-glycyl-lysine methyl ester-ribose assay and bovine-serum albumin assay (BSA) glucose assay(Xi et al., 2010). Terpenes like astragalosides isolated from Astragalus radix which can alter the bond formation between reducing sugars and amino acids hence reducing Advanced Glycation End Products (AGES) like carboxyl methyl lysine results in inhibiting protein-glycation process(Motomura et al., 2009). In another experiment Kuang et al (2011) reported that euscaphic acid and p-counaroylursolic acid were isolated from the root of Sanguisorba tenufolia family Rosaceace showed inhibitory effect on α-glucosidase activity with IC_{50} value of 0.67 and 0.62 Mm. Guo et al (2015) reported some new terpenoids like 3-O-olean-11,13 [18]-diene 23, 28-dioic acid was isolated from and Anoectochilus elwesii plant that acts on insulin resistant human HepG2 cells leads to a reduction in glucose uptake activity Triterpenoids isolated from Agrimonia pilosa Ladeb showed a significant sensitization of insulin through activating $PPAR_{\gamma}$ and downstream controlled genes. Curcuma longa, family zinzberaccae was used to isolate a tricyclic diterpenoids, tetraterpenoids from the leaves which showed antidiabetic activity and oxidative stress(Motomura et al., 2009).

Fibres

Fibres are the complex food derived from plants that cannot be broken into simpler parts by digestive enzymes. Fibre improves intestinal digestive efficiency, cholesterol reduction, and an increase in microbial mass. Chemically, dietary fibre is a complex carbohydrate and lignin group of vegetable origin that supports laxation and decrease fasting blood glucose level. The diet contains a high amount of mono, disaccharides, and fat increases higher chances of diabetes as compared to diet having high fibre content (Gittelsohn et al., 1998). (Chau et al (2003) reported that dietary fibre which is water-soluble as well as alcohol soluble obtained from the peel of Citrus sinesis, family Rutaceae showed a reduction in glucose diffusion and inhibition of α-amylase. McKeown et al (2002) reported that intake of dietary fibre with daily diet maintains the BMI (Body Mass Index), total cholesterol, WHR (Waist-to-Hip Ratio) and fasting insulin level. He also concluded that an increase in insulin sensitivity reduces the chances of diabetes. It may due to the intake of whole-grain cereals and dietary fibres. There is a reduction in fasting insulin level by 2.9 % by the intake of dietary fibres by 7gm/day as reported by Botnia Dietary (Ylönen et al., 2003).

Polysaccharides

Polysaccharides are the complex macromolecules and long polymer chain of monosaccharides that are linked by glycosidic bonds. Plant cellulose, starch, glycogen are major classes of polysaccharides. They have the general formula $Cx\ (H_{20})y$ composed of long-chain units of monosaccharides $(CH_2O)_n$, where n is the number of repeating units. Glucose, fructose, galactose, mannose, arabinose, rhamnose, and xylose are important monosaccharides (Zong et al., 2012). Kumar Bhateja & Singh, (2014) reported an antidiabetic property of aqueous extract of Acacia tortilis gum exudates. Aconintans A, B, C, and D, the four glycans were isolated from the roots of Aconitum carmichaeli, family Ranunculacae showed an antihperglycemic activity in alloxan-induced diabetic mice (Gray & Flatt, 1997). Six glycan molecules named saccharans A, B, C, D, E, and F were extracted from the stalk of Saccharum Officinarum, family Poaceae exhibited a prominent reduction in the blood glucose level in alloxan-induced hyperglycemic mice(Hikino et al., 1985). Polysaccharide isolated from corn silk was found to be hypoglycemic and hypolipidemic in streptozotocin-induced hyperglycemic mice. Such polysaccharides were also effective in reducing blood glucose levels, total glycogen, and serum total cholesterol in diabetic mice (Zhao et al., 2012).

