

## Chalcones in the Therapeutics of Diabetes Mellitus

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**Abstract:** Diabetes mellitus is a metabolic disorder which affects the wide range of the population worldwide. Most of the pharmacotherapeutic agents available today might provide the symptomatic relief, but do not cure the disease completely. Further their limitations make the researcher look forward to the newer and the safer pharmacotherapeutic agents. Aim of the present work is to describe the role of the chalcones in the treatment of diabetes mellitus. Information regarding the chalcones was collected from the various site such as PubMed, Google, google scholars and science direct. It has been concluded that the chalcones have the key potential due to their structural property that might exert the beneficial effects of diabetes and the associated pathological conditions.

**Keywords:** Diabetes, chalcones, flavonoids, glucose, insulin, hyperglycemia.

### INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterised by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is correlated with long-term damage, dysfunction, and failure of various organs, particularly the eyes, kidneys, nerves, heart, and blood vessels. It is reported that the common cause of DM is the ineffective production and utilization of insulin in the body which is further responsible for the rise in blood glucose levels and different metabolic abnormalities seen in the patients of DM. Thus, the degree of hyperglycemia reflects the severity of the underlying metabolic process.

DM is characterized by the presence of various symptoms including polyuria, polydipsia, weight loss and blurred vision. Long-term complications of DM include retinopathy, gastrointestinal, genitourinary and cardiovascular dysfunction [1].

Type-1 DM is also known as insulin-dependent DM (IDDM) or childhood-onset DM. It is an autoimmune disease characterized by the destruction of pancreatic  $\beta$  cells [2]. Type 1 diabetogenesis, consisting of sequential steps: (1) Genetic predisposition; (2) initiation of immune response or trigger; (3) autoimmunity; (4) beta cell destruction; and (5) clinical diabetes [3]. However, it remains unclear why the autoimmunity in Type-1 Diabetes mellitus is specific to insulin-producing  $\beta$  cells [2]. Type-2 DM is also known as non-insulin-dependent DM (NIDM) or adult onset DM because the body cannot effectively utilize the insulin so produced. T2DM is thus characterized by the presence of insulin resistance [4]. It has been reported that  $\beta$ -cells of the pancreas have very low levels of antioxidant enzymes and therefore they are particularly at risk of oxidative stress. Once glucose enters the cells, it is primarily and progressively metabolized to glyceraldehyde-3-phosphate, 1:3 bis-P-glycerate,

glyceraldehyde-3-phosphate, and pyruvate. Pyruvate then enters tricarboxylic acid (TCA) cycle to undergo oxidative phosphorylation, during which formation of adenosine triphosphate (ATP) and reactive oxygen species (ROS) occurs. So, the excess glucose led to the formation of increased ROS and increased the formation of ROS has been implicated in the insulin resistance seen in the NIDM [5].

### Factors responsible for the development of Hyperglycemia

Factors which are responsible for hyperglycemia include [6].

- Reduced insulin secretion from pancreatic  $\beta$ -cells
- Elevated glucagon secretion from pancreatic  $\alpha$  cells
- Increased production of glucose in the liver
- Neurotransmitter dysfunction and insulin resistance in the brain
- Enhanced lipolysis
- Increased renal glucose reabsorption
- Reduced incretin effect in the small intestine
- Impaired or diminished glucose uptake in peripheral tissues such as skeletal muscle, liver, and adipose tissue.

Whenever somebody takes the meal, there is a rise in blood glucose level that stimulates insulin secretion resulting in an increase in transportation, biotransformation and storage in muscles and fat tissues. In fasting conditions, glucose in the blood is provided by the liver that is used by the brain, without any dependency on insulin. Besides the storage of glucose, insulin also inhibits the secretion of glucagon and lowers the concentration of serum fatty acids leading to a decline in liver glucose production. Insufficient insulin or resistance to insulin in the body results in reduced tissue uptake of glucose that results in intracellular hypoglycemia and extracellular hyperglycemia. The intracellular hypoglycemia causes gluconeogenesis and glycogenesis that leads to fats breakdown and decreases protein synthesis and gamma globulins (causing cachexia, polyphagia, and impaired wound healing), while the extracellular hyperglycemia results in the oxidative stress which further produces stress damage to various body cells [7].

