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Mechanisms of Action of Flavonoids in the Management of Diabetes mellitus

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Abstract

Management of diabetes mellitus is a challenge for clinicians. Uncontrolled hyperglycemia increases the risk of microvascular and macrovascular complications, damaging the body systems. Although a number of antidiabetic drugs are available for therapeutic intervention, toxicity, loss of efficacy in chronic use and high cost of treatment have necessitated the search for new molecules to manage diabetes. Safety and cost are the main prerequisite for the new antidiabetic molecules. Medicinal plants and their purified phytochemicals have shown promising antidiabetic potential in the past few years. The flavonoids can be widely classified into different categories like anthocyanins, catechins, flavanols, flavones, flavanones etc. Some flavonoids have hypoglycemic properties. They may improve al-tered glucose and oxidative metabolisms of diabetic states. The hypoglycemic effect of some herbal extracts has been confirmed in human and animal models of type 2 diabetes mellitus (T2DM). Some of the important phytoconstituents from the classes of flavonoid have been discussed here. The current review summarizes the antidiabetic activity of flavonoids, the mechanism-based action of flavonoids that target the various metabolic pathways in humans.

Keywords: Diabetes mellitus, Flavonoids, Medicinal plants, mechanisms of action, T2DM

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INTRODUCTION

DM is a metabolic disorder characterized by chronic hyperglycemia together with disturbances in the metabolism of carbohydrates, proteins and fat, which in general results from an insulin availability and need imbalance[1-4]. DM can be manifested as type 1 (T1DM), or type 2 (T2DM)[5,6]. T2DM is the most common presentation of DM, resulting from both cell dysfunction (with altered insulin levels) and impaired insulin action (insulin resistance)[6-8]. Management of Diabetes mellitus employs modifications of diet, change of lifestyle, intake of oral hypoglycemic, administration of exogenous insulin and herbal remedies[9]. Synthetic drugs are fraught with adverse side effects[10,11]. Natural products such as plants and herbs have the capacity to reduce blood glucose values and ameliorate diabetes with reduced adverse side effects. They achieve this owing to the presence of phytochemicals such as flavonoids, saponins, alkaloids, tannins, glycosides, terpenes etc. The aim of this review is to highlight the importance of flavonoids in the management of D. mellitus. The mechanisms by which these active principles of flavonoids origin bring about their effects are also discussed.

FLAVONOIDS

Flavonoids are a group of plant metabolites that constitute a family of soluble polyphenolic compounds. They are made up of two benzene rings attached by a short three carbon chain[12]. Flavonoids that occur in nature are classified into six classes namely: anthocyanidins (e.g. cyanidin, delphinidin, malvidin, peonidin, petunidin etc), flavan-3-ols (e.g. catechin, epicatechin, gallocatechin etc), flavonols (isorhamnetin, kaempferol, myricetin, quercetin), flavones (e.g. apigenin, luteolin, baicalein, chrysin), flavanones (eriodictyol, hesperetin, naringenin) and isoflavones (daidzein, genistein, glycitein, biochanin A)[12,13]. The anti-diabetic properties of flavonoids are attributed partly to their antioxidant potentials and partly due to their ability to modulate some cell signalling. Dietary flavonoids occur in fruits, vegetables, beverages, chocolates, herbs and plants[14,15]. The following flavonoids isolated from plants have been shown to possess anti-diabetic properties.

(a) Diosmin

Diosmin is a flavonoid that occurs in citrus plants naturally. Experimental evidencs have revealed its potent anti-diabetic activities mediated by decreases in the level of glycosylated haemoglobin, increases in the activities of glutathione peroxidases[16,17], significant reductions in plasma glucose values, increases in hepatic hexokinases and glucose-6-phosphate dehydrogenases[18], increasing insulin levels and ameliorating oxidative stress as evidenced by assay of superoxide dismutase, catalase and glutathione peroxidase activities. It also increased the levels of vitamins C and E[19]. Diosmin is isolated from *Scrophularia nodosa*, an anti-diabetic plant.

