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UNVEILING THE ANTI-DIABETIC POTENTIAL OF QUERCETIN AS A NATURAL BIOACTIVE COMPOUND - A REVIEW

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ABSTRACT: Quercetin, a flavonoid with diverse health benefits, has anti-allergic, anti-inflammatory, antiviral, and anti-cancer properties. Found in fruits and vegetables like onions, apples, and berries, Quercetin has shown potential in combating cancer growth, chronic inflammation, and oxidative stress. Various studies suggest Quercetin may effectively manage type 2 diabetes and its complications, offering a safer alternative to conventional treatments. Conventional treatments for type 2 diabetes often involve costly medications with adverse side effects. In contrast, Quercetin offers a natural, cost-effective solution with minimal risks. It has been identified as a potential anti-diabetic agent due to its ability to modulate glucose metabolism, improve insulin sensitivity, and mitigate oxidative stress. This review aims to summarize the current evidence on the anti-diabetic effects of quercetin, its underlying mechanisms, and its potential as a therapeutic agent for the management of type 2 diabetes. Overall, quercetin appears to be a promising anti-diabetic agent, warranting further investigation for its potential use in the prevention and treatment of type 2 diabetes.

INTRODUCTION: Diabetes Mellitus (DM) is one of the most common chronic metabolic disorders spreading alarmingly worldwide and diagnosed as a result of elevated glucose levels in the blood, characterized by defective insulin secretion by pancreatic β -cells or the inability of insulin-sensitive tissues to respond to insulin ¹. The high blood sugar or hyperglycemia produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst), and polyphagia (increased hunger) and long-term complications of diabetes include retinopathy with the potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputations, and Charcot's joints; and autonomic neuropathy causing gastrointestinal, genitourinary,

and cardiovascular symptoms and sexual dysfunction. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are often found in people with diabetes ². American Diabetes Association has classified DM as Type1 Diabetes Mellitus, Type 2 Diabetes Mellitus, and GDM (Gestational Diabetes Mellitus).

I. Type 1 Diabetes: (Caused β -cell destruction, usually leading to absolute insulin deficiency which may be immune-mediated or idiopathic).

II. Type 2 Diabetes: (May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance) ^{3, 4}.

III. Gestational Diabetes Mellitus: (Glucose intolerance which is first detected during pregnancy) ⁵.



IV. Other Specific Types: (May be due to genetic defects of β -cell or insulin action; diseases of exocrine pancreas-pancreatitis, cystic fibrosis, etc; chemically induced vapor, thiazides, etc) ³.

The type 2 diabetes mellitus (T2DM) is more prominent and accounts for 90-95% of those with diabetes ³⁻⁶. The pathogenesis of T2DM is characterized by metabolic abnormalities including impaired insulin action, insulin secretion dysfunction, obesity, and increased endogenous glucose output ⁷.

It estimated that nearly 366 million people had DM in 2011 and by 2030 this would have risen to 552 million. DM caused 4.6 million deaths in 2011, and by 2030, it is estimated that 439 million people will have type 2 Diabetes Mellitus which will increase in the next two decades and much of the increase will occur in developing countries where the majority of patients are aged between 45 and 64 ⁶.

The WHO (World Health Organization) has projected the global prevalence of diabetes to increase from 8.8% (8.4–9.5) in 2015 to 10.0% (9.5–10.7) in 2030 and the number of diabetes-related deaths from 3,148,325 (3,012,705–3,327,410) in 2015 to 4,180,852 (4,001,358–4,411,778) by 2030 ⁸.

In 2011, approximately 25.6 million people in the US had been diagnosed with diabetes. By 2021, this number increased to 29.7 million people, accounting for 8.9% of the US population ⁹.

T2DM is mainly controlled by lifestyle or dietary changes and the use of oral anti-diabetic drugs like biguanides (metformin), sulfonylureas (glibenclamide), meglitinides, thiazolidinedione's (pioglitazone), GLP-1 mimetics, DPP-IV inhibitors, SGLT2 inhibitors and use of insulin in severe cases which tend to be costly producing notable adverse side effects ¹⁰.