#### Different categories of the agents used for the treatment of Type-2 Diabetes mellitus

The major classes of oral antidiabetic medications include:

- **Biguanide-** Metformin is the first-line oral drug used in the treatment of T2DM. Metformin activates adenosine monophosphate-activated protein kinase (AMPK) in the liver, causing hepatic uptake of glucose and inhibiting gluconeogenesis, e.g. metformin [6, 8].
- **Sulfonylureas-** Sulfonylureas lower blood glucose level by increasing the insulin secretion from the pancreas by blocking  $K_{ATP}$  channels. They also limit gluconeogenesis, decrease the breakdown of lipids to fatty acids and reduce clearance of insulin [6, 8].
- **Meglitinide-** Meglitinide also binds to the sulfonylurea receptor present on the  $\beta$ -cells of the pancreas. However, the binding of meglitinide to the receptor is weaker than sulfonylurea, and thus recognised as short-acting insulin secretagogues, which gives flexibility in its administration. Also, a raised blood sugar level is required before it can stimulate  $\beta$ -cells, resulting in the insulin secretion, making it less effective than sulfonylureas. Drugs commonly used are repaglinide, nateglinide [6, 8].
- **$\alpha$ -Glucosidase inhibitors (AGIs)-** These drugs inhibit the enzyme  $\alpha$ -glucosidase responsible for the breakdown of complex carbohydrates into the simpler units which are further absorbed into the blood circulation accountable for the rise in the blood glucose levels. Drugs commonly used are acarbose, miglitol, voglibose [8].

- **Thiazolidinediones (TZDs)-** TZDs act as an agonist at peroxisome proliferator-activated receptors (PPAR receptor) and facilitate increased glucose uptake in numerous tissues including adipose, muscle, and liver. Mechanism of action includes diminution of free fatty acid accumulation, reduction in inflammatory cytokines, rising adiponectin levels, and preservation of  $\beta$ -cell integrity and function, all leading to improvement of insulin resistance and  $\beta$ -cell exhaustion. Drugs commonly used are rosiglitazone, pioglitazone [6, 8].
- **Incretin Mimetics-** They are insulinotropic agents, stimulates the release of insulin in response to the entry of food into the small intestine. These include a glucose-dependent insulinotropic polypeptide (GIP, or incretin) and glucagon-like peptide (GLP-1). However, these peptides have a short half-life, as these are rapidly hydrolyzed by DPP-4. It is reported that the incretin effect is reduced or absent in patients of T2DM [6, 8].
- **Dipeptidyl peptidase 4 (DPP-4) inhibitors-** Dipeptidyl peptidase 4 inhibitors inhibit hydrolysis of the Glucagon-like peptide (GLP) and Gastric inhibitory polypeptide (GIP) and increased their plasma half-life. The gliptins have not been reported to create the higher incidence of hypoglycemic events compared with controls. In diabetic patients with coronary heart disease, that treatment with sitagliptin improved cardiac function, and coronary artery perfusion [6, 8] further suggested their advantage increased under the burden and worry underdiagnosis of diabetes mellitus.

