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REVIEW ARTICLE

Review on Diabetic Complications and their Management by Flavonoids and Triterpenoids

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Abstract: Diabetes mellitus, together with its numerous consequences, is rapidly becoming a major health issue. Natural products are secondary metabolites found in plants that have a wide range of biological functions. The development of anti-diabetic medications derived from natural compounds, particularly those derived from plants having a documented folk-use history in the treatment of diabetes, is gaining traction. Many studies have shown the usefulness of natural flavonoids with hypoglycemic properties in the management of diabetic problems, along with their advantages. This paper describes the mechanisms of action of several natural flavonoids whose hypoglycemic effects have been confirmed. Comprehensive lifestyle treatments can help those at high risk of diabetes to avoid or delay the start of the disease, according to the results of randomized controlled trials. Terpenoids are a type of natural substance that have been identified as an anti-diabetic agent in various studies. Some of them are in various phases of preclinical and clinical testing to conclude whether they can be used as anti-diabetic drugs. These compounds can block the enzymes involved in insulin resistance, facilitate glucose metabolism, and positively affect plasma glucose and insulin levels. By blocking multiple pathways implicated in diabetes and its consequences, flavonoids and triterpenes can operate as potential agents in the treatment of diabetic retinopathy, neuropathy, and nephropathy, as well as poor wound healing. However, there have been few attempts to investigate the biological effects of triterpenes and clinical research investigating their use in the treatment of diabetes. As a result, it is critical to pay close attention to these chemicals' therapeutic potential and to contribute fresh information to the scientific community. This review focuses on current advancements in flavonoids and triterpenes chemistry, derivatives, biological interventions, and therapeutic applications, with a focus on diabetes and related illnesses.

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1. INTRODUCTION

Diabetes mellitus is regarded as one of the leading causes of noncommunicable diseases. According to the International Diabetes Federation (IDF), the number of people living with diabetes will increase from 463 million in 2019 to 700 million by 2045 [1]. T2DM accounts for nearly 90% of all diabetics, and the predicted rise in incidence has a direct impact on the burden of neuropathy, retinopathy, and nephropathy, generally referred to as the typical diabetic microvascular sequelae [2]. T2DM onset and early development is a silent process; however, microcirculatory damage is commonly present at the time of diagnosis, with multiorgan effects [3, 4]. Diabetic microvascular problems are directly linked to the progression of long-term or uncontrolled disease and can lead to severe disability such as diabetic foot ulcers, blindness, and end-stage renal disease (ESRD), as well as higher expenditures for patients and society [5]. Unfortunately, current glucose-lowering medicines have been found to be ineffective in preventing or slowing diabetic microvascular damage [6]. To acquire fresh insights into the basic function of diabetic microvasculature and successfully improve unmet treatments, newer preclinical techniques are required [7].

It is estimated that half of the diabetic patients are uninformed of their condition, making them more vulnerable to diabetic complications. In terms of money spent and lives lost, however, coping with diabetes can be costly. Diabetes was responsible for nearly 5.0 million deaths in 2015, despite the fact that the condition and its consequences accounted for more than 12% of global health spending that year [8]. Diabetes complications are prevalent in patients with either type 1 or type 2 diabetes, but they also cause severe morbidity and mortality. Microvascular and macrovascular problems of diabetes are generally classified, with the former having a substantially higher prevalence than the latter. Neuropathy, nephropathy, and retinopathy are examples of microvascular problems, while cardiovascular disease,

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stroke, and peripheral artery disease are examples of macrovascular complications (PAD). Diabetic foot syndrome is characterized as a foot ulcer accompanied by neuropathy, PAD, and infection, and it is a leading cause of lower-limb amputation [9]. Finally, there are other problems of gestational diabetes that are not covered in the two categories above, such as dental disease, lower infection resistance, and delivery issues in women with gestational diabetes [10]. The goal of this special issue is to highlight a diverse range of research and review papers that address recent basic improvements in our understanding of diabetes complications.

