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The multifaceted role of flavonoids in mitigating diabetic complications: A systematic overview

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Abstract
Diabetes mellitus (DM) is a metabolic disease that is widespread around the world. Its frightening rate of occurrence places a heavy load on medical professionals. Diabetes is a chronic disease which is mainly caused by the decreased production of insulin. DM leads to various complications because of high severity of Hypertension, which leads to mortality and morbidity. Macro-vascular complications of diabetes, includes coronary heart disease, stroke and peripheral vascular disease. Micro-vascular complications include End-stage renal disease (ESRD or Nephropathy), retinopathy and neuropathy. Flavonoids are phenolic chemicals found in fungus, fruits, and vegetables as secondary metabolites. Flavonoids are further classified into 6 sub classes: flavonols, flavones, flavanones, isoflavones, flavanols, and anthocyanidins. Curcumin, quercetin, and rutin are Flavonoids with high antioxidant potential that are used to treat a broad spectrum of diabetic ailments. Flavonoids isolated from nature have anti-diabetic properties. Flavonoids, also improve diabetes pathogenesis and complications by regulating glucose metabolism, hepatic enzyme activity, and lipid profile. Quercetin has been clinically shown to help patients with diabetic retinopathy. The natural product kaempferol has potent anti- diabetic effects. Naringenin is a plant-based product used to treat diabetes and other metabolic diseases. The majority of research shows that some dietary flavonoids have a beneficial effect on diabetes. This review aims to shed light on the possible roles of flavonoids in avoiding or alleviating problems associated with diabetes.

Keywords: Diabetes mellitus, neuropathy, nephropathy, retinopathy, macro-vascular complications, micro-vascular complications, flavonoids

Introduction

Diabetes Mellitus

Diabetes is a chronic disease which is mainly caused by the decreased production of insulin (Hormone which regulates the blood glucose levels). Diabetes mellitus is disorder of decreased susceptibility to insulin. In this condition, the level of glucose in the blood increases, which is termed as hyperglycemia. Now a days diabetes is a common ailment in adequate ages [1].

In accordance with statistics from the International Diabetes Federation (IDF), in 537 million persons,110 people in between the ages of 20 and 79 have diabetes. The extensiveness of DMT2 accounts for nearly 85.0–95.0% of all cases of diabetes. Mainly because of the above reason prevention and treatment of Diabetes becomes the most elevated topic of present days.

Classification of DM

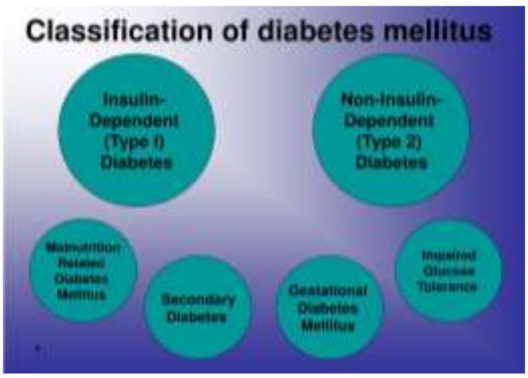


Fig 1: Classification of diabetes mellitus [2]

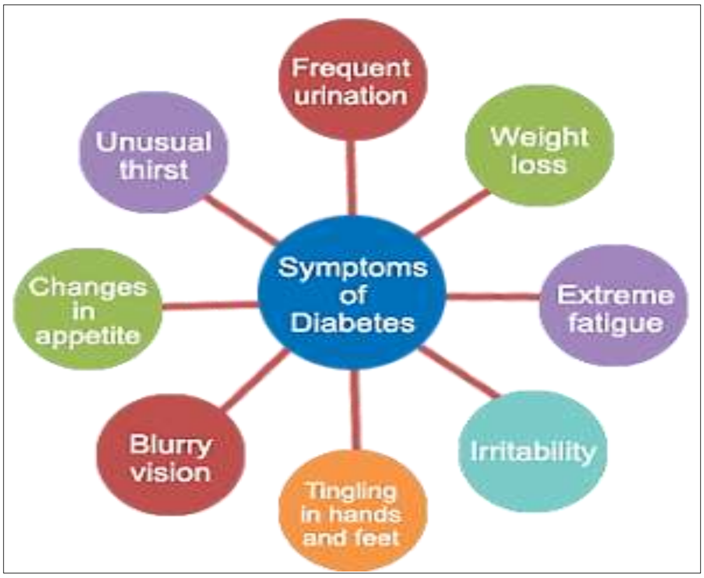


Fig 2: Symptoms

Diabetic complications

DM leads to various complications because of Hypertension, which leads to mortality. Complications of DM mainly classified into two types.

1. The Macro Vascular Complications
2. The Micro Vascular Complications

The macro-vascular complication is defined as the complications that affects the large blood vessels. The macro vascular complications are Coronary Artery Disease, Cerebrovascular disease and Peripheral artery Disease [3]. The micro-vascular complication is defined as the complications that affects the smaller blood vessels of peripheral nerve, kidney(renal) and retinal that lead to neuropathy, nephropathy and retinopathy Disease [3]. Generally Hypoglycemic medicinal therapy is used in the practice of treatment of DMT2.However, as of right now, most hypoglycemic medications have certain harmful side effects. Hence, many specialists are researching for more potent and secure ways of treatment Diabetes mellitus type2 (DMT2) [3].

What are Flavonoids?

Flavonoids are poly-phenolic secondary metabolites which are frequently found in plant fruits and vegetables, as well as in fungus. The chemical structure of flavonoid includes two phenolic rings, a hetero cyclic ring with an oxygen incorporated in it, and fifteen carbon atoms [4]. Based on ethnobotanical evidence, about eight hundred plants could have anti-diabetic qualities [5].

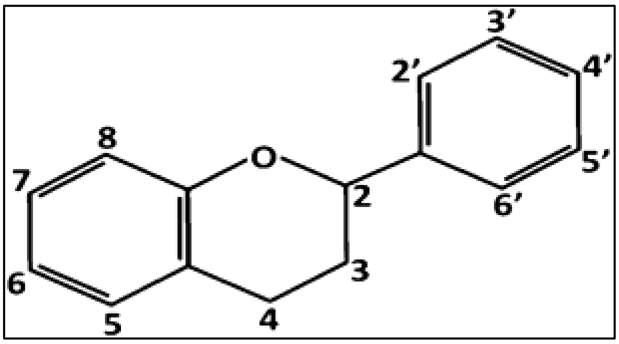


Fig 3: Basic structure of flavonoid

Why only flavonoids?

Flavonoids are highly present in the plant source like fruits and vegetables. Flavonoids consists of different biological activities like organ protection, anti-inflammatory activity, lipid lowering, Anti-oxidative effect and hypoglycemic effect. Flavonoids plays an important role in improving the pathogenesis of diabetes and its complications in many ways like regulation of glucose metabolism, hepatic enzyme activities and a lipid profile. This paved the way for the developing of novel flavonoid-based hypoglycemic drugs.(6)
6 subdivisions comprise the flavonoid family: flavonols, flavanones, iso flavonoids, flavones, flavan, and anthocyanidins.

Sub-classes of flavonoids

1. Flavanols: Quercetin, Kaempferol, Isohamnetin, Rutin, Fiestin, Myricetin.
2. Flavanones: Naringenin, Hesperidin, Naringin, Silybin.
3. Isoflavonoids: Genistein, Daizein, Glycitein [7].
4. Flavones: Apigenin, Luteolin, Tangeretin [7].
5. lavan: Epicatechin gallate, Catechins, Theaflavin, Proanthocyanidins.
6. Anthocyanins: Cyanidin, Delphinidin, Malvidin, Peonidin, Petunidin.