#### Problems associated with the current therapy

DM is characterized by the rise in the blood glucose levels and pancreas release the insulin, which lowers the blood glucose levels and the failure of release and the action of insulin is responsible for the development of persistent hyperglycemia which is seen in the patients of Diabetes mellitus (DM). Oral hypoglycemic agents generally stimulate the failing pancreas to release more insulin which does not make correct sense actually [9]. Because of the failure of the pancreas to release insulin is one of the main causes of DM further if any drug stimulated the failed pancreas to produce insulin, it evolves more damage. Metformin monotherapy is not normally accompanied by hypoglycemia, interferes with vitamin B<sub>12</sub> absorption and cannot be used in the patients of renal dysfunction because its use may increase the risk of lactic acidosis that might cause potentially fatal complication. The major problem associated with sulphonylureas is hypoglycemia, which can be life-threatening. Alpha-glucosidase inhibitors (AGIs) are less effective in lowering glycemia than metformin or the sulphonylureas.

AGIs results in the increased delivery of carbohydrate to the colon commonly result in increased gas production and gastrointestinal symptoms, and therefore in clinical trials, 25-45% of participants have discontinued  $\alpha$ -glucosidase inhibitor use. TZDs results in the weight gain and fluid retention, responsible for twofold increased risk for congestive heart failure. Further TZD, e.g. rosiglitazone increased the risk of myocardial infarction. TZDs increase the incidence of fractures. Exenatide increased the frequency of gastrointestinal disturbances, with 30-45% of treated patients experiencing one or more episodes of nausea, vomiting or diarrhea [10]. Current drugs for diabetes, in which treatment strategies focus on insulin replacement therapy (type 1) and reducing insulin resistance (type 2), do not directly target the underlying pathophysiology of the loss of  $\beta$ -cells [11]. Further, the prolonged exposure to sulphonylureas has been associated with  $\beta$  cell exhaustion, desensitization and possibly expedition of oxidative stress and apoptosis, causing a progressive reduction of insulin production capacity and deterioration of glycemic control over time [12, 13].

### Chalcones

Chalcones are also known as benzyl acetophenone or benzylidene acetophenone. In chalcones, two aromatic rings are joined together by an aliphatic three carbon chain. Chalcones (trans-1, 3-diaryl-2-propen-1-ones) are  $\alpha$ ,  $\beta$ -unsaturated ketones consisting of two aromatic rings (ring A and B) having a diverse array of substituents. Rings are interconnected by an extremely electrophonic three carbon  $\alpha$ ,  $\beta$ -unsaturated carbonyl system that pretends a linear or nearly planar structure [14-16]. They contain ketoethylenic group ( $-\text{CO}-\text{CH}=\text{CH}-$ ). Chalcones contains conjugated double bonds and a completely delocalized  $\pi$ -electron system on both benzene rings. Chalcones have been used as an intermediate for the preparations of compounds having therapeutic value [17-19]. Chalcones have been recognised as interesting compounds that are correlated with several biological activities. The most common chalcones found in foods are phloretin and its glucoside phloridzin (phloretin 2'-O- $\beta$ -glucopyranoside), and chalconaringenin. From plants, stable chalcone moiety can't be isolated because of the presence of enzyme chalcone synthetase (CSH) which immediately converts chalcone into flavanone. The structure of the parent molecule of chalcones consists of two phenyl rings (A and B) and one  $\alpha$ ,  $\beta$  unsaturated double bond. The ring A must contain an electron deficient moiety like ethyl, methyl or alkyl groups for better activity. The ring B must contain the hydrophobic groups like halogens, nitro and cyano for the better activity. The unsaturated double bond plays an important role in the activity, but marginal modifications in this bond don't have much effect on the activity. Para position of the ring B is important for the activity. The ortho position of ring B also enhances the activity, but in comparison with the para position, it is

low. 3D QSAR and in-house QSPR studies of chalcones have proved all these facts [20].