(b) Fisetin

This flavonoid brings about its anti-diabetic effect by inhibiting gluconeogenesis through inhibition of mitochondrial pyruvate transport and a decrease in the cytosolic NADH/NAD redox[20]. Decreasing of glycogen breakdown, plasma glucose levels, glycosylated haemoglobin, mRNA and protein expression levels of gluconeogenic genes like phosphoenol pyruvate carboxykinase and by increasing plasma insulin are among the mechanisms by which fisetin brings about its anti-diabetic actions[21]. Moreover, hypoglycaemic activities of fisetin flavonoids have been associated with significant decreases in nuclear factor kappa B (NF-kB) p65 unit, interleukin-1β (IL-1β)and serum nitric oxide (NO)21. Fisetin, produced by Cotinus coggygriaScop and also found ubiquitously in strawberry, apple, grape, onions and cucumber has been advocated for use in the prevention of diabetes [22,23].

(c) Morin

Morin-treated diabetic rats showed anti-diabetic activities by improvement of antioxidant agents, reduction of insulin resistance, decrease in oxidative stress parameters, normalization of lipids and lipoproteins and decreases in the levels of tumour necrosis factor alpha (TNFα)24. Experimental evidence also suggests that morin reduced inflammatory cytokines IL-1β and IL-6 in diabetic animals[25]. Recovery of hepatic insulin and leptin sensitivity, reduction in hyperlipidaemia and liver-lipid accumulation have been fingered as mechanisms by which morin brings about its anti-diabetic actions[26]. Morin has been shown to reduce glucose-6-phosphatase activities, increase hexokinase, and glucose-6-phosphate dehydrogenase activities and insulin levels[27]. Morin is contained in many medicinal herbs such as *Prunus dulcis(Mill)*, *Chlorophora tinctoria(L)*, *Psidium guajava*[28,29].

(d) Eriodictyol

Suppression of oxidative stress, up-regulation of mRNA expression of peroxisome proliferator-activated receptor gamma (PPARγ) and adipocyte-specific fatty acid-binding protein together with the protein levels of PPARγ2 in differentiated 3T3-L1 adipocytes are key mechanisms involved in the anti-diabetic activity of eriodictyol. It has also been implicated in the reduction of retinal TNFα, intercellular adhesion molecule-1 (ICAM-1), vascular endothelial growth factor (VEGF), endothelia nitric oxide synthase (eNOS) and lipid peroxides[30,31]. Lemon fruits contain eriodictyol in abundance[32].

(e) Hesperidin

This flavonoid is ubiquitous in plants of the genus citrus especially Citrus aurantium[33,34]. Like eridictyol, hesperidin exhibits anti-diabetic activity by down regulating the generation of free radicals and the release of pro-inflammatory cytokines[35-37]. Normalization of the lipids and adiponectin together with alterations of the activities of glucose metabolizing enzymes decreases in the levels of thiobarbituric acid reactive substances (TBARS) and increases in the activities of lactate dehydrogenase (LDH) have been reported with hesperidin administration[38,39].

(f) Naringenin

Citrus fruits and tomatoes contain naringenin in abundance, which confers antioxidant properties to these fruits[40]. Cochlospermun also contains naringenin in large amount[41]. Naringenin inhibits α glucosidase activities. It also inhibits glucose uptake in vitroand interferes with genes associated with lipid metabolism[42,43]. Activation of 5′AMP-activated protein kinase (AMPK), enhancement of antioxidant activities, reduction of insulin resistance and improvement in hepatic function markers are also thought to be the mechanism of action of naringenin[44-46].

(g) Apigenin

This flavone flavonoid is ubiquitous in citrus, onions, vegetables, tea and nut[47]. Its mechanism of action is through the improvement of antioxidant parameters, enhancement of glucose transporter 4 (GLUT4) translocation and beta cell preservation[48,49].