TABLE 1: SOME ADVERSE EFFECTS OF ANTI-DIABETIC DRUGS

Type 2 Anti-Diabetic Agents	Adverse Effects	Reference
Metformin (Biguanides)	Lactic Acidosis, Cholestatic hepatitis, Vitamin B12 deficiency	10, 11, 12
Insulin	Hypoglycemia Hypersensitivity reactions Lipoatrophy Oedema	12
Glibenclamide (Sulfonylureas)	Hypoglycemi, Hypersensitivity reactions, Blurred vision, GI disturbances, Intrahepatic cholestasis	10, 12
Meglitinides	Mild headaches, Weight gain, Arthralgia, Dizziness, nausea	10, 13

Various plant-based medicines have emerged as an alternative for the treatment of diabetes mellitus which are affordable with low side effects. The scope of alternative medicine is enormous ¹⁴.

Quercetin Chemical Properties: Quercetin, a flavonoid and bioactive molecule, has been the subject of extensive research owing to its diverse pharmacological activities, including antioxidant, antiviral, immune-modulatory, anti-diabetic, and anticancer activity with a low toxicity profile. Quercetin is derived from the word quercetum meaning oak woodland, in honor of Quercus, which has been in use since 1857 ¹⁵.

The scientific name for quercetin according to the International Union of Pure and Applied Chemistry (IUPAC) is (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one), molecular formula $C_{15}H_{10}O_7$ has two aromatic rings linked by a bridging heterocyclic unit along with five hydroxyl groups at 3,5,7,3' and 4' positions.

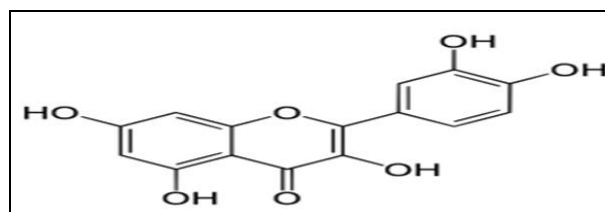


FIG. 1: STRUCTURE OF QUERCETIN

Quercetin is a yellow crystalline solid with a melting point of 316°C and a density equal to 1.80 g/cm³. Moreover, it has a high degree of solubility in organic solvents such as dimethyl sulfoxide, dimethyl formamide, methanol, and ethanol. While it readily dissolves in organic solvents like DMSO, DMF, methanol, and ethanol, its hydrophobic nature limits its water solubility and bioavailability. However, attaching sugar molecules enhances its water solubility. Therefore, scientists have turned to conducting many studies to improve its water solubility and bioavailability, which reflects positively on its pharmacological properties. Metal

chelation is considered one of the methods used to improve its water solubility and bioavailability¹⁶.

Absorption and Metabolism: A lipophilic quercetin molecule can be easily absorbed by the stomach and then secreted in the bile¹⁷. The absorption rate of quercetin glycoside in healthy individuals ranges from 3% to 17% following a 100-mg dose.

Specifically, quercetin-bound compounds like rutin, attached to oligosaccharides or polysaccharides, undergo de-glycosylation by entero-bacteria in the large intestine, allowing aglycone absorption. Quercetin is metabolized in various organs, including the small intestine, colon, liver, and kidney. Metabolites of quercetin (methylated, sulfated, and glucuronated forms) are formed in the small intestine and liver by biotransformation enzymes as a result of phase II

metabolism. The quercetin metabolism results in the formation of phenolic acids in the small intestine and colon, along with the fragmentation of the quercetin skeletal structure. The half-life of quercetin metabolites varies from 11 to 28 hours, which is quite high. Furthermore, quercetin has high bioavailability compared to other phytochemicals¹⁸.

Various Sources of Quercetin: Quercetin is widely distributed in flowers, bark, stems, roots, wine, vegetables, tea, fruits such as apples, berries, cilantro, onions, capers, honey, raspberries, red grapes, radish, cherries, pears, tomatoes, coriander, green tea, red lettuce, fennel, green beans, asparagus, green pepper, sweet potato, citrus, dill, etc. The table shows the natural sources of Quercetin¹⁹.