Flavanols

Flavanols are generally present in Apples, berries, Brassica vegetables, capers, grapes, onions, shallots, tea, and tomatoes, as well as many seeds, nuts, flowers, barks and Green leafy vegetables, including spinach and kale, and herbs such as dill, chives, and tarragon. Flavones are highly available in numerous plants. Some of the flavones are Quercetin, Kaempferol, Rutin, Fiestin.

Quercetin

Controlling hyperglycemia in diabetes has proven challenging due to the high doses of oral anti-diabetic agents and insulin necessary. Due to higher and prolonged usage of the drugs cause toxicity. Hence naturally obtained flavanols are used in the treatment of DM [8]. Quercetin is the main member of class of flavonoids family. Quercetin is abundantly present in vegetables and fruits, such as onions, apples, berries, multiple nuts, seeds, barks, flowers, and tea. Quercetin possesses anti-oxidant activity and might enhance beta-cell function and insulin secretion from the Langerhans islets in the pancreas, making it a viable alternative to pharmaceutical therapy for diabetic patients [5].

Quercetin confers its anti-diabetic potential by activating multiple targets for the treatment of type 2 diabetes, and it leads to metabolism of glucose in L6 myotubes via the AMPK-P38 MAPK pathway.

- Quercetin plays an important role in enhancing the activity of β cell through:
- Increase in secretion of insulin.
- By Protecting the β cell from being damaged.
- Elevated proliferation of β cells
- Quercetin acts on the Islets of beta cells and reduces the plasma cholesterol, fasting plasma insulin and glucose postprandial.

In diabetic retinopathy patients, by inhibiting NF-B cells, monocyte chemo-attractant protein 1 (MCP-1), and the inter cellular adhesion molecule 1, quercetin might decrease inflammation and oxidative stress, two important causes of problems associated with diabetes. (ICAM1) [5]. Quercetin has a higher safety profile than commercially available diabetes medications.

Quercetin can also be produced on a large scale using a novel fermentation-based glycosylation strategy using low-cost substrates such as food waste [9]. Quercetin produced in this manner can be converted to nano-particles or encapsulated to improve its low bio availability. A highly pure version of quercetin (QU995) was classified as "generally recognized as safe" by the FDA in 2010 [9].

Kaempferol

The natural product kaempferol has potent anti-diabetic effects. Kaempferol chemically known as 3,5,7-trihydroxy-2-[4-hydroxyphenyl]-4H-1- benzopyran-4-one [10]. Kaempferol is highly present in traditional medicines, such as *Sophora japonica*, ginkgo, and galangal, and in foods, such as beans, cauliflower, cabbage, gooseberry, grapes, cabbage, strawberries, tea, and tomatoes [11]. Natural plants, such as *Ginkgo biloba*, galangal, and Pueraria, have a long tradition of cultivation, especially throughout Asia. Three main viewpoints constitute the basis of the kaempferol mechanism. Initially, kaempferol enhances insulin resistance and controls lipid metabolism to lessen lipo-toxicity. Second, kaempferol lessens glucose toxicity by enhancing insulin signaling and reestablishing the equilibrium between glucose synthesis and utilization. Lastly, kaempferol balances the imbalance between autophagy and apoptosis to safeguard B cells. Therefore, one of kaempferol's anti-diabetic actions is to stop the development of the "obesity-IR-b-cell apoptosis cycle" [11, 12]. Kaempferol is the major natural flavonoid drug used in the treatment of diabetic neuropathy. Kaempferol does not significantly alter blood plasma glucose levels; however, it significantly lowers plasma glucose levels in diabetic rats after 45 days of treatment [13].

Insulin resistance (IR); Type 2 diabetes mellitus (T2DM)

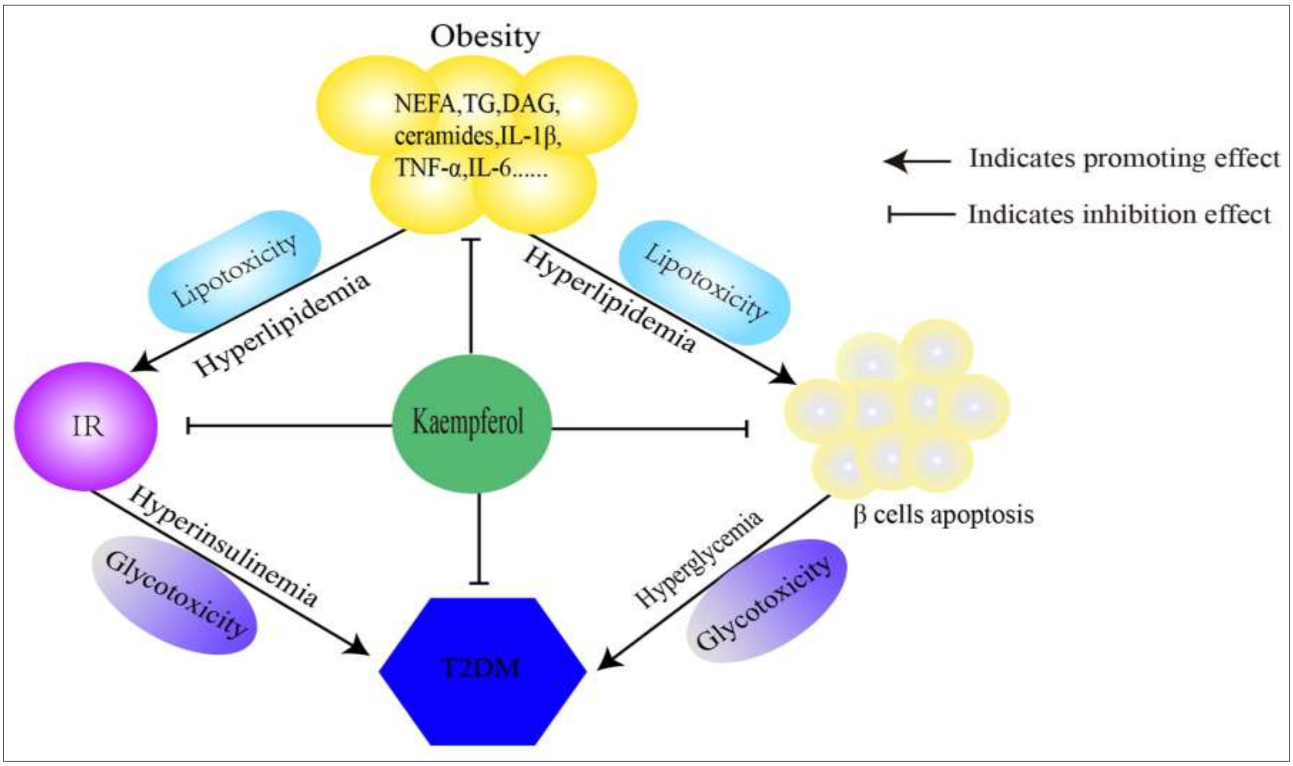


Fig 4: Mechanism of kaempferol(14)

Rutin

Rutin (3,3′,4′,5,7-pentahydroxyflavone-3-rhamnoglucoside) belongs to the flavonoid of the flavonol class found all throughout the plant kingdom [15]. Because Ruta graveolens contains rutin, the name "rutin" is derived from the plant [13].