### History of chalcone discovery

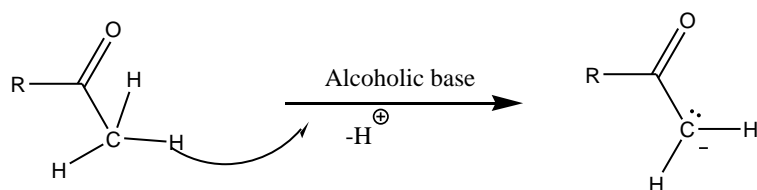
Chalcones are natural compounds that are widely distributed in plants, fruits, and vegetables. The first aldol condensation product was reported by Kostanecki, and he gave the name "Chalcones" or 1,3-diaryl-2-propen-1-ones. They belong to the flavonoid group of molecules, and some of them display numerous biological activities. Chalcones are the precursors in the biosynthesis of anthocyanins and flavones. The nature of chemistry they consist of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon  $\alpha$ ,  $\beta$  -unsaturated carbonyl system. Chalcones possess conjugated double bonds and a completely delocalized  $\pi$ -electron system on both benzene rings. Molecules possessing such system have relatively low redox potentials and have a higher probability of undergoing electron transfer reactions. An interesting feature of chalcones pharmacophore is that they serve as starting materials for the synthesis of five and six-membered heterocyclic compounds such as Pyrimidines, Pyrazolines, Flavones, Flavonols, Flavanones, Aurones and Benzoylcoumarones as well as certain compounds like Deoxybenzoin and Hydantoin which are of some therapeutic application. The chalcones or phenyl styryl ketones are  $\alpha$ ,  $\beta$  -unsaturated ketones containing the reactive keto-ethylenic group ( $-\text{COCH}=\text{CH}-$ ). The chalcones are colored compounds because of the presence of the chromophore ( $-\text{COCH}=\text{CH}-$ ). The pharmacological properties of chalcones are due to the presence of both  $\alpha$ ,  $\beta$ -unsaturation [21-24].

### Claisen-Schmidt condensation reaction: Reaction involved in the synthesis of chalcone

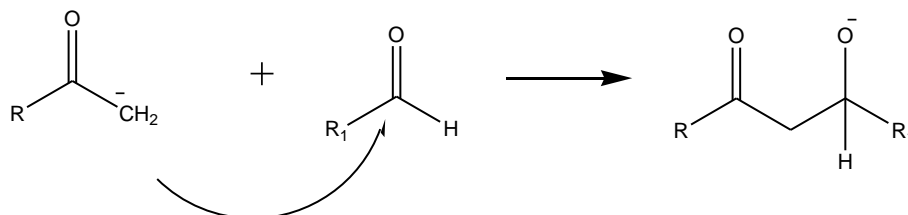
The mechanism involved the formation of  $\alpha$ ,  $\beta$  unsaturated carbonyl moiety. The basic principle involved in the condensation is dehydration followed by nucleophilic addition. In these four steps are involved for the mechanism of formation [25]:

- Initially, the abstract of a proton from the methyl ketone is done by the alcoholic basic pH medium. Usually, alkali like NaOH or KOH of ethanol or methanol medium is used.
- The abstraction of proton results in the formation of carbanion species and can act as a nucleophile in this condensation. Nucleophilic addition of carbanion to the aldehyde followed by the addition of proton form corresponding  $\alpha$ ,  $\beta$ -hydroxy carbonyl compound;
- In the final step, dehydration takes place from  $\beta$ -hydroxy carbonyl compound to form corresponding  $\alpha$ ,  $\beta$  unsaturated carbonyl compound. In the presence of electron donating group in the aldehyde or presence of a hetero nucleus, the final chalcone was achieved by the utilization of mineral acid such as HCl.

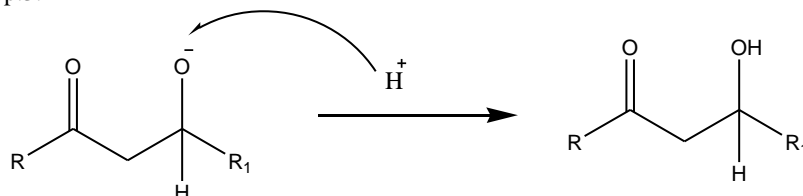
Step.1: Formation of nucleophile from methyl ketone