2. DIABETIC COMPLICATIONS

Diabetes can impact a variety of organ systems in the body, leading to major consequences over time. Diabetic complications are defined as either microvascular or macrovascular. Damage to the neurological system (neuropathy), the renal system (nephropathy), and the eyes (ophthalmopathy) are all examples of microvascular consequences (retinopathy). Cardiovascular disease, stroke, and peripheral vascular disease are examples of macrovascular consequences of diabetic complications shown in Fig. (**1**). Peripheral vascular disease can cause bruising or non-healing injuries, gangrene, and, in the worst-case scenario, amputation [11].

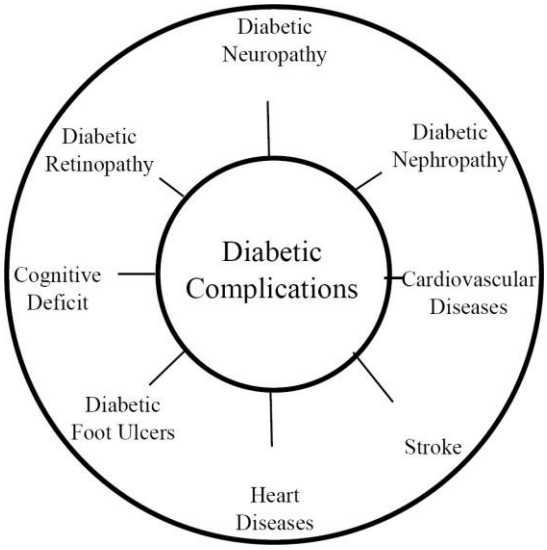

Fig. (1). Complications of diabetes.

3. MICROVASCULAR COMPLICATIONS

3.1. Retinopathy (Blindness)

The most common microvascular condition affecting diabetics is diabetic retinopathy, which accounts for around 10,000 new cases of blindness annually. Furthermore, retinopathy is sluggish in forming and some study indicates that it may begin developing up to 7 years before a clinical diagnosis of type 2 diabetes. It is also connected to persistent hyperglycemia. By 2005, the age-adjusted prevalence of visual impairment had decreased to about 17.7 per 100 people with diabetes, from 23.7 per 100 in 1997. 9 With age comes a greater prevalence of visual impairment in diabetes patients [12].

3.2. Nephropathy (Renal Disease)

Persistent proteinuria (greater than 500 mg of protein or 300 mg of albumin per 24 hours) in patients without a urinary tract infection or other conditions that are causing proteinuria is known as diabetic nephropathy. Clinical nephropathy develops rather slowly in people with type 1 diabetes, but diabetic proteinuria may already be present in people with type 2 diabetes at the time of diagnosis.

3.3. Peripheral Neuropathy

Diabetic peripheral neuropathy (DPN) is a common consequence of diabetes that affects 30% to 50% of people with the disease. Hyperglycemia is the most common cause of DPN. Age, disease duration, cigarette smoking, hypertension, increased triglycerides, greater BMI, alcohol intake, and taller height are all independent risk factors [13].

The most prevalent type of DPN is chronic sensorimotor distal symmetric polyneuropathy [14]. Pain, muscle weakness, and sensory loss are all signs of polyneuropathy. A delayed onset of sensory impairment, such as burning and numbness in the feet, is how polyneuropathy typically manifests. The disease may take years to become apparent since its onset is so slow. Neuropathic pain can be quite painful when it is present, however, it is known to affect between 11% and 32% of people with polyneuropathy [15].

4. MACROVASCULAR COMPLICATIONS

4.1. Heart Disease and Stroke

Hypertension, hypercholesterolemia, and smoking are all risk factors for cardiovascular disease in persons with diabetes, just as they are in those without diabetes. However, it appears that having even one of these risk factors leads to inferior results in those with diabetes as compared to those who do not have diabetes. Data on trends in cardiovascular disease complications linked with diabetes are available for various populations from the 1950s to 2003, and these data show that the incidence of cardiovascular problems among persons with diabetes has decreased significantly over time. The most dramatic reductions appear to have occured in the 1980s and 1990s, coinciding with considerable advancements in glycemic control and blood pressure control medications [16, 17].