Rutin is found in numerous plants, which includes *Ruta graveolens*, *Morus alba*, asparagus, and buckwheat. Rutin is a polyphenolic compound that belongs to the flavonoid class and is one of the most abundant. Rutin can lower blood sugar levels; however, it should only be used with caution in diabetics who are taking blood sugar-lowering medications. When rutin supplements are taken along with medications, blood sugar levels may fall too low, contributing to hypoglycaemia (low blood sugar) [16]. Rutin is widely used to treat macro vascular complications caused by DMT2. Multiple research investigations have shown that rutin inhibits two enzymes that catalyse carbohydrate digestion, -glucosidases and -amylase, which indirectly helps in glucose regulation [13].

Fiestin

Fiestin (3,3′,4′,7-tetrahydroxy flavone) is a structurally related flavan-3-ol found in plants such as apple, strawberry, grape, persimmon, cucumber, and onion [13]. By restoring the balance between histone acetylation and deacetylation, fiestin suppresses the release of proinflammatory cytokines via the nuclear factor-B signaling pathway. The impact of fiestin on the activity of histone deacetylases (HDAC) and acetyltransferases (HAT), NF-B acetylation, and the expression of inflammatory genes [17].

Fiestin shows its anti-diabetic activity by various modes of action like, by reducing the activity of carbohydrate metabolism enzymes, inhibition of glycogenolysis and gluconeogenesis, by reducing the activity of the enzymes glucose 6 phosphate dehydrogenase (G6PD) and glucose 6-phosphatase (G6Pase) and by inhibition of high glucose biomolecule-induced cytokine production [13].

Naringenin

Naringenin (4,5,7-trihydroxy-flavanone) is a type of natural flavonoid that comes from citrus and grapefruits. Naringenin belonged to the sub class flavanones [18]. One of the major biologically active components of *Sambucus nigra L.* (elderflower) is naringenin, which significantly increases glucose uptake [13]. Many researches confirmed the benefits of phytoconstituents with anti-diabetic effects in the management of diabetes mellitus [19]. Naringenin has a wide range of pharmacological actions, including as anti-inflammatory, anti-tumor, nephroprotective, anti-immunomodulatory, atherosclerotic, neuroprotective, hepatoprotective, anti-cancer, and antidiabetic properties [19]. Naringenin therapy lowered intestinal sleeve and renal glucose uptake in a dose-dependent manner [18].

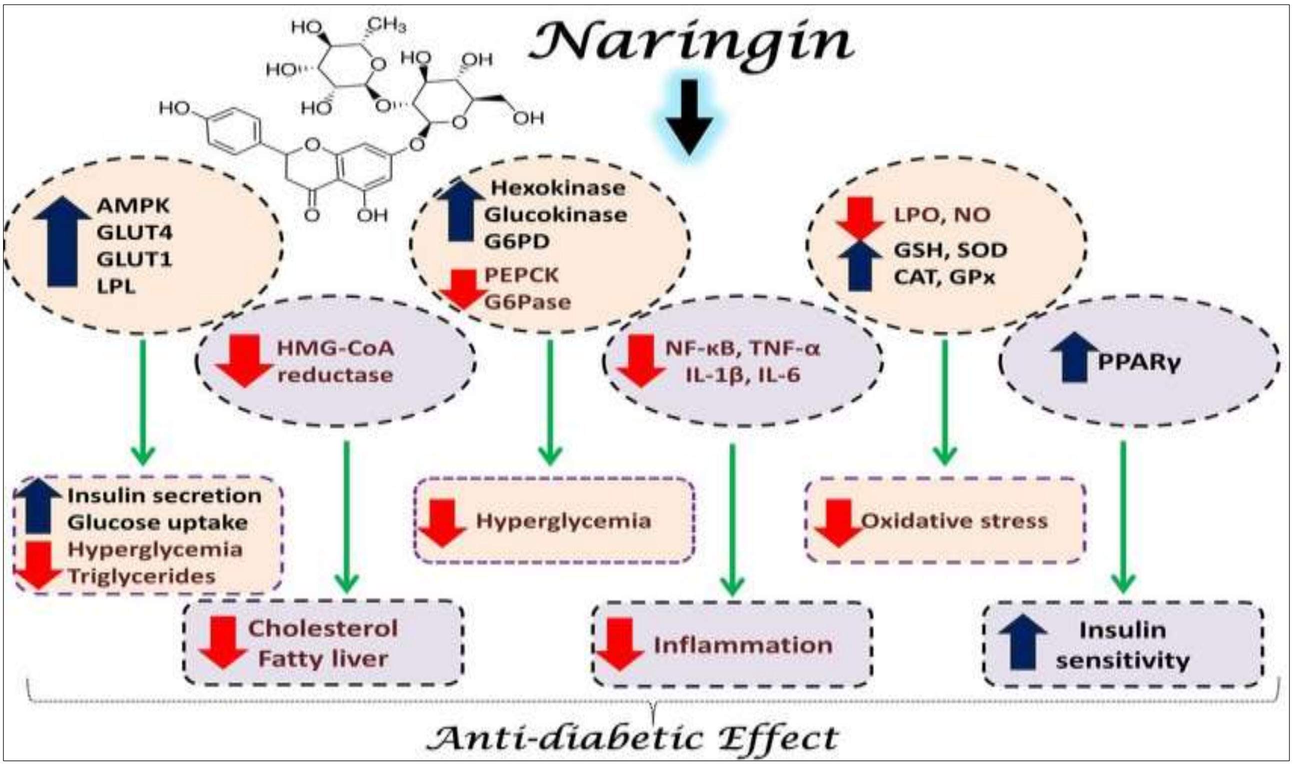


Fig 5: Anti-diabetic activity of naringenin

Morin

Morin (3,5,7,29,49-pentahydroxyflavone a natural bio flavonoid and an important component of traditional medicinal herbs, has been identified from Moraceae family members and is found in various plants, fruits, and wine. Morin, a dietary flavonoid derived from *Psidium guajava* [20]. Morin's has ability to protect against hyperglycemia-induced alterations in the apoptotic pathway. Hepatocytes can be shielded by morin from the apoptosis and dysfunction brought on by high blood sugar. Morin has a systemic protective effect and assists in reducing the harmful side effects of numerous medications without interfering with their action [13]. Morin was also discovered to suppress the production of advanced glycation end products, which was linked to long-term diabetes issues [21]. Flavonoids have the power to alter insulin resistance, hyperglycemia, dyslipidemia, and adipose tissue metabolism. They may additionally reduce inflammatory processes, stress-sensitive signaling pathways, oxidative stress, and inflammatory processes [22].