(h) Baicalein

Baicalein scavenges free radicals, induces insulin production, reduces glycosylated haemoglobin, suppresses the activation of NF-kB, decreases the expression of inducible nitric oxide synthase (iNOS) and transforming growth factor beta (TGF-β)[50,51]. Another major mechanism by which Baicalein operates is by up-regulation of AMPK44. This flavonoid is present in the roots of Scutellaria baicalensisand fruits of Oroxylum indicum[52,53].

(i) Chrysin

It is a major component of *Oroxylum indicum*. It has also been isolated from *Passiflora caerulea,* Pelargonium peltatum, Tilia tomentosa, bee pollen, honey, fruits and vegetables[54-56]. Treatment with chrysin has been associated with suppression of TGF-β, fibronectin, and collagen-IV protein expression in the kidney. Serum levels of IL-1β and IL-6 were also reduced. With these observations, chrysin is thought to prevent nephropathy[51]. Chrysin administration also improves insulin levels and reduces lipid peroxidation[57].

(j) Luteolin

Luteolin is known to potentiate insulin action and increase transcriptional activation of PPARγ[58]. Luteolin also decreases circulating levels of inflammatory molecules, Monocyte Chemotactic Protein-1 (MCP-1), resistin and elevates adiponectin levels in obese mice[59]. It is also on record that luteolin improves insulin secretion60. Luteolin is found in abundance in carrots, peppers, cabbage, apple, vegetables and fruits[61-63].

(k) Tangeretin

Tangeretin administration decreased total cholesterol, leptin, resistin, IL6 and MCP-1[64]. It is also in the literature that its administration significantly decreased glycosylated haemoglobin, improved insulin levels, enhanced glycolytic enzymes, controlled glucose metabolism in hepatic tissues and decreased an insulin-resistant factor, MCP-1 in 3T3-L1 adipocytes[65]. Rinds of citrus fruits contain tangeretin.

(l) Wogonin

This is obtained from the root of *Scutellaria baicalensis*[66]. Wogonin interferes with insulin sensitivity and lipid metabolism through its effect on AMPK and PPARα[67].

(m) Isorhamnetin

It is an anti-diabetic principle isolated from *Hippophae rhamnoides*, *Oenanthe javanica* and *Ginkgo biloba*. Its administration reduces oxidative stress, inhibits sorbitol accumulation and interferes with lipid metabolism[68-70].

(n) Kaempferol

This flavonol is present in *Ginkgo biloba*, tea, grapefruits, edible berry and vegetables[71-73]. Its administration is associated with the inhibition of apoptosis, reduction of caspase-3 activity in beta cells, improvement of cAMP signalling and enhancement of insulin synthesis and secretion[74]. It is also associated with the enhancement of antioxidant production and reduction of IL-1β, TNFα, lipid peroxidation, nitrite and glycosylated haemoglobin[75,76].

(o) Rutin

Oranges, grapes, buckwheat, lemons, limes, berries and peaches contain rutin[77,78]. Proposed mechanisms for the antihyperglycemic effect of rutin include a decrease of carbohydrates absorption from the small intestine, inhibition of tissue gluconeogenesis, an increase of tissue glucose uptake, stimulation of insulin secretion from beta cells, and protecting Langerhans islet against degeneration. Rutin also decreases the formation of sorbitol, reactive oxygen species, advanced glycation end-product precursors, and inflammatory cytokines. These effects are considered to be responsible for the protective effect of rutin against hyperglycemia- and dyslipidemia-induced nephropathy, neuropathy, liver damage, and cardiovascular disorders.[79,80].

(p) Quercetin

It is a flavonol flavonoid present in onions, berries, apples, pepper and coriander[81,82]. Its anti-diabetic actions are exhibited by increases in anti-oxidant enzymes, decreases in lipid peroxidation, reduction in intestinal glucose absorption by inhibiting GLUT2[83,84]. Quercetin blocks tyrosine kinase and also the recovery of cell proliferation85.