4.2. Peripheral Arterial Disease

The narrowing of blood arteries that supply blood to the arms, legs, stomach, and kidneys causes peripheral arterial disease (PAD, also known as a peripheral vascular disease [PVD]). The age, duration of diabetes, and presence of neuropathy all raise the risk of PAD in diabetics. Other cardiovascular diseases risk variables, such as C-reactive protein and homocysteine levels, have also been linked to an increased risk of PAD. Two signs of peripheral artery disease include intermittent claudication (or intermittent pain, soreness, or discomfort that occurs during activity or walking but disappears with rest) and pain at rest (which is caused by ischemia in the limb, indicating inadequate blood flow to the

affected limb). A significant risk factor for lower-extremity amputation is peripheral artery disease [8].

4.3. Lower-extremity Amputations

LEAs (nontraumatic lower-extremity amputations) are serious diabetic complications. Amputations are performed on up to 15% of diabetics during the course of their lives. Diabetes patients are 10 to 20 times more likely than non-diabetic patients to develop LEAs. About 55 percent of diabetic individuals with nontraumatic LEAs are over the age of 65 [18].

5. MANAGEMENT OF DIABETIC COMPLICATIONS

Numerous diabetes patients are interested in complementary or alternative therapies employing herbal medicines, as seen in Fig. (**2**). The possibility of increasing glycemic control or lowering reliance on insulin injections by employing herbal medicines is unquestionably alluring because many well-known herbs are reported to reduce blood glucose levels. The choice of herbs, however, may be influenced by a number of variables, including the stage at which the patient's diabetes is progressing, the types of comorbidities they are experiencing, their accessibility and cost, as well as their safety profile. Preclinical research has broken the threshold of labs and arrived at the patients' bedsides. In recent years, some clinical trials in human patients have demonstrated that medicinal plants such as *Scoparia dulcis*, [19] *Cinnamomum cassia*, *Ficus racemosa* bark, and *Portulaca oleracea* L. seeds have antidiabetic potential. Diabetic patients have benefited from further laboratory research on herbal medications under the brand names Diabecon®, Glyoherb®, and Diabeta Plus®. As a result, herbal supplements can be used as a supplement or as an alternative therapy for diabetics [20].

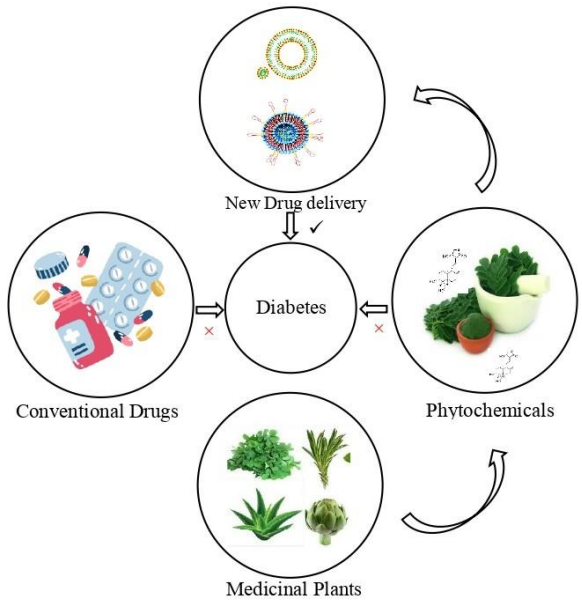

Fig. (2). Treatment of diabetes by phytochemicals preparation. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. Mechanisms of action of natural flavonoids for the treatment of diabetes.

Flavonoid	Mechanism
Quercetin	Protection of β-cells from damage [31], Inhibition of α-glucosidase [32]
Myricetin	Stimulation of glucose uptake [33]
Kaempferol	Protection of β-cells from damage [34]
Isorhamnetin	Inhibition of α-glucosidase [35]
Flavones	
Apigenin	Protection of β-cells from damage [36]
Eupatilin	Enhancement of pancreatic β-cell function to increase insulin [37]
Baicalein	Stimulation of glucose uptake [38]
Tangeritin	Stimulation of glucose uptake [39]
Luteolin	Inhibition of α-glucosidase, α-amylase [39]
Isoflavones	
Genistein	Protection of β-cells from damage and proliferation of islet β-cells inhibition of G-6-Pase [40]
Daidzein	Activation of glucose transport reduction of the breakdown of glycogen [41]
Kakkalide	Insulin-receptor signaling [42]
Flavanonols	
Eriodictyol	Stimulation of glucose uptake [43]
Naringenin	Inhibition of α-glucosidase [44]
(-)-Epicatechin	Protection of β-cells against oxidative stress [45]
Flavone C-glycosides	
Vitexin	Inhibition of α-glucosidase [46]
Isovitexin	Inhibition of α-glucosidase [46]
Swertisin	Inhibition of α-glucosidase [47]
Flavanone Glycosides	
Hesperidin	Reduction of breakdown of glycogen [48]
Flavonol Glycosides	
Isoquercetin	Inhibition of α-glucosidase [32]
Isorhamnetin-3-O-rutinoside	Inhibition of α-glucosidase [47]
Kaempferitrin	Stimulation of glucose uptake [49]
Rutin	Activation of signaling in β-cells [50]