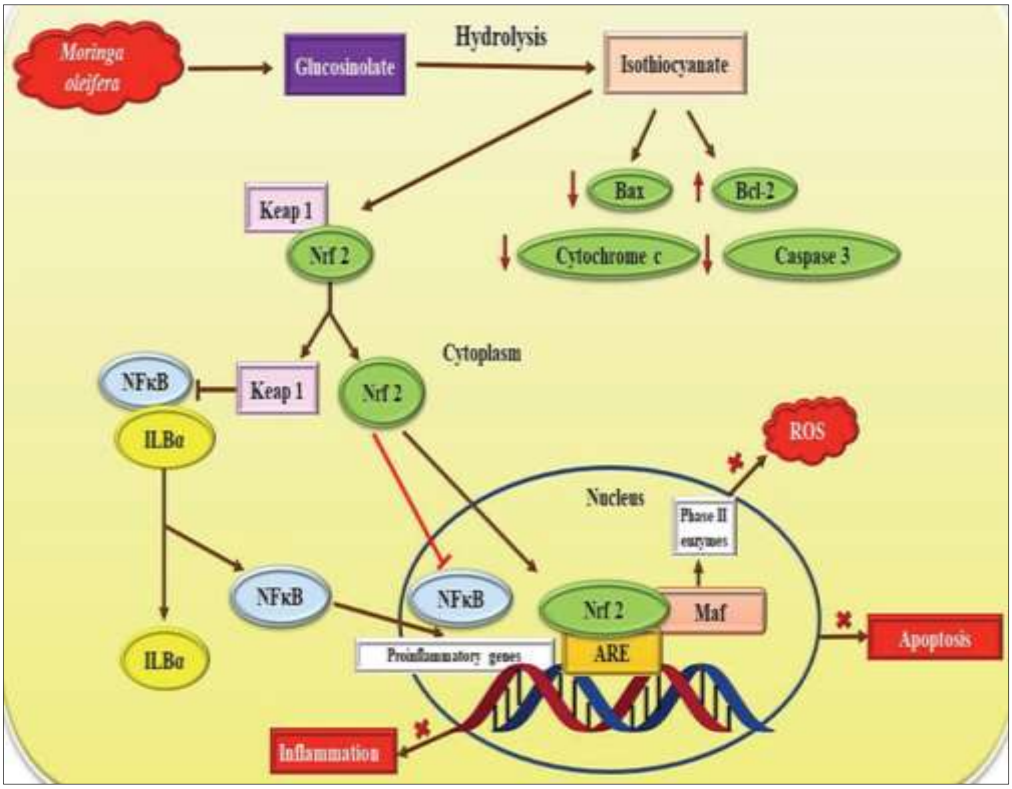
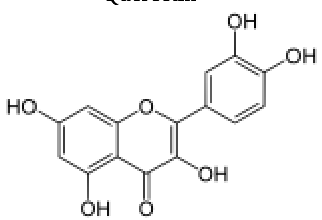
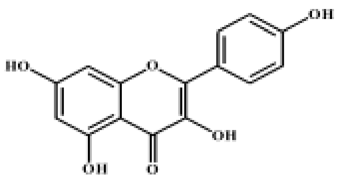
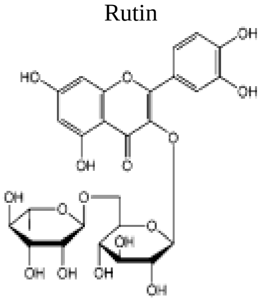
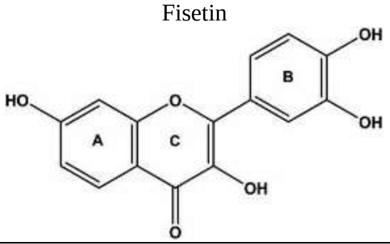
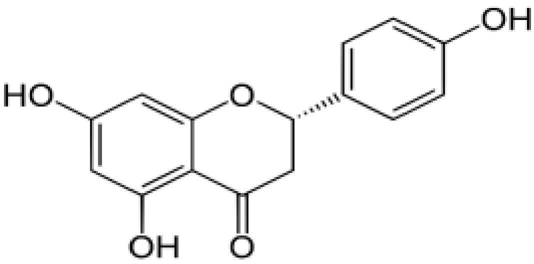
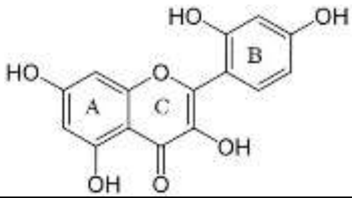


Fig 6: Mechanism of morin

Table 1: Different flavonoid and their sources

Flavonoids	*Mechanism of action*	Plants
Quercetin [8] 	1. Inhibits the glucose transporters activity. 2. Increases glucose uptake in skeletal muscle cells by activating the AMPK signaling pathway 3. Has a negative impact on -glucosidase. 4. Aids in the regeneration of beta cells and guards against damage to pancreatic islet beta cells [12]. 5. Lowers hepatic glucose production [4, 6].	*Vaccinium vitis-idaea* L [8, 23]. *Allium cepa* L. *Alliumfistulosum* *Camelliasinensis* *Capsicumannum* *Euonymus alatus* [13]
Kaempferol [11] 	1. Inhibitory control on *α*-glucosidase [12]. 2. Improves the expressions of AMPK and GLUT4 3. Beta cells are protected against hyperglycemia-induced *β*-cell toxicity [4, 13].	*Ginkgo biloba* *Tilia spp.* *Sophora japonica* [11]
Rutin 	1. The presence of antioxidants. 2. The enzymes amylase and glucosease are inhibited 3. Promotes muscle cell glucose uptake. Enhances Ca2+ ion uptake and influences insulin secretion [4].	*Ruta graveolens* *Morus alba* *Amaranthus viridis*
Fisetin 	1. Reduces enzymes involved in carbohydrate metabolism. 2. Reduces gluconeogenesis and glycogenolysis [24]. 3. Reduces glucose 6-phosphate dehydrogenase (G6PD) and glucose 6-phosphatase (G6Pase) activity. 4. Stops high glucose compounds from causing the generation of cytokines [4, 13].	*Cotinus coggygria* *Butea frondosa* *Gleditsia triacanthos* *Quebracho Colorado* *Curcuma longa* *Rhus verniciflua* *Acacia greggii* *Acacia berlandieri* [13]

Naringenin 	1. activates the AMPK signaling pathway, which increases the absorption of glucose in skeletal muscle cells. 2. Prevents the apoptosis of the -cells. 3. Effect on -glucosidases that inhibits them. Reduces gluconeogenesis by AMPK up regulation [4, 13].	*Sambucus nigra* L. *Madagascar periwinkle* *Catharanthus roseus* *Elaeodendron croceum* [13]
Morin [25] 	1. Presence of Anti-Oxidant characters. 2. Promotes insulin secretion from the pancreas. Enhances insulin resistance [4, 13].	*Psidium guajava* [20] *Prunus dulcis* [20] *Chlorophora tinctoria* *Maclura pomifera* [13]

Complications

Micro vascular complications of diabetes include Retinopathy,Nephropathy and Neuropathy. Macro vascular complications of diabetes include Cardio vascular diseases, Stroke and Peripheral artery disease (26).