TABLE 2: VARIOUS SOURCES OF QUERCETIN

Food Source	Quercetin Content (mg/100 g)
Fruits	
Apple with skin (<i>Malus domestica</i>)	4.42
Fig (<i>Ficuscarica</i>)	5.47
Prickly pear (<i>Opuntia spp.</i>)	4.86
Blueberry (<i>Vaccinium caesarian</i>)	7.67
Cranberry (<i>Vaccinium macrocarpon</i>)	14.84
Common juniper (<i>Juniperus communis</i>)	46.61
Elderberry (<i>Sambucus spp.</i>)	26.77
Vegetable Products	
Coriander (<i>Coriandrum sativum</i>)	52.9
Golden poppy (<i>Eschscholzia californica</i>)	26.3
Drumstick tree (<i>Moringa oleifera</i>)	16.65
Fennel (<i>Foeniculum vulgare</i>)	48.80
Leaf cabbage (<i>Brassica oleracea</i>)	7.71
Red lettuce (<i>Lactuca sativa</i>)	7.61
Okra (<i>Abelmoschus esculentus</i>)	20.97
Onions (<i>Allium cepa</i>)	20.3
Sweet potato (<i>Ipomoea batatas</i>)	16.94
Spices and Herbs	
Caper bush (<i>Capparis spinosa</i>)	180.77
Dill (<i>Anethum graveolens</i>)	55.15
Oregano (<i>Origanum vulgare</i>)	7.3
Turmeric (<i>Curcuma longa</i>)	4.92
Buckwheat (<i>Fagopyrum esculentum</i>)	15.38

Various Ethno-pharmacological Properties of Quercetin:

Cardio-Protective: Numerous studies showed the cardio-protective role of quercetin using experimental animal and human models. Researchers reported the cardio-protective activity of quercetin and its role in the improvement of

myocardial injury resulting from high-fat diet intake in an adult male albino rat model. Quercetin can exert beneficial effects on arrhythmias by affecting cardiac ion channels, calcium homeostasis, gap junction, and mitochondrial channels to inhibit mitochondrial oxidative stress, and by suppressing cardiac fibrosis, inflammation,

modulating autophagy and apoptosis, improving ischemia/reperfusion injury and gut microbiota²⁰. Quercetin directly inhibits or regulates critical signaling pathways and key molecules involved in

arrhythmias. In summary, Quercetin can prevent and treat arrhythmias from multiple targets, pathways, and directions, which has great potential and clinical application value¹⁵.

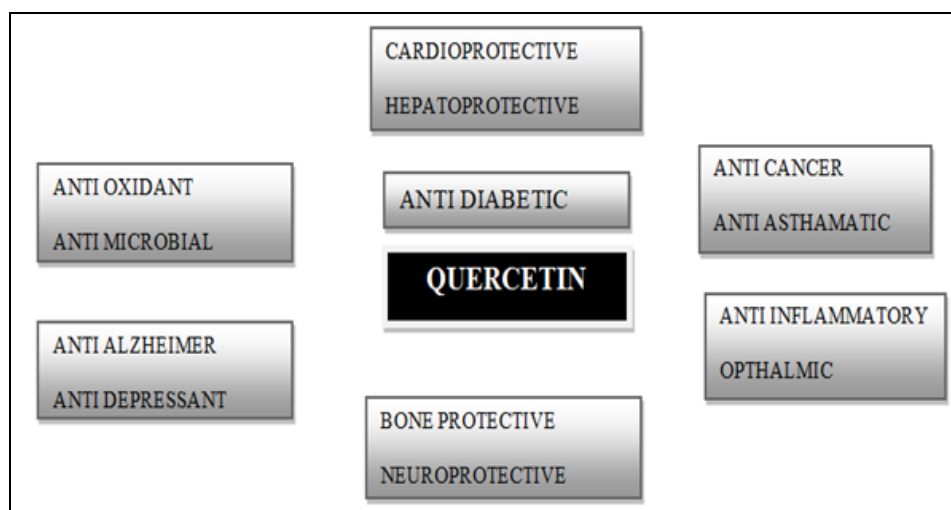


FIG. 2: PHARMACOLOGICAL PROPERTIES OF QUERCETIN – ABSORPTION AND METABOLISM

Anti-Cancer: Quercetin has been shown to have an anti-proliferative and proapoptotic effect on various cell lines, numerous studies have reported that quercetin can induce apoptosis and cell cycle arrest in different cancer cell lines and has a Synergistic effect against breast, prostate, lung, and colon cancer, leukemia when combined with anticancer drugs¹⁹⁻²¹. Quercetin acts as an anticancer agent via various mechanisms, cellular signaling, and inhibition of carcinogen-activated

enzymes by binding to the cellular receptors and proteins. The review article provides information on the role of quercetin in many types of cancer, such as breast cancer, colon cancer, liver cancer, lung cancer, prostate cancer, bladder cancer, gastric cancer, bone cancer, blood cancer, brain cancer, cervical cancer, head and neck cancer, skin cancer, eye cancer, thyroid cancer, ovarian cancer, kidney cancer, and mesothelioma cancer and its mechanism²².