5.1. Natural Flavonoids Used for Treatment of Diabetes and Diabetic Complications

Flavonoids are a class of secondary metabolites with a flavone backbone that is present in plants (2-phenylchromen-4-one). Table **1** displays the flavonoid's mechanism. There are several significant subgroups of flavonoids that can be distinguished by functional groups joined to the flavonoid

structure, including flavanols, flavonols, flavones, isoflavones, flavanones, flavanonols, and anthocyanins. They have a wide range of biological functions, and numerous studies have been done on their possible role in the treatment of diabetes and its consequences. *In vitro* and *in vivo* bioassay data on natural flavonoids used to treat conditions that are symptoms of diabetes are compiled in this review. It summarizes the most recent discoveries in the study of natural flavonoids, with an emphasis on diabetes and its consequences. Information on the mechanisms of action of natural flavonoids in the treatment of diabetes is supplied at the outset due to the multiple pathogenicities of diabetes [21] structures of some important flavanoids are shown in Fig. (**3**).

5.2. Mechanisms of Action of Natural Flavonoids for the Treatment of Diabetes Mellitus

Injections of insulin and oral administration of antidiabetic medicines currently serve as the cornerstone of treatment for diabetes mellitus. In the western market, antidiabetic medications such as sensitizers, secretagogues, insulin analogues, α-glucosidase inhibitors, amylin analogues, and others are used singly or in combination to improve blood glucose control. Unfortunately, the majority of them have serious side effects and can't stop diabetes complications from emerging. International pharmacologists are searching for novel strategies to treat this metabolic condition [22].

5.3. Action on Islet β-cells and Release of Insulin from β-cells

The endocrine pancreas' cells release insulin, a hormone that controls glucose levels, into the bloodstream as blood sugar levels rise [23].

5.4. Enhancement of Glucose Utilization in Tissues and Organs

For glucose utilization, cellular glucose transport, which is mediated by a family of facilitative glucose transporters (GLUTs) as solute carriers *via* an insulin receptor tyrosine kinase-involved signaling cascade, is necessary. This intricate