Schematic-overview-of-mechanisms-contributing-diabetic-Complications-

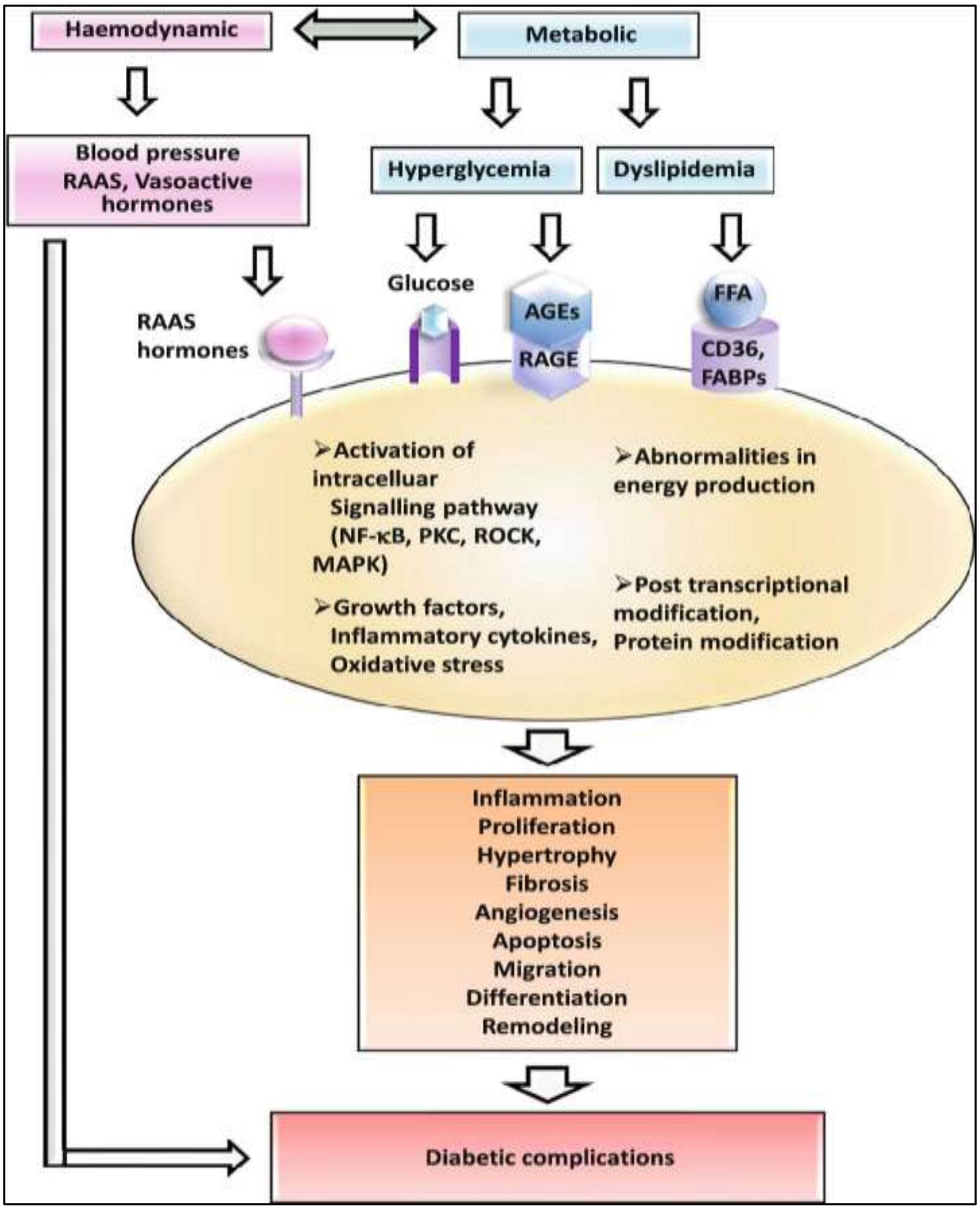


Fig 7: Mechanism of Diabetic Complications

Micro vascular complications
Diabetic Retinopathy

Diabetic Retinopathy (DR) is the most common micro vascular complication of DM which is responsible for more than 10000 new cases of blindness alone in United states [27, 28]. In the U.K. Prospective Diabetes Study (UKPDS), DR is primarily developed in DM patients based on the degree of hyperglycemia and the existence of hypertension0.Retinopathy usually develops in DMT1 individuals almost 20 years after the disease is first diagnosed. However, in DMT2 patients, retinopathy can appear as early as two years before the condition is identified [28]. Diabetic Retinopathy is classified clinically into two stages: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) [29]. NPDR is the first stage of DR, characterized by a rise in vascular permeability and capillary blockage in the retinal vasculature. Even if the patients are asymptomatic, fundus photography can detect retinal diseases such as micro aneurysms, hemorrhages, and hard exudates. Neovascularization characterizes PDR, a more advanced stage of DR. Patients may experience severe vision impairment during this stage if the new aberrant arteries flow into the vitreous (vitreous haemorrhage) or if tractional retinal detachment is present [29].

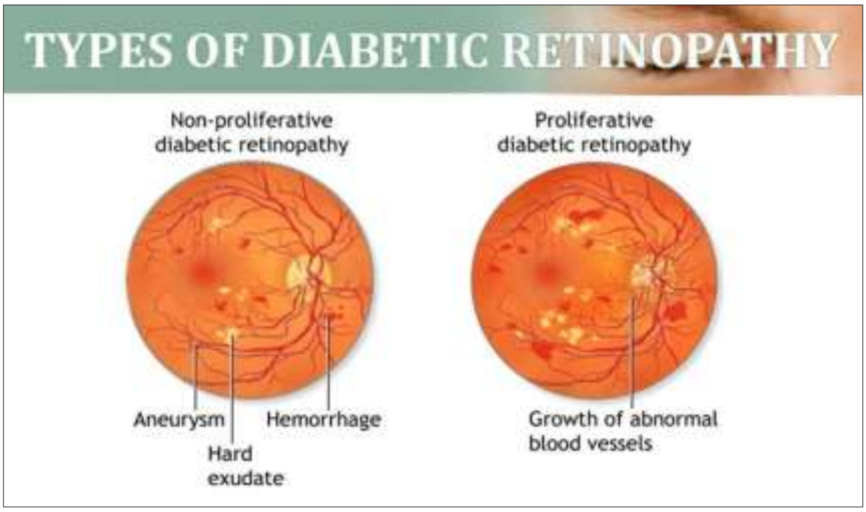


Fig 8: Diabetic retinopathy (DR)

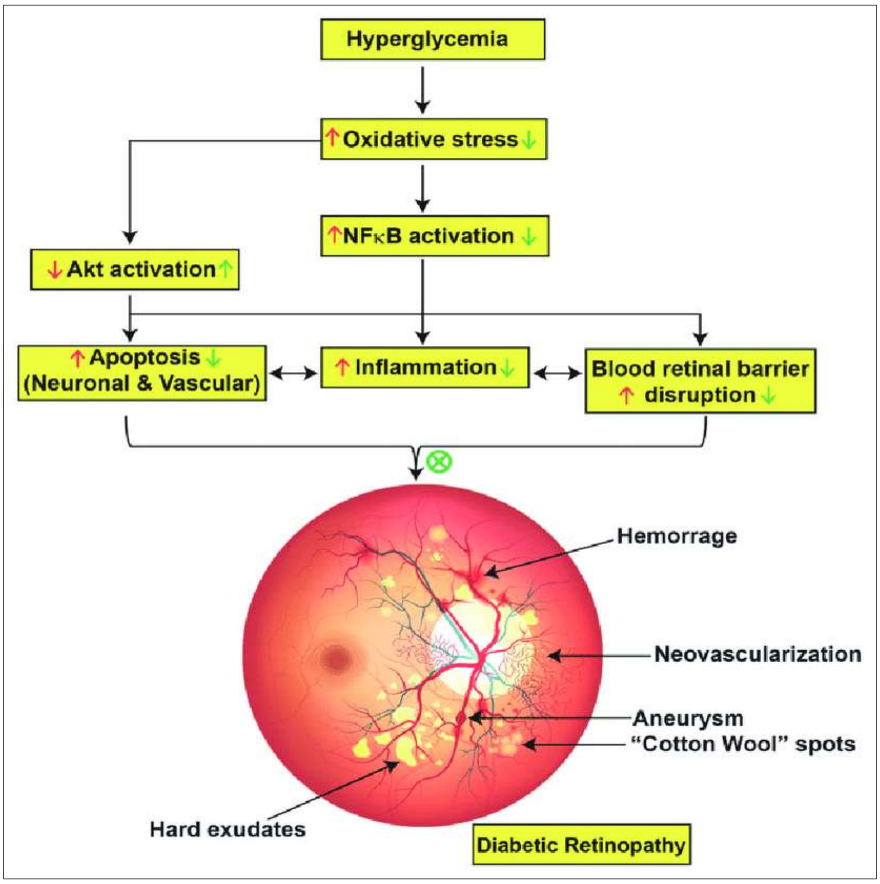


Fig 9: Pathogenesis of Diabetic Retinopathy

Table 2: Flavonoids on diabetic retinopathy (DR)