(q) Genistein

This is an isoflavone flavonoid present in legumes. *Sophora subprostrala* and *Genista tinctoria* contain genistein[86]. Renal TBARS were reduced upon genistein administration. It also improves glucose tolerance and increases blood insulin level without affecting body weight[87].

(r) Daidzein

Daidzein, an isoflavone flavonoid is present in nuts, soybeans and fruits. Daidzein improves lipid and glucose metabolism, improves insulin sensitivity and enhances AMPK phosphorylation in muscles[88-91].

(s) Cyanidin

Cyanidin, an anthocyanin flavonoid exhibits its anti-diabetic actions by inhibiting α-glucosidase and pancreatic α-amylase[92]. It also prevents pancreatic apoptosis and improves antioxidant status[93,94].

(t) Delphinidin

This is anthocyanin present in berries, tomatoes, egg plant, vegetables, carrots, sweet potatoes, red cabbage and red onions. Its anti-diabetic activity is mediated through its antioxidant effects and reductions in albumin and haemoglobin glycations[95].

(u) Pelargonidin

It is present in blackberries, cranberries, ripe raspberries and blueberries[96]. Its administration relieves oxidative stress, nitrite levels and stimulates insulin secretion. In diabetic rats, pelargonidin showed it reduces the formation of thiobarbituric acid reactive substances (TBARS) and antioxidant defensive enzymes levels [97,98]. Structure of some flavonoids shown in Figure 1.

PLANT DERIVED FLAVONOIDS AND THEIR METABOLIC PATHWAYS

Plants contain numerous chemical compounds having medicinal values and include alkaloids, amino acids, amines and carboxylic acid derivatives, anthranoids, carbohydrates, glycosides, flavanoids, minerals, vitamins and inorganic compounds, peptidoglycans, polyphenol and its derivatives, saponins, and so on. These compounds are extracted from different parts of the various plants. This review aims to document and summarize the present knowledge about the mechanism-based action of antidiabetic plants, with emphasis on their flavonoids that target the various metabolic pathways in humans. The review has been organized according to various flavonoids, targeted metabolic pathways and plant sources in Table 1.