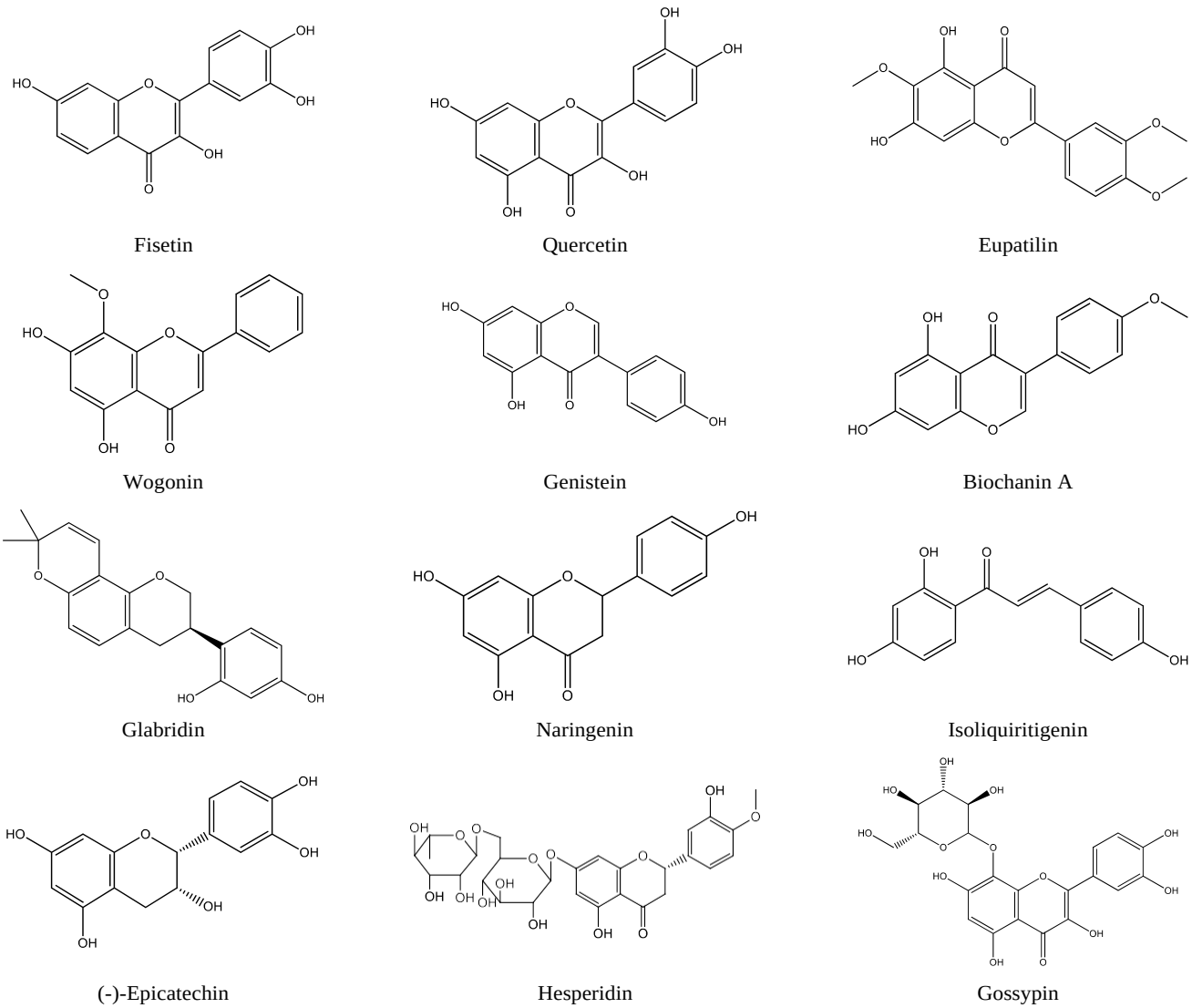

Fig. (3). Structures of flavonoids for diabetic complications.

mechanism of insulin-stimulated whole-body glucose consumption is impaired in diabetes as a result of defective GLUT-4 translocation and aberrant insulin signal transduction [24].

5.5. Reduction of Breakdown of Glycogen

Glucokinase phosphorylates glucose to glucose-6-phosphate during digestion, which is followed by glycogen synthesis, glycolysis, or triglyceride synthesis. Insulin suppresses gluconeogenesis and glycogenolysis by influencing the transcription of hepatic and muscle enzyme genes including phosphoenolpyruvate carboxykinase and glucose-6-phosphatase (G6-Pase) [25].

5.6. Inhibition of α-glucosidase to Reduce Intestinal Glucose Absorption

Carbohydrates are hydrolyzed to their corresponding monosaccharides by intestinal brush-border enzymes before absorption. The most essential of these enzymes in carbohydrate digestion is α-glucosidase. As a result, α-glucosidase inhibitors diminish the blood sugar effect of carbs. Fasting and postprandial blood glucose, glycosylated haemoglobin (HbA1c), and insulin sensitivity in Type 2 diabetics can all be reduced with acarbose, α-glucosidase inhibitor [26].

5.7. Triterpenes Used for the Treatment of Diabetes and Diabetic Complications

There have been reports of many traditional medicinal herbs being used to treat diabetes and diabetic complications. Due to the existence of bioactive pentacyclic triterpenoids such as oleanolic acid, glycyrrhizin, glycyrrhetinic acid, ursolic acid, betulin, betulinic acid, and lupeol, plants including *Glycyrrhiza* sps, *Gymnema* sps, *Centella asiatica*, *Camellia sinensis*, multiple biological effects on glucose absorption, glucose uptake, and insulin secretion helped to prevent diabetic vascular damage, retinopathy, and nephropathy [27].