S. No	Sub class	Drugs	Source	Mode of action
1	Flavanones	Eriodyctiol	*Eriodyctiol californicum*	Decreases the intensity of inflammation in the retina [29]. Minimize plasma lipid per-oxidation. Blood retinal barrier stability.
		Hesperidin	*Citrus paradise* [28]	Reduces blood retinal degradation. Increases retinal thickness. Reduces blood glucose level. Reduces aldose reductase activity.
2	Flavanols	Epicatechin [28]	*Camillia sinensis*	Inhibition of ocular neovascularization.
3	Flavanols	Myricetin [28]	*Solanum lycopersicum*	Inhibition of advanced glycation.
		Rutin [16, 28]	*Malus pumila*	Increases brain derived neurotropic factor [15, 16, 28].
		Icariin [28]	*Epimedii herba*	Increases the nerve growth factor and glutathione.
4	Isoflavones	Puerarin	*Pueraria lobata*	Reduces retina pigment epithelial apoptosis. TR-Ibrb2 cells showed reduced IL-1-mediated leukostasis and apoptosis.
5	Flavones	Scutellatin	*Scutellaria barbata*	Reduces angiogenesis effects caused by high glucose.
		Silybin	*Silybum marianum*	Prevents the formation of destroyed the capillaries.
6	Anthocyanins	Peonidin	*Vaccinium oxycoccus*	Alternative therapy to DR. Natural anti-oxidant.

Diabetic Nephropathy

Diabetic nephropathy (DN) is the most prevalent consequence of diabetes, affecting at least 30% of diabetic individuals and posing a significant public health burden [30]. DN is characterized by a complicated pathogenic mechanism that includes hyperglycemia, elevated levels of reactive oxygen species (ROS), and defective podocyte autophagy. The main risk factor of the DN is, it directly effects the cardio vascular system of the patient who is suffering with diabetic neuropathy. Dyslipidaemia is occurred by diabetic nephropathy as a risk factor.

The schematic overview of inflammatory mechanisms in the pathophysiology of DN

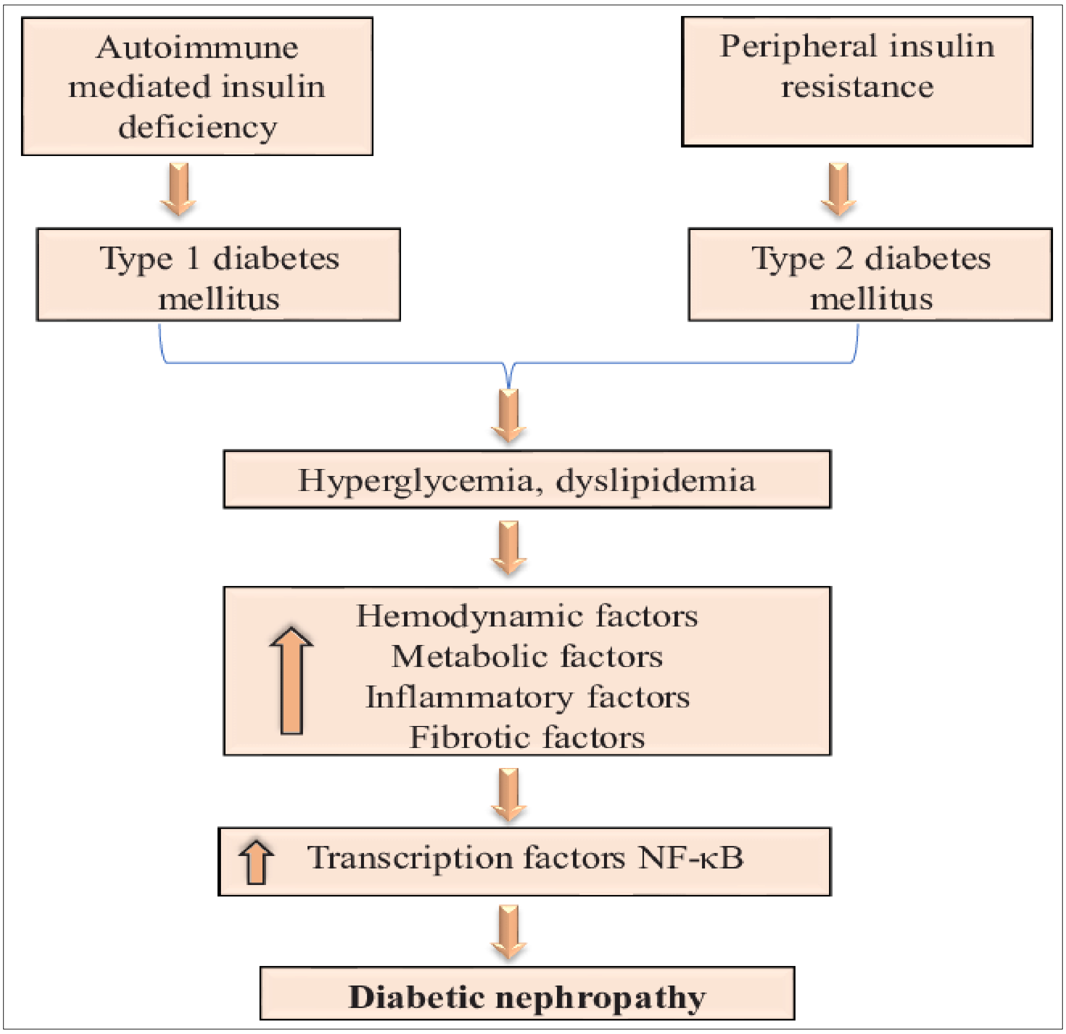


Fig 10: Pathophysiology of DN

Table 3: Flavonoids on DR

S. No	Drugs	Mode of Action	Source
1	Quercetin	Reduces oxidative stress Eliminates free radicals Reduces inflammation [30]	Buck wheat
2	Baicalin	Increases the levels of sirtuin 1 [31] Inhibits the NF-Kb pathway	*Scitellaria baicalensis*
3	Kolaviron	Reduces lipid peroxidation [32]	Garcina kola seeds
4	Myricetin [33]	Increases the activity of glutathione peroxidase and xanthane oxidase.	*Myrica rubra* [34, 35]
5	Luteolin	Increases anti-oxidant properties Increases anti-inflammatory properties [30]	*Chrysanthemum indicum* var. albescens, *Codariocalyx motorius* (Houtt.) H. Ohashi, and *Artemisia asiatica* [36]
6	Hidrosmin [37]	Blocks the action of several important pathogenic processes, including oxidative stress, inflammation, vasoprotective factor, and early aging.	Citrus fruits
7	Eriodictoyl	Eriodictyol enhances nephroprotective mechanisms such as antioxidant and anti-inflammatory functions [38]	*Eriodictyon californicum*
8	Genistein [39]	Decrease RAAS excessive activity by lowering upstream oxidative stress and inflammatory processes, resulting in DN relief.	*Helianthus annus* [39] *Carum carvi* [39]
9	Apigenin [40]	Apigenin therapy improves renal function, reduces oxidative stress, and reduces fibrosis [40].	*Petroselinum crispum*
10	Proanthocyanidin [41]	Decrease lipid peroxidation, platelet aggregation, and inflammation.	*Malus domestica*

Diabetic Neuropathy

Diabetes neuropathy is the most prevalent consequence of type 2 diabetes. Diabetic neuropathy is generally termed as Diabetic peripheral neuropathy (DPN) [42] DPN has primarily concentrated on peripheral nerves, such as axonal degeneration, demyelination, Schwann cell disease etc. DPN condition is multifactorial and characterized by hyperglycemia, dyslipidaemia, oxidative stress, mitochondrial dysfunction, and calcium homeostasis loss [43].