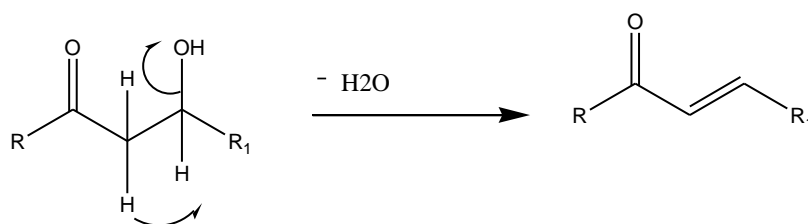
Step.2: Nucleophilic addition of carbanion to the aldehyde



Step.3: Addition of proton to form beta hydroxy ketone



Step.4: Dehydration of beta hydroxy ketone to form chalcone



Mechanism Of reaction of chalcone formation

**Note-** A variety of methods are available for the synthesis of chalcones, the most suitable method is the one that involves the Claisen-Schmidt condensation of equimolar quantities of substituted acetophenone with substituted aldehydes in the presence of aqueous alcoholic alkali. In the Claisen-Schmidt reaction, the concentration of alkali used usually ranges between 10 and 60 %. The reaction is carried out at about 50°C for 12-15 hours or at room temperature for one week. Under these conditions, the Cannizzaro reaction also takes place and thereby decreases the yield of the desired product [26].

#### Flavonoids- the Chalcones of Natural origin

Flavonoids are synthesized via the phenylpropanoid and polyketide pathway, which starts with the condensation of one molecule of CoA-ester of cinnamic acid or derivatives such as coumaric or ferulic acid, and three molecules of malonyl-CoA, yielding a naringenin chalcone as a major product. This reaction is carried out by the enzyme chalcone synthase (CHS). Chalcone synthase condenses 4-coumaroyl-CoA and malonyl-CoA to form the open-chain flavonoid naringenin chalcone, which is converted to naringenin by chalcone isomerase [27]. From these central intermediates, the pathway diverges into several branches, each resulting in a different class of

flavonoids. Flavanone 3-hydroxylase (F3H) catalyzes the stereospecific 3 $\beta$ -hydroxylation of (2S)-flavanones to dihydroflavonols. For the biosynthesis of anthocyanins, dihydroflavonol reductase (DFR) catalyzes the reduction of dihydroflavonols to flavan-3,4-diols (leucoanthocyanins), which are converted to anthocyanidins by anthocyanidin synthase (ANS). The formation of glucosides is catalyzed by UDP glucose-flavonoid 3-O-glucosyl transferase (UFGT), which stabilizes the anthocyanidins by 3-O-glucosylation [28]

### Chemistry of flavonoids

Flavonoids are composed of a 15-carbon (C6–C3–C6) skeleton, and two benzene rings joined by a linear 3-carbon chain. Structurally, flavonoids consist of 2 aromatic rings (A and B rings) linked by a 3-carbon chain that forms an oxygenated heterocyclic ring (C ring). Flavonoids are classified as flavan-3-ols, flavanones, flavonols, anthocyanidins, flavones, and isoflavones based on differences in the generic structure of the C ring, functional groups on the rings, and the position at which the B ring is attached to the C ring. Within each subclass, individual compounds are characterized by specific hydroxylation and conjugation patterns [29]. The antioxidant activity of the flavonoids depends on the structure of flavonoid [30]. It is generally accepted that the number and position of hydroxyl groups on B and A rings, and the extent of conjugation between the B and C rings are the main features affecting the flavonoids' antioxidant activity [31]. The structural features of flavonoids that are necessary to exert radical scavenging and/or the antioxidative actions are described by the three criteria: (1) the *ortho*-dihydroxy (3',4'-diOH, i.e., catechol) structure in the B ring, giving high stability to the flavonoid phenoxyl radicals via hydrogen bonding or by expanded electron delocalization; (2) the C2-C3 double bond (in conjugation with the 4-oxo group), which confers the co-planarity of the hetero-ring and contributes to radical stabilization via electron delocalization over all three ring systems; (3) the presence of both 3-OH and 5-OH groups for the maximal radical scavenging capacity and the strongest radical absorption. Also, the lack of *o*-dihydroxy substituents in a catechol structure on the A ring: this feature represents a larger determinant of flavonoid antiradical activity. The basic flavonoid structure is essential for the antioxidant activity only when a catechol configuration is absent. Glycosylation of flavonoids decreases their antioxidant activity. The block or the removal of the C3 OH group results in a reduction of antioxidative properties of flavonoids [31,32].