Triterpenoid chemicals found in *Agrimonia pilosa* may stimulate preadipocyte development by activating PPAR- and downstream-controlled genes. Triterpenes have been shown to increase the expression of PPAR, CCAAT enhancer binding protein (C/EBP), and sterol regulatory element binding protein 1, as well as GLUT4 and adiponectin [28]. As an adjuvant treatment for diabetic nephropathy, *Abelmoschus esculentus* contains pentacyclic triterpene ester [29] studied diabetic renal epithelial to mesenchymal transition (EMT), which suppresses high glucose-stimulated vimentin, AT-1, TGF-1, DPP-4, and restores E-cadherin in tubular cells and plays a key role in fibrosis. *Agrimonia pilosa* includes triterpenoid compounds that have been demonstrated to target oxidative stress and postprandial hyperglycemia by scavenging the DPPH, ABTS, and hydroxyl radicals, as well as glucosidase inhibitory actions in the carotene-linoleic acid assay. As a result, it shows great promise in the treatment of diabetes mellitus [30]. The structures of some important triterpenes are shown in Fig. (**4**).

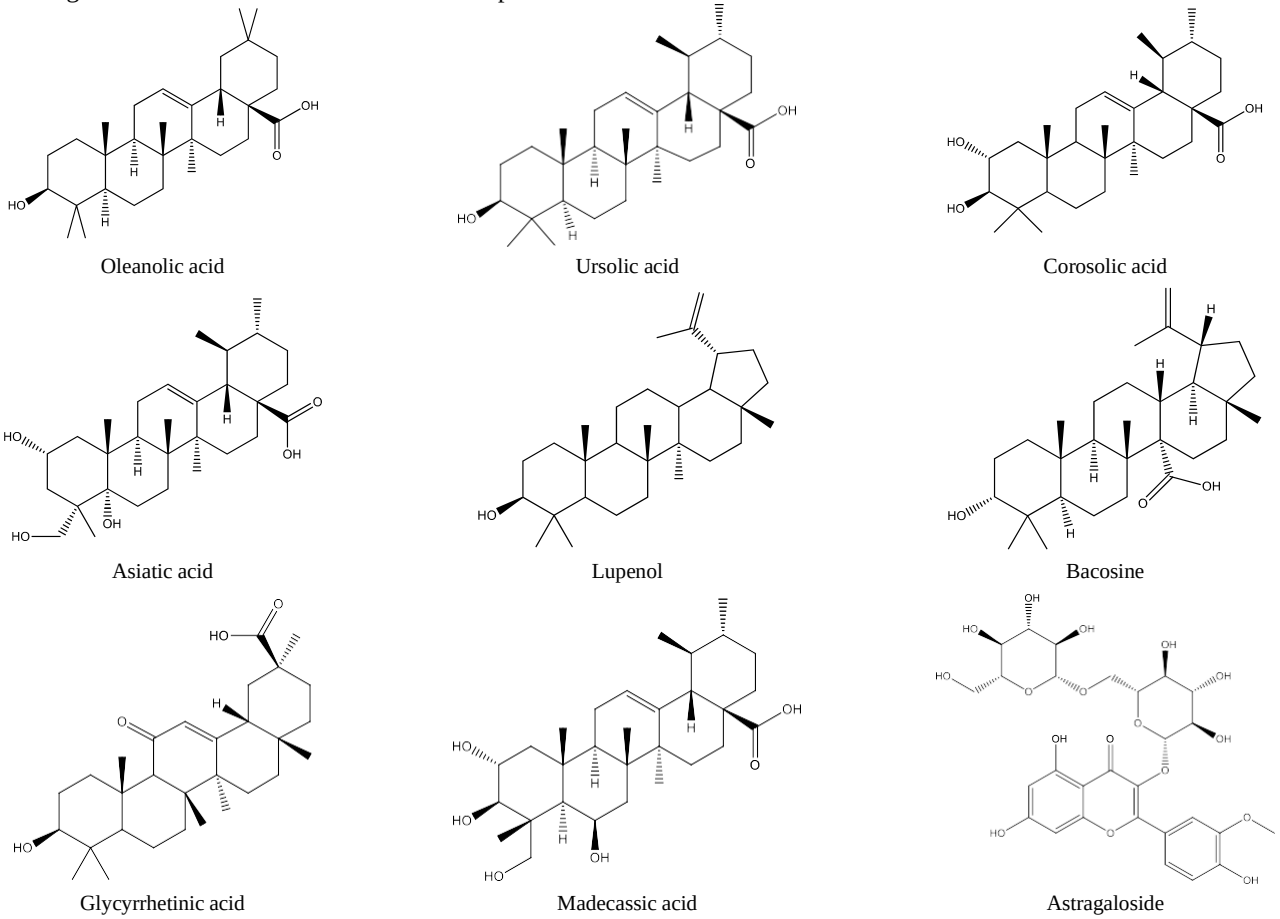

Fig. (4). Structures of flavonoids for diabetic complications.

Table 2. Effects of flavonoids in the treatment of diabetic complications.

Flavonoid	Diabetic Complication	Effects
Epigallocatechin	Diabetic nephropathy	Decrease the serum urea nitrogen, serum creatinine, creatinine clearance, and urinary protein excretion [51]
Apigenin	Hyperlipidemia	Decrease lipid accumulation [52]
Breviscapine	Diabetic nephropathy	Inhibition of the albumin excretion rate in urine [53]
Catechins	Diabetic nephropathy	Inhibition in urinary albumin excretion rate [54]
Daidzein	Cardiovascular disease	Decrease mechanical malfunction in ventricular myocytes [55]
Genistein	Diabetic nephropathy	Mechanical malfunction in ventricular myocytes (↓) [55]
Hesperetin	Diabetic retinopathy	Decrease glial fibrillary acidic protein [56]