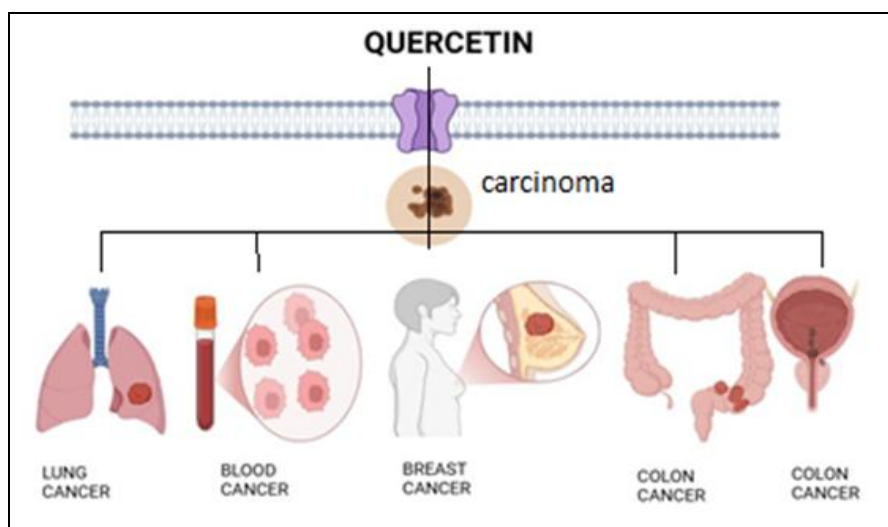


FIG. 3: QUERCETIN ACTION IN VARIOUS CANCERS

Antioxidant: Quercetin is a potent scavenger for free radicals in the flavonoid group. The hydroxyl group in the structure of quercetin acts by providing active hydrogen and thus oxidizes the

free radicals making them highly stable and therefore preventing unsaturated fatty acid oxidation and safeguarding cells against oxidative damage. By mitigating the detrimental effects of

oxidative stress, quercetin protects the body against the harmful impact of prolonged exposure to pollutants and toxins by its ability to bind with metal ions such as copper, manganese, and iron, enhancing its bioavailability and therapeutic potential¹⁵⁻²³. Quercetin is a powerful in vitro antioxidant with anti-ageing and rejuvenating properties²⁴.

Anti-Inflammatory: Some studies show that quercetin, like other flavonoids, can exert a broad-spectrum of biological activities. Various studies in cells of human and animal models suggest that quercetin exhibits anti-inflammatory activities. In vitro studies in the epithelial cells of guinea pigs show that quercetin inhibits the activity of inflammatory enzymes cyclooxygenase (COX) and lipoxygenase (LOX) thereby decreasing inflammatory mediators such as prostaglandins and leukotrienes^{25, 26}.

Antimicrobial: Quercetin has been reported to exhibit antimicrobial activity against various microorganisms. Its proposed mechanisms in microbial infections include inhibition of bacterial growth, biofilm formation, virulence factors, and modulation of the host immune response. Quercetin has been shown to exert antibacterial effects against Gram-negative and Gram-positive bacteria, including antibiotic-resistant strains¹⁹. The study showed that the flavonoids; quercetin and kaempferol in combination with the regular antibiotics expressed remarkable activity against the clinically isolated methicillin-resistant *Staphylococcus aureus* (MRSA) strain²⁷.

Antiobesity: Quercetin exhibits various approaches to combating obesity by modulating various physiological processes. It inhibits adipogenesis, preventing the formation and differentiation of fat cells, while also reducing inflammation in adipose tissue through its anti-inflammatory effects. Additionally, it regulates lipid metabolism by promoting fatty acid oxidation and reducing triglyceride synthesis. Quercetin also suppresses appetite by influencing neurotransmitters, leading to reduced food intake. By targeting the pathways, quercetin demonstrates significant potential as a natural anti-obesity agent²¹.