### Classification of flavonoids

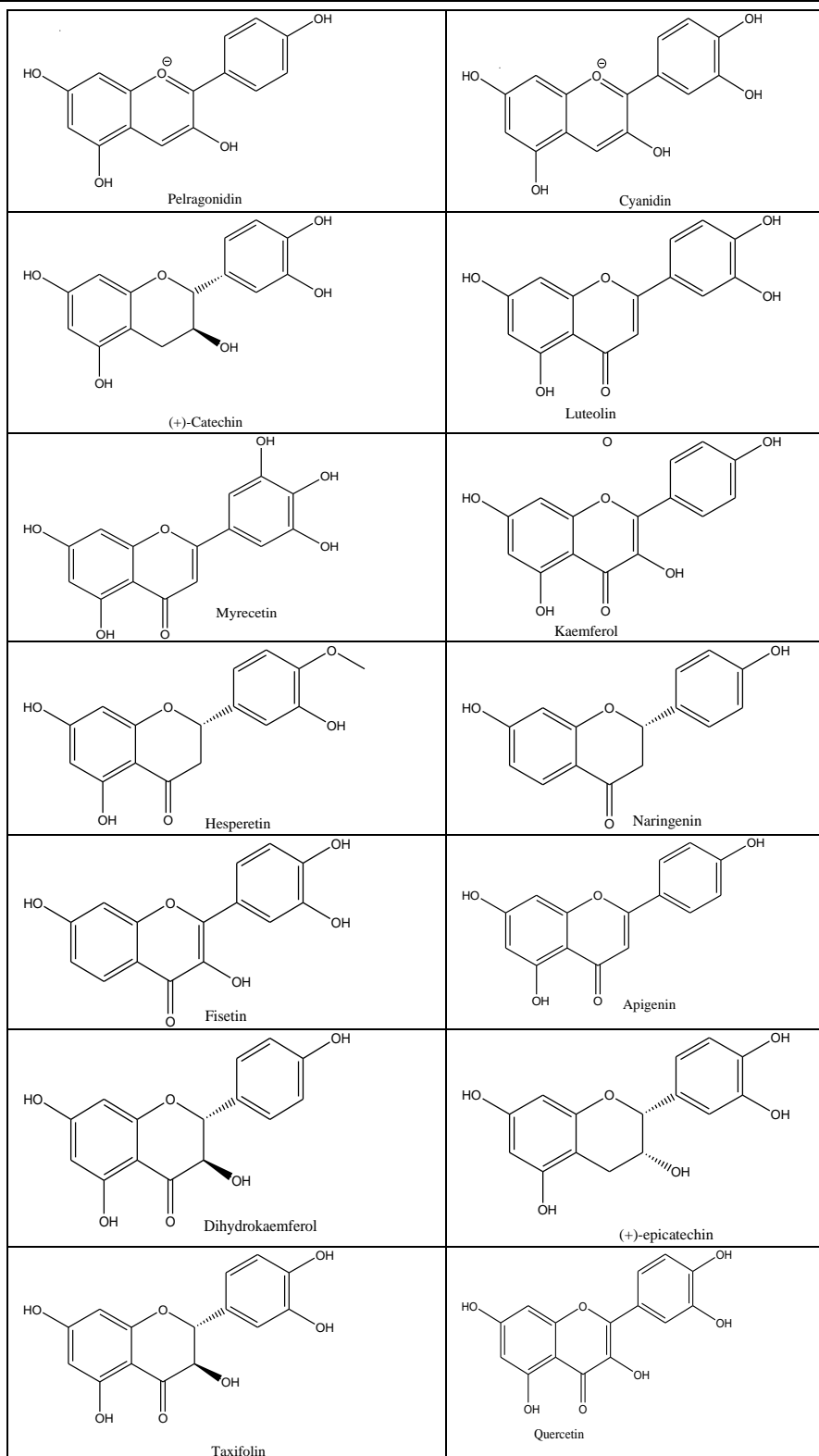
Flavonoids can be classified into multiple subgroups according to the substitution patterns of the ring C, and flavonoids within the same class can be differentiated by the substitution of A and B [33-35]. There are six major subgroups of flavonoids, including flavonols (including quercetin, kaempferol, and myricetin), flavanones (including eriodictyol, hesperetin, and naringenin), isoflavonoids (including daidzein, genistein, and glycitein), flavones (including apigenin and luteolin), flavans-3-ol (including catechin), and anthocyanins (including cyanidin, delphinidin, malvidin, pelargonidin, peonidin, and petunidin).