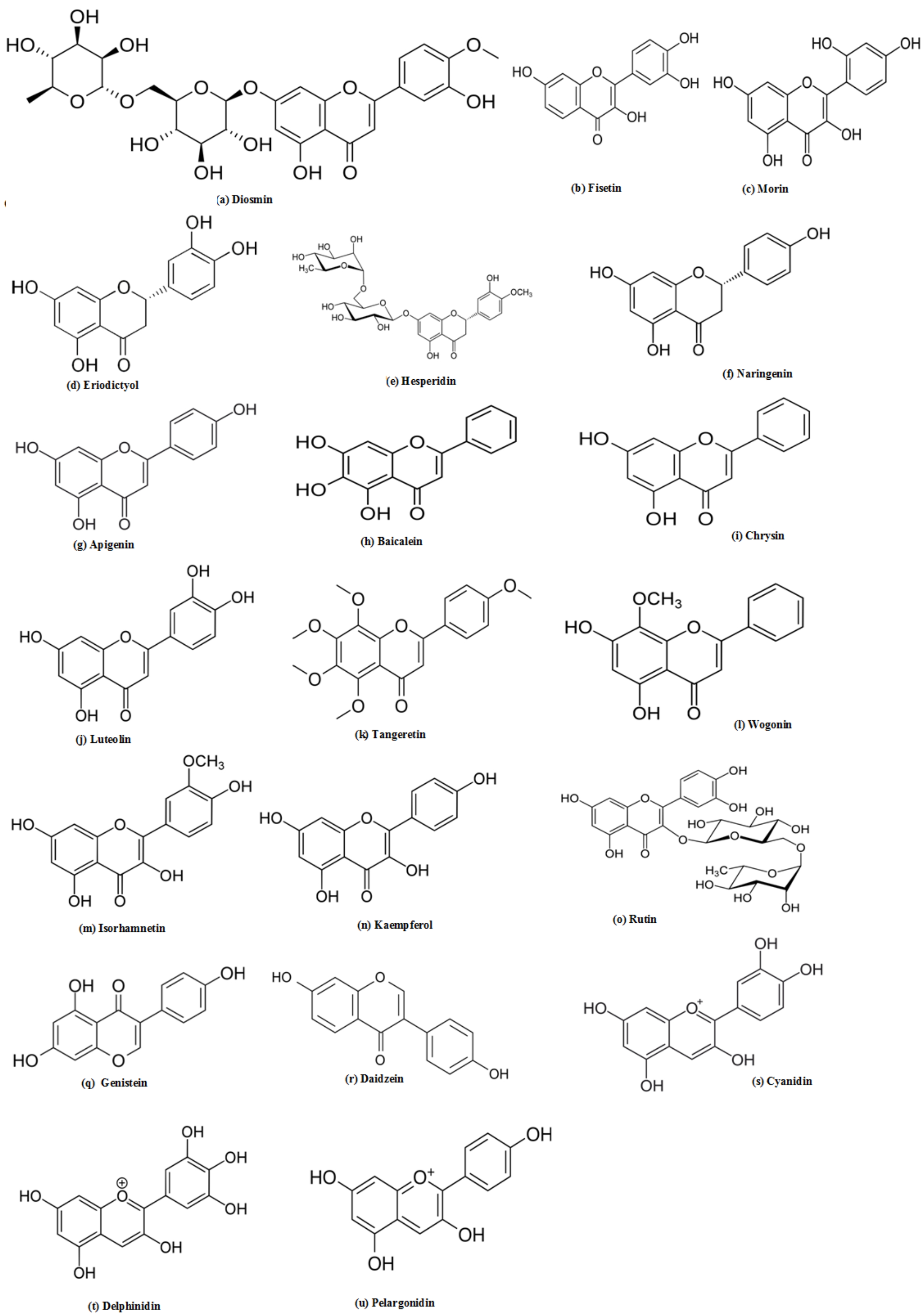

Figure 1: Structure of some flavonoids

Table 1: Various flavonoids having hypoglycaemic potential that regulate intermediates of different metabolic pathways.

S. N.	Flavonoids	Targeted metabolic pathways	Plant Source	Ref
1	Chrysin, isoquercitrin	Insulin secretion	*Morus alba*	[99]
2	Epigallocatechin-gallate, gallocatechin, epicatechin, (+) catechin, (−) epicatechin	Free radical scavenging activity, insulinonematinactivity	*Camellia sinensis, Punica granatum, Satureja khuzestanica,Bauhinia forficate*	[100-102]
3	Myrciaphenones A and B,myrciacitrins I and II	Insulin secretion	*Myrcia multiflora*	[103]
4	α-Cephalin, myricetin-3'-glucoside, ambrettolide	Insulin secretion	*Abelmoschus moschatus*	[103]
5	Cytrus bioflavonoids (hesperidin, naringin)	Glycogen synthesis,glycolysis, gluconeogenesis	*Camellia sinensis*	[104]
6	Flavanols, flavones,flavanones	Insulin secretion	*Panax notoginseng*	[105]
7	Quercetin, quercetrin, apigenin, rutin, apigenin-7- O-glucoside	Insulin secretion	*Urtica dioica, Bauhinia varigtla, Ginkgo biloba*	[106]
8	Naringenin	Insulin secretion	*Camellia sinensis*	[101]
9	Soy isoflavones (genistein, diadzein)	Lipid and glucose metabolism, PPAR activation	*Glycin max, Curcuma longa*	[107, 108]
10	Proanthocyanidins	Insulinonematic activity	*Vitis vinifera*	[109]
11	α-Terpineol, hexanol	Insulin secretion	*Agaricus campestris*	[110]
12	Kaempferitrin	Glycolysis	*Bauhinia candicans, Bauhinia forficate*	[111]
13	(+) Catechin, (−)epicatechin, chiorogenic acid, liquiritigenin, isoliquiritigerin	Insulinomematic activity	*Phylanthus embelica, Acacia Arabica, Pterocarpus marsupium, Phylanthus embelica*	[112]
14	Silymarin, silybin, silychristin, silidianin	HMG Co A suppression	*Silybum marianum*	[113]
15	Kaempferol, isorhamnetin	Free radical scavenging activity	*Ginkgo biloba*	[106]
16	Tribulusamides A and B, kaempferol-3-β-D-(6'P- coumaroyl)glucoside, kaempferol-3-glucoside	Insulin secretion, free radical scavenging activity	*Tribulus terrestris*	[114, 115]
17	Leucopelargonidin, dulcitol	Insulin secretion	*Casearia esculenta*	[116]
18	Matteuorien, matteuorienin matteuorienate A, B, C	Insulin secretion	*Matteuccia orientalis*	[117]