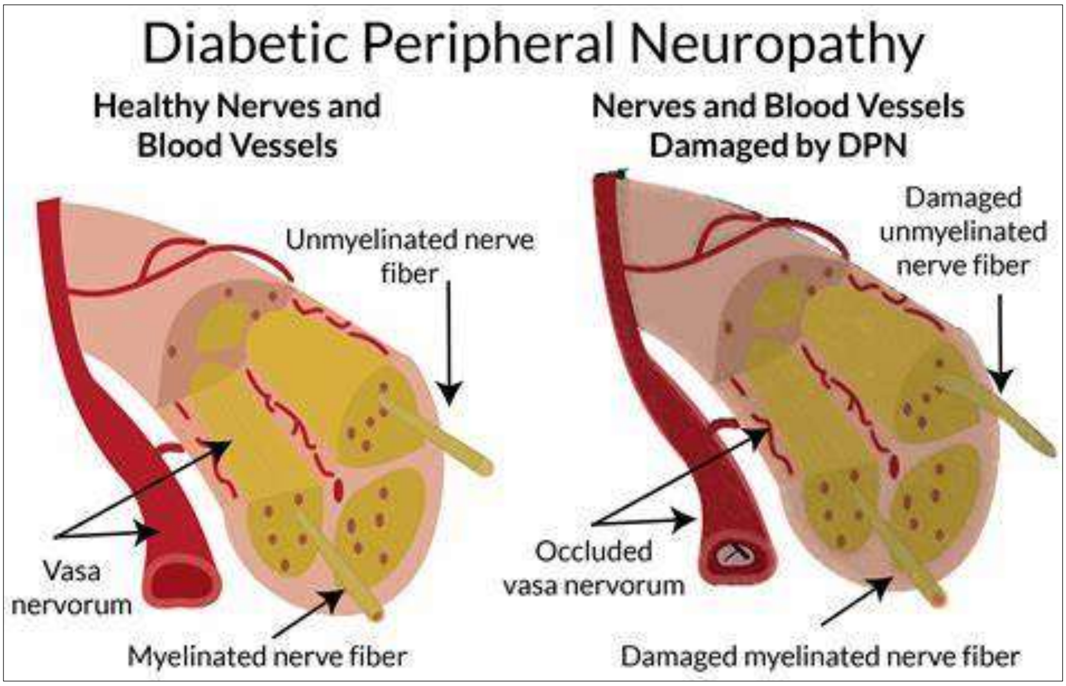


Fig 11: Diabetic peripheral neuropathy (DPN)

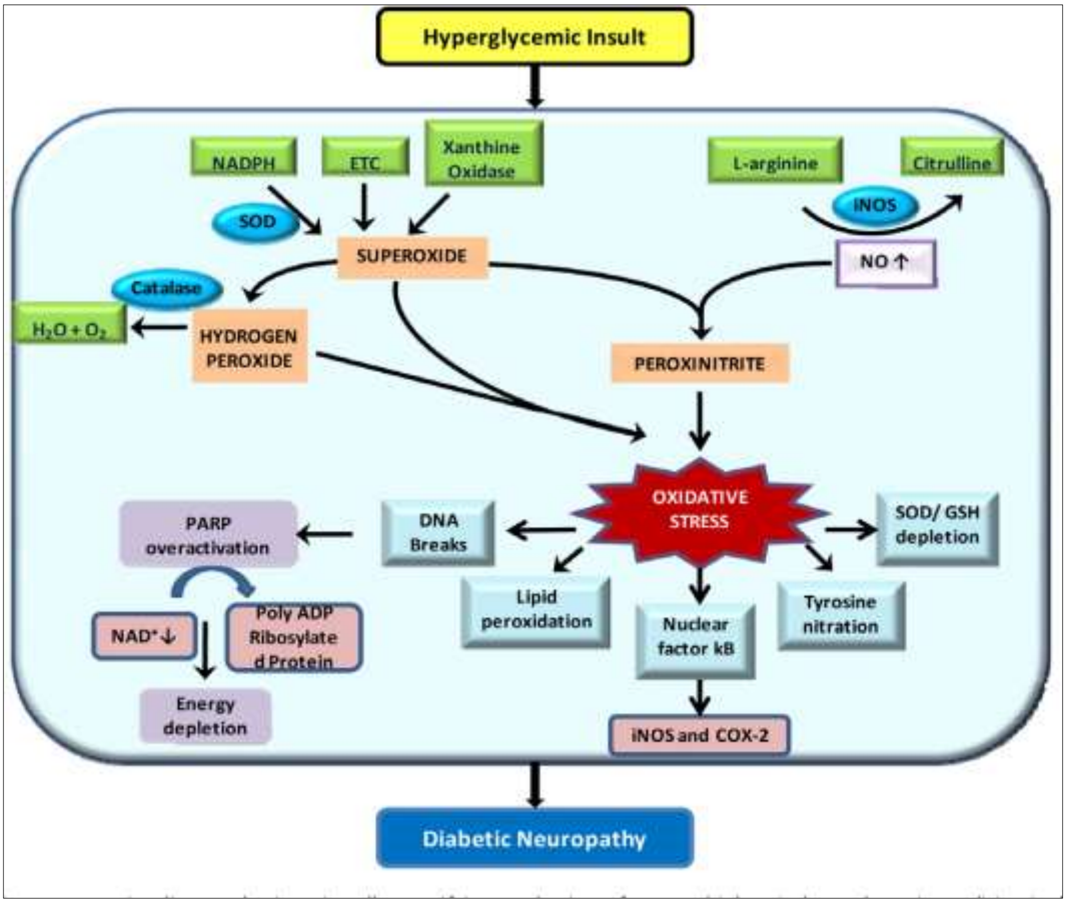


Fig 12: Pathophysiology of Diabetic peripheral neuropathy (DPN) [44]

At least 50% of diabetics eventually develop diabetic neuropathy. Controlling blood sugar considerably reduces the development of diabetic neuropathy in people with type 1 diabetes; in people with type 2 diabetes, the effects are less noticeable [42].

Table 4: Flavonoids on diabetic neuropathy (DPN)

S. No	flavonoids	Mode of action	Plant sources
1	Proanthocyanidins	Maintain proper morphology of nervous system.	*Vitis vinifera*
2	Epigallocatechin-gallate (EGCG)	Increases velocity of nerve conduction. Protects cellular DNA from reactive oxygen species (ROS). Reduces lipid per oxidation. Prevents neuronal hyperactivity.	*Camellia sinensis*
3	Quercetin	Reduction of severity of numbness and jolting pain.	*Brassica oleracea*
4	Puerarin	Increases hemorheological index.	*Pueraria tuberosa*
5	Naringenin	reduces oxidative stress and nerve growth factor contrast in diabetic neuropathy.	*Citrus sinensis*
6	Baicalein	reduces motor and sensory nerve conduction velocity impairments, as well as thermal hypoalgesia.	*Scutellaria baicalensis*
7	Curcumin	helps with nerve regeneration and functional recovery.	*Curcuma longa*
8	Diosmin	Back up the lost weight.	*Citrus limon*

Macrovascular complications

Cardiovascular disease

Diabetes is widely acknowledged for increasing the morbidity and mortality linked to cardiovascular disease [27]. cardiovascular diseases (CVD) are the leading cause of high death rate globally. Currently, age and gender are two main influencing factors of cardiovascular diseases. Cardiovascular diseases are mainly the conditions of structure and functions of heart. Those conditions include Arrhythmia, Marfan`s syndrome, coronary artery disease, peripheral artery disease, Atherosclerosis etc.