### Flavonoids and diabetes

Flavonoids have the ability to scavenge free radicals and chelate metals [36]. Given the hypothesized relation between diabetes and inflammation [37, 38] and the potential for flavonoids to protect the body against free radicals and other pro-oxidative compounds [39, 40], it is biologically plausible that consumption of flavonoids or flavonoid-rich foods may reduce the risk of diabetes [41, 42]. These functional foods and phytomedicines play positive roles in maintaining blood glucose levels, glucose uptake and insulin secretion and modulating immune function to prevent specific DM [43, 44]. Flavonoids regulate carbohydrate digestion, insulin secretion, insulin signalling, and glucose uptake in insulin-sensitive tissues through various intracellular signalling pathways [45].

Flavan-3-ols exist as monomers (epicatechin and catechin) or oligomers (proanthocyanidins). Catechin and epicatechin are the main flavan-3-ols in fruits and cocoa, whereas epicatechin gallate (ECG), gallic catechin, epigallocatechin (EGC), and epigallocatechin gallate (EGCG) are found in tea, grapes and seeds of certain leguminous plants [46]. EGCG improved mitochondrial function and functional integrity of mitochondria in high glucose-exposed pancreatic  $\beta$ -cells [47]. EGCG also protect insulin-producing  $\beta$ -cells from pro-inflammatory cytokine stimulated apoptosis [48] and had beneficial effects on fatty acid-induced insulin resistance [49] and at pharmacological doses improves glucose intolerance [50].

Flavanones, i.e. naringin and hesperidin, present in citrus fruits. Hesperidin and naringin treatment also led to the activation of PPAR $\gamma$  [51] and improves glucose homeostasis by stimulating GLUT4 production. Thus, hesperidin and naringin may treat hyperglycemia in T2D by regulating gene expression of glucose-regulating enzymes which may be mediated via PPAR $\gamma$ , a major target of T2D drugs.



Anthocyanidins are widely distributed and are responsible for colours of the fruits and the flowers [52]. The six most commonly occurring anthocyanidins are cyanidin, delphinidin, malvidin, peonidin, pelargonidin, and petunidin [53]. Anthocyanins enhance GLUT4 translocation to plasma membranes of skeletal muscle and thereby enhanced glucose uptake. Anthocyanins also improved insulin signalling by

stimulating IR phosphorylation, leading to a greater tyrosine kinase activity in the  $\beta$ -subunit of the IR and anthocyanins increased the  $\beta$ -cell viability and cellular function in diabetic rats [54].