Astilbin	Cardiovascular disease	Decrease in infarct volume, myocardial damage [57]
Isoquercetin	AGE formation	Inhibition of glycation [57]
Myricetin,	Osteopenia	Exhibition cell survival, ALP activity, collagen [58]
Naringin	Diabetic neuropathy	Reduced apoptosis [59]
Luteolin	Cardiovascular disease	Reduced myocardial apoptotic death [60]
Quercetin	Cardiovascular disease	Inhibition in body mass, TG, cholesterol, myocardial fructose decrease in immobility period [61]
Sylibin	Diabetic nephropathy	No effect on oxidative stress and podocyte injury [62]
Diosmin	Diabetic neuropathy	Exhibit GSH stimulation and no effct SOD activity [63]
Silymarin	Diabetic nephropathy	Decrease MDA, NO and Increase total thiol molecular [64]

Table 3. Anti-diabetic triterpenods and their mechanism of actions.

Terpenoids	Source	Anti-diabetic Activity	References
Oleanolic acid	*Aralia elata*	Lowering blood sugar levels	[65]
Ursolic acid	*Campsis grandiflora*	Increase insulin stimulation	[66]
Gymnemic acid	*Gymnema sylvestre*	Lowering blood sugar levels	[67]
Bartogenic acid	*Barringtonia racemosa*	Inhibiting pancreatic α-amylase	[68]
Corosolic acid	*Eriobotrya japonica*	Promotes 3*H*-glucose uptake	[69]
Oleanolic acid	*Gypsophila oldhamiana*	Hepatic glycogen phosphorylase [gp]	[70]
Oleanolic acid	*Gypsophila oldhamiana*	Hepatic glycogen phosphorylase [gp]	[70]
Asiatic acid and Madecassic acid	*Centella asiatica*	Increased the level of serum insulin	[66]
Glycyrrhetinic acid	*Glycyrrhiza uralensis*	Improvement in glucose tolerance	[71]
Lupenol	*Aegle marmelos*	B-cell protection	[72]
Oleanolic acid	*Aralia elata*	Reduction in blood glucose levels	[72]
Astragaloside	*Astragalus membranaceus*	Decrease in renal ages formation	[73]
Bacosine	*Bacopa monniera*	Enhancing glucose utilization	[74]
Gymnemic acid	*Gymnema sylvestre*	Promotes insulin secretion	[67]
Bartogenic acid	*Barringtonia racemosa*	Pancreatic α-amylase inhibition	[74]

(Table 3) Contd….