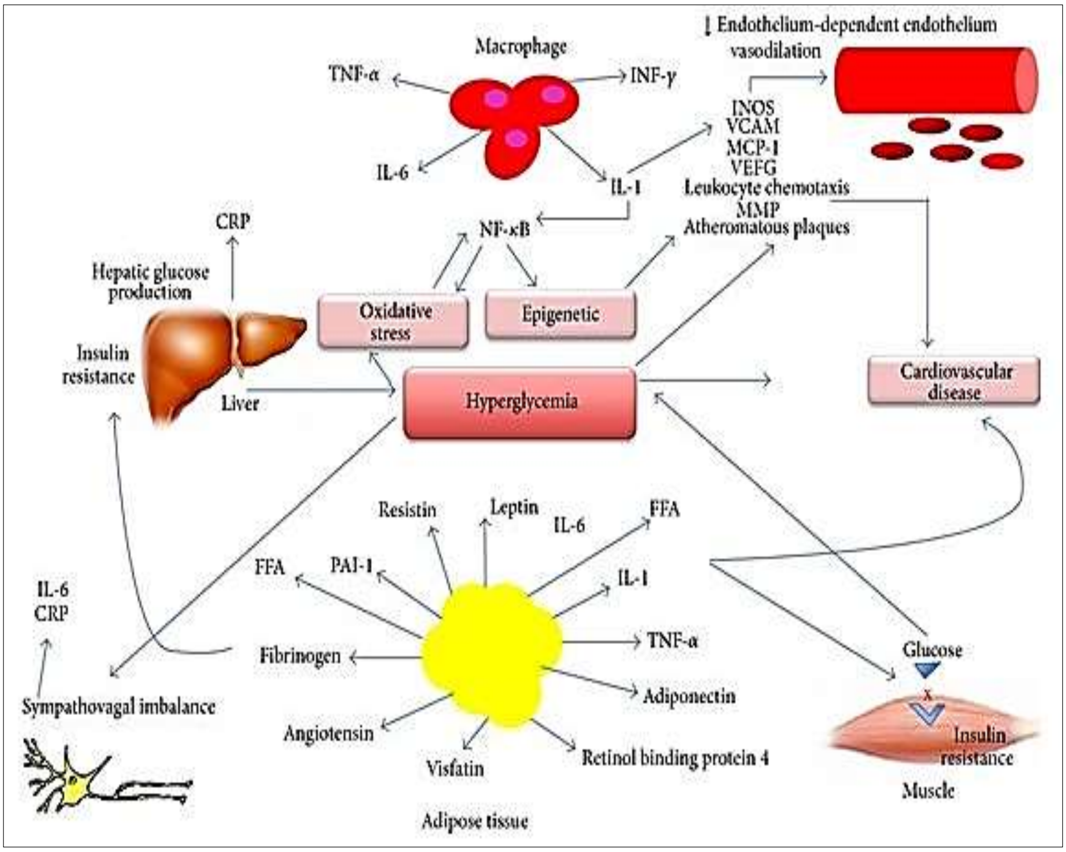


Fig 13: Pathogenesis of cardiovascular disease in diabetes

There are multiple natural flavonoids are used in the therapy of diabetes cardio vascular disease. The combination of flavonoids is widely used in the treatment of the diseases.

Atherosclerosis is a chronic, inflammatory, fibroproliferative condition that affects mostly the big and medium-sized conduit arteries [45].

Table 5: flavonoids in macro vascular complications

Disease	Flavonoid	Source	Mode of action
Atherosclerosis	Anthocyanidin [46] Quercetin	Citrus plant Red onions, kale	Decreases the inflammation and oxidative stress. Inhibits the lipid lowering characters [45]
Ischemia	Wogonin	*Scutellaria baicalensis* Georgi	Reduce cell suffering induced by cardiac or cerebral ischemia by increasing endothelial nitric oxide concentrations [46]
Hypercholesterolemia	Genistein Kaempferol Bavachin	*Flemingia vestita* *Camellia sinensis* *Psoralea corylifolia*	Increases the high-density lipoprotein and decreases low density lipoprotein [45]. Inhibits the acetyl coenzyme a transferase activity.
Myocardial infraction	Astilbin	*Smilax china* L.	Reduces myocardial damage.
Hypertension	Silymarin	*Silybum marianum* [27]	Changed the levels of renal anti-oxidant enzymes.

Cerebrovascular disease

Cerebrovascular disease is mainly termed as the set of conditions which involves in the affect of blood flow to the brain. stroke, intracranial stenosis, carotid stenosis, vertebral stenosis, aneurysms, and vascular abnormalities are some of the frequent disorders that might be classed as cerebrovascular illness [47].

Human and animal nutritional supplementation studies with flavonoid-rich plant or food extracts have showed improvements in cognition function, presumably by shielding fragile neurons, increasing existing neuronal function, or encouraging neuronal regeneration [48].

Table 1: Drugs in cerebrovascular diseases

S. No	Drugs	Mode of action	Sources
1	Apigenin	Protects neurons against oxidative damage [49].	*Allium cepa*
2	Luteolin	Prevents neuroinflammation.	*Allium porrum*
3	Genistein	Elevates the cerebral blood flow.	*Glycine max*
4	Proanthocyanins	Increases neuronal spine density.	*Prunus dulcis*
5	Taxifolin	Anti-glycation activity. Anti – oxidant activity [49].	*Taxodium distichum*
6	Kaempferol	Anti-oxidant activity.	*Brassica olarecea Brassica oleracea var. botrytis*

Conclusion

Diabetes mellitus is a metabolic and endocrinological condition with a growing global frequency and incidence(50). A considerable corpus of flavonoids may have positive effects in the battle against diabetes problems. The antioxidative, anti-inflammatory, and antihyperglycemic characteristics of flavonoids have been noted in the scientific literature, all of which play important roles in lowering the possibility and effect of diabetic complications such as retinopathy, nephropathy, neuropathy, and cardiovascular disease. Furthermore, flavonoids may benefit in glycemic management by boosting the sensitivity of insulin and glucose metabolism. Although not fully understood, the molecular and cellular mechanisms involve a wide number of metabolic pathways and are being researched. Further research is necessary to completely understand the mechanisms of action of flavonoids. These results enhance the necessity of well-powered, randomized, placebo-controlled intervention trials in patients with complications related to diabetes. Additionally, randomized controlled trials utilizing the most recent anti-diabetic medications should be carried out, as flavonoid activity may be more effective when used as an adjuvant rather than a primary medical treatment. Trials for each of the aforementioned diabetic problems, in our opinion, are required since they could give a stronger platform for future therapeutical approaches. Further research may give additional insight on the best approaches to use these naturally occurring substances to enhance the quality of life for diabetics and minimize the burden of diabetic complications.

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