Research into D. mellitus and its management in recent times has been geared towards isolation of efficacious active anti-diabetic agents of natural origin. A lot of studies have been carried out in various medicinal plants in this regard. Results have not only indicated that many medicinal plants possess anti-diabetic potentials but have demonstrated specific bioactive anti-diabetic principles and various mechanisms of actions of these agents. Bioactive anti-diabetic principles of plant origin are mainly phytochemicals, these phytochemicals act in a number of diverse mechanisms to bring about their anti-diabetic effects. Some of the mechanisms involved include increase in insulin secretion, decreases in hepatic glucose output, regulation of certain enzymes involved in carbohydrate metabolism such as α-glucosidase inhibitors, modulation of certain regulation molecules such as PPARγ, hypolipidaemic activities, antioxidant effects, interference with the activities of some glycolytic enzymes such as phosphoenolpyruvate carboxykinase activities, amelioration of glycosylated haemoglobin, enhancement of the expression of glucose transporters and others.

Flavonoids were observed to be the most popular anti-diabetic principle among the phytochemicals. These naturally occurring secondary plant metabolites (Phytochemicals) hold great potential for production of marketable, novel and effective anti-diabetic drugs in near future. In general, bioactive anti-diabetic agents of plant origin constitute a group of natural products that have recently gained popularity in the health sector for management of various ailments such as diabetes mellitus. Satisfactory management of D. mellitus in future is pivotal on medicinal plants.

CHALLENGES USING FLAVONOIDS

Flavonoids have been proven to be strong candidates to reduce the pathogenesis of diabetes and its complications. The modulatory anti-diabetic effects of flavonoids reduce apoptosis and insulin resistance and enhance insulin secretion and GLUT 4 translocation[118]. Efforts have been made to establish an optimal human dietary consumption level of flavonoids worldwide, the consumption level of flavonoids depend on dietary habits, geographical location, socioeconomic status, food processing and preparation method, solubility of flavonoids, and the ethnicity of the population. To date, no recommended dosage of flavonoids has been reported due to the heterogeneity of their molecular structure and the limited information about their bioavailability. Major advances in understanding flavonoids bioavailability have been made, but the challenge to overcome problems, such as cellular permeability, solubility, excretion, and metabolic alternation, are still lacking. Research groups are trying to enhance flavonoids bioavailability by targeting absorption sites, improving metabolic stability and intestinal absorption[119].

CONCLUSION

Diabetes is possibly the world's fastest growing meta-bolic disease, and as knowledge of the heterogeneity of this disorder increases, so does the need for more appropriate therapies. Traditional plant medicines are used throughout the world for the management of diabetes because it is easily and cheaply available. The scientific validation of several plant species has proved the efficacy of the botanicals in management of diabetes acting through various mechanisms. There is a tapping need to search and develop new herbal formulations and nutraceuticals from natural resources especially with pure phytochemicals for the treatment of diabetes and to avoid serious diabetic complications. A systematic research and development in the form of drug delivery systems are necessary to explicate the pharmacological activities of herbal remedies being used nowadays to treat diabetes mellitus. The study of such medicines might offer a natural key to unlock a diabetologist's pharmacy for the future.

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