Terpenoids	Source	Anti-diabetic Activity	References
Ursolic acid	*Crataegus pinnatifida*	Insulin stimulation	[75]
Astragaloside	*Astragalus membranaceus*	Decrease in renal ages formation	[74]
Madecassic acid	*Centella asiatica*	Decreased blood sugar levels	[76]
Bacosine	*Bacopa monniera*	Decreased blood glucose	[66]
Glycyrrhetinic acid	*Glycyrrhiza uralensis*	Enhance insulin-stimulated glucose uptake, Improve glucose tolerance	[77]
Corosolic acid	*Eriobotrya japonica*	Promotes 3H-glucose uptake	[78]
Lupenol	*Aegle marmelos*	By β-cell protection	[79]
Ursolic acid	*Crataegus pinnatifida*	Decreased formation of ages	[80]

5.8. Studies on Flavonoids used for the Treatment of Diabetic Complications

Diabetes must be carefully managed, otherwise, it can lead to a variety of consequences, including heart disease, renal failure, nerve damage, and blindness. Flavonoids provide a wide range of health benefits and are engaged in the treatment of a variety of diabetes problems. Table **2** lists their unique bioactivities on various diabetes problems, as well as the metrics that were examined [51-64].

5.9. Triterpenes from Medicinal Plants as Anti-diabetic Agents

There have been reports of many traditional medicinal herbs being used to treat diabetes and diabetic complications as shown in Table **3** [27, 65-80].

CONCLUSION AND FUTURE PROSPECTS

As the prevalence of diabetes patients increases globally, medical researchers are under more pressure to provide effective treatments for the condition due to the complexity and diversity of the disease's etiology as well as its myriad effects. In the production of pharmaceuticals, natural products and their derivatives have shown to be a trustworthy source of bioactive chemicals. The impact of flavonoids on diabetes, diabetic complications, and their mechanism of action have been the subject of significant scientific advancement; however, more research will be required to fully understand the pharmacokinetic factors of flavonoids, including absorption, biotransformation, metabolism, and toxicological aspects. Current analyses of absorption and metabolism focused on a restricted set of dietary flavonoids suggest that the chemical structure of ingested flavonoids has an impact on their absorption after consumption. Although the focus of this study is on pure natural flavonoids, plant extracts have been demonstrated to have beneficial benefits in the treatment of diabetes mellitus. Unlike a single chemical entity focused on a single target, multi-flavonoid rich plant extracts were able to ameliorate diabetes mellitus symptoms, most likely through an integrated impact on several target sites. Flavonoids are abundant in a variety of edible fruits and vegetables that we consume on a regular basis. Plant extracts should, without a doubt, be considered a viable supplemental therapy for diabetes. Despite the fact that various classes of unique natural products have been produced for treatment, their value is limited due to the adverse effects of pharmacological therapy. Terpenoids play a potential role in the prevention and treatment of diabetes and diabetic complications such as retinopathy, nephropathy, neuropathy, embryopathy, and other vascular dysfunctions as a result of this.

LIST OF ABBREVIATIONS

TC	=	Total Cholesterol
TBARS	=	Thiobarbituric Acid Reactive Substances
AMPK	=	AMP- Activated Protein Kinase
ACC	=	Acetyl-CoA Carboxylase
MDA	=	Malondialdehyde
SOD	=	Superoxide Dismutase
CAT	=	Catalase
GSH-PX	=	Glutathione Peroxidase
GSH	=	Glutathione
ALP	=	Alkaline Phosphatase
TG	=	Triglyceride
LDL	=	Low-density Lipoprotein
HDL	=	High-density Lipoprotein
Akt	=	Protein Kinase B
LDH	=	Lactate Dehydrogenase
HMG-CoA	=	3-hydroxy-3-methylglutaryl-coenzyme A
HP	=	Hydroperoxides
LPL	=	Lipoprotein Lipase
LCAT	=	Lecithin-cholesterol Acyltransferase
NO	=	Nitric Oxide

Symbol meaning: ↑ = Increase

↓ = Decrease

→ = Normalize

CONSENT FOR PUBLICATION

Not applicable.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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