Flavonols include kaempferol, quercetin, and fisetin [55]. Fisetin is a tetrahydroxyflavone, and the fistein treatment increased the glycogen content and the

activity of glycogen synthase whereas it suppressed glycogen phosphorylase and thus improve glucose homeostasis by modulating these regulatory enzymes of carbohydrate metabolism [56]. Kaempferol improved the synthesis and secretion of insulin in  $\beta$ -cells and islets and protected the  $\beta$ -cells from apoptosis [57–59]. Quercetin and quercetin aglycone enhances insulin-independent glucose uptake and stimulates AMPK in muscle cells. Quercetin protects clonal  $\beta$ -cells against cytokine-induced cell death [60]. Quercetin also inhibits the  $\alpha$ -glucosidases and exerts more potent effect than that of acarbose [61]. However, it is not clear whether this inhibitory effect of quercetin on  $\alpha$ -glucosidases is specific, which is essential for the nutritional or pharmacological use of this compound to decrease postprandial glucose load because it was discovered that some  $\alpha$ -glucosidase inhibitors such as acarbose also cause inhibition of  $\alpha$ -amylase [62–64].

Flavones such as apigenin and luteolin have been recognized as a potential chemopreventive agent [65]. Apigenin increases the phosphorylation of AMPK [66], and apigenin has beneficial effects in diabetes by regulating the AMPK-dependent energy metabolism [67]. Luteolin improves insulin sensitivity and enhances Akt2 phosphorylation in adipocytes via activation of PPAR $\gamma$  [68].

Isoflavones are daidzein and genistein, are present primarily in soy foods. Dietary supplementation of genistein led to improved glucose metabolism and insulin levels in T1D animals [69, 70]. Soy intake led to enhanced phosphorylation of AMPK and favourable metabolic changes associated with AMPK activation, including phosphorylation and inactivation of ACC, increased mitochondrial biogenesis and expression of genes involved in peroxisomal fatty acid oxidation, and increased glucose uptake in skeletal muscle [71]. Genistein exerts anti-diabetic effects by improving plasma lipids [72], thereby increasing insulin sensitivity. Genistein exerts its beneficial effects on glucose homeostasis by influencing  $\beta$ -cell mass and function, and insulin signalling in animal models.

## CONCLUSION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Oral hypoglycemic agents generally stimulate the failing pancreas to release more insulin which does not make correct sense. Further the current drugs for diabetes, in which treatment strategies focus on insulin replacement therapy (type 1) and reducing insulin resistance (type 2), do not directly target the underlying pathophysiology of the loss of  $\beta$ -cells. Chalcones are also known as benzyl acetophenone or benzylidene acetophenone and identified as interesting compounds that are associated with several biological activities. Chalcones are aromatic ketone with two phenyl rings that are precursors of flavonoids and isoflavonoids and

exert several biological and pharmacological activities. Generally, natural chalcones occur as petal pigments and have been found in the heartwood, bark, leaf, fruit, and root [73]. Different studies have shown that chalcones present antihyperglycemic properties, while chalcone with iodine substitution showed great potential in reducing glucose medium concentration, [74] increasing insulin secretion [75] and increasing glucose uptake [76]. In a study published Hu *et al.* it was reported that 2',4'-dihydroxy-6'-methoxy-3',5'-dimethyl chalcone might increase insulin secretion under the condition of elevated glucose by mimicking glucagon-like peptide-1 (GLP-1) and to promote the expression of GLUT2 and glucokinase (GCK). On the other hand, the 2',6'-dihydroxy-4'-methoxy-3',5'-dimethyl chalcone might stimulate the secretion of insulin by increasing the GLUT2 and GCK. The GLUT 2 facilitates the transport of glucose and thus initiates the GSIS by the uptake of glucose [77]. After, glucose is then phosphorylated by glucokinase and further metabolized through the glycolytic route. Thereby, this process increases the production of ATP into the cell that increases calcium influx and leads to insulin secretion. Thus, chalcones might be the promising agents for the treatment of the diabetes mellitus

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