Glycosides

Glycosides are the macromolecules and acetal derivatives forms when a monosaccharide reacts with alcohol. The bond results due to such linkage known as a glycosidic bond. Previous research work has been proven that glycosides have high potential in curing diabetes mellitus. Vennekens et al, 2017 reported a new type of glycosides, stevioside and rebandioside A which was isolated from Stevia rebanundiana showed decrease in plasma glucose level in the hyperglycemic wild rat by improvement in the secretion of glucose-induced insulin by TRPM5 (Transient Receptor Potential cation channel subfamily M member 5) channel(Philippaert et al., 2017). Liu & Li (2016) reported that new phenolic glycosides- 4-acyl-2, 6-dimethoxyphenol glucoside (6), and lipariglycoside K-O (1-5) was isolated from Liparis odorta was identified as an inhibitor of PTP1B (Protein Tyrosine Phosphatase 1B) and α-glucosidase. Vitexin, 3-O-β-D rutinoside, and isovitexin were glycosides isolated from the leaves of Microcos pinaculata, family tilicae, and were

observed to exhibit inhibitory activity against α-glucosidase (Chen et al., 2013).

Besides these organic compounds, inorganic compounds have also a vital role in the treatment of diabetes mellitus. Such inorganic compounds are highly efficient in intervening in the mechanism of diabetes mellitus and inhibiting the enzymatic activity associated with it. High manganese content leaves of Medicago sativa, family Fabaceae was found to be highly effective in IDDM (Insulin Dependent Diabetes Mellitus) patients and it has also been reported that manganese is an important factor in phosphorylation of insulin receptor (Luo et al., 1998). Sulfur-containing the amino acid, S-allyl cysteine sulphoxide, allicin obtained from Allium sativum is highly efficient in reducing blood glucose level in diabetic mice (Yatsunami et al., 2003).

DISCUSSION

Diabetes mellitus is recognized as the most common chronic metabolic disorder causes high morbidity and mortality. There is no such concrete and an efficient method is developed so far to cure it. Unhealthy lifestyle, unbalanced BMI (Body Mass Index), less physical work, consumption of high calorific value diet, smoking, alcoholism, some genetic and environmental factor are the main causes of diabetes. From decades strategies are made to lower the glucose level and the drug was designed to stimulate the secretion of insulin as well as insulin controlled glucose uptake by the tissues. But they are facing the problem of side effects and serious complications. This review reveals that several molecules are involved in the molecular mechanism of diabetes. Inhibition or affecting their activity may result in lowering blood glucose levels or reduce the complexities associated with diabetes. Synthetics drugs can reduce such complexities but they are facing the problems of lethal adverse effects. Hence, due to side effects patients stops taking these medicines. Herbal drugs containing antidiabetic phytochemicals are much efficient in the treatment of diabetes mellitus. It has been successfully demonstrated that synthetic drugs when incorporated with herbal drugs have a better therapeutic result with fewer side effects (also called synergism). Research reports have suggested that phytochemicals are much capable of working on specific targets by inhibiting their activities, like α-amylase, α-glucosidase, and Dipeptidyl Peptidase-4 (DPP4). Unfortunately, most of the in-vitro and invivo studies have shown their activities on only a few enzymes and molecules as the majority of target molecules are involved in diabetes mellitus and are still not considered for testing phytochemical activities. These enzymes are well known for their role in increasing blood glucose levels and insulin resistivity. There must be ongoing necessities to find more effective drugs that have multiple targets with much fewer side effects as the single-target drug has shown limited therapeutic effects. As phytochemicals have very much side effects with the promise of better therapeutic activities there is a need for continuous focus on the determination of their activities and mechanism of action on available multiple targets.

CONCLUSION

Medicinal plants and phytochemicals have much importance in the present scenario in developing countries where resources are limited. So far in this review, it has been demonstrated that phytochemicals are highly efficient in the treatment of diabetes mellitus by acting on their specific targets. Regular uptake of herbal medicines containing these phytochemicals can be beneficial in reducing blood glucose levels and other complications. Such complications are promoted by the majority of enzymes and molecules. Hence, there is a need for some additional pathway or multi-targeted approach that can be used to overcome the risk of renal, eye, cardiovascular complexities. Phytochemicals have therapeutic potential to bind with the specific target but their activities have been determined on a limited number of enzymes and molecules. Identifying the potential multidrug target is crucial to drug development and identification of phytochemicals mechanism towards multi-target molecules can be a matter of huge research and provide a landmark in achieving efficient therapeutic against diabetes without causing any side effects.

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