Anti-Asthmatic: Quercetin has been found to play a role in scavenging free radicals that can lead to

cell death by damaging DNA and cell membranes. It has also been reported that quercetin may inhibit the production and release of histamine and other mediators responsible for the development of allergic reactions in mast cells and thus may be effective against asthma. In a study, it was emphasized that quercetin may have an important role in the treatment of respiratory inflammatory diseases such as asthma through its ability to regulate the Th1 (T helper type 1)/Th2 (T helper type 2) balance¹⁸.

Polycystic Ovary Syndrome (PCOS): PCOS is treated by several medicated herbs²⁸. Research reveals that quercetin exhibits remarkable therapeutic benefits in managing PCOS. Quercetin's multifaceted effects operate through various pathways, modulating metabolic, endocrine, and molecular pathways, ultimately reducing symptoms and improving quality of life²⁹. Metabolic regulation includes lowering insulin, blood glucose, cholesterol, and triglyceride levels to improve metabolic health; Endocrine modulation includes balancing pituitary-ovarian axis function, reducing testosterone and luteinizing hormone levels, and normalizing LH/FSH ratios; Molecular regulation such as influencing Glucose transporter type 4 (GLUT4) gene expression to enhance glucose metabolism³⁰.

Hepatoprotective Effect: Quercetin is an effective hepatoprotective agent, and its pharmacological effects in liver diseases have been extensively studied³¹.

Studies have shown that Quercetin has garnered attention for its potential benefits in NAFLD (Non-Alcoholic Fatty Liver Disease) management. Its antioxidant, anti-inflammatory, and anti-fibrotic properties may help mitigate NAFLD progression. Additionally, quercetin inhibits lipogenesis, suppressing the formation of new fat cells, and prevents hepatic stellate cell activation, a precursor to liver fibrosis. Furthermore, quercetin enhances fatty acid oxidation and mitochondrial function, promoting efficient energy production and reducing hepatic lipid accumulation. In a study, quercetin was shown to improve liver and pancreatic functions by inhibiting cyclin-dependent kinase inhibitor p21 gene expression and improving cell proliferation^{32, 33}.

Bone Protective: Quercetin may represent a useful prophylactic or therapeutic option in the management of skeletal diseases, with the evidence showing that the effects of quercetin on the skeleton are primarily protective. Different quercetin derivatives seem to have more potent bone-protective effects than free quercetin and the combination of other phytochemicals may inhibit the anti-osteoporotic effects of quercetin. The study reveals quercetin's potential as a novel therapeutic agent for rheumatoid arthritis (RA), demonstrating superior anti-inflammatory, immunosuppressive, and protective effects compared to methotrexate in a collagen-induced arthritis (CIA) model. Quercetin significantly reduced the severity of clinical symptoms, protected cartilage and bone from destruction, and decreased circulating pro-inflammatory cytokines (TNF- α , IL-1 β , IL-17, and MCP-1). Quercetin's therapeutic potential in RA treatment is underscored by its ability to mitigate arthritic inflammation, safeguard joint integrity, and exhibit non-toxicity at effective concentrations^{34, 35}.

Anti-Depressant: The studies on the antidepressant effects of quercetin were mainly based on rats and mice models with different stress stimuli has shown promise in preclinical and clinical studies as a novel antidepressant agent³⁶.

Ophthalmic: Quercetin's impressive biological profile, featuring potent antioxidant, anti-inflammatory, and neuroprotective properties, has sparked significant interest in ophthalmology research. Its potential as a therapeutic agent for various eye diseases is substantial³⁷.

Neuroprotective

Alzheimer's: Quercetin is a lipophilic compound with low bioavailability that easily diffuses across the blood-brain-barrier (BBB) such that it can reach the target organ, that is, the brain, and perform neuroprotective actions. Experiments have shown that Quercetin (40 mg/kg, p.o., 16 weeks) is known to improve learning and recognition memory, reduce scattered senile plaques, attenuate mitochondrial dysfunction, as indicated by increasing mitochondrial membrane potential and ATP levels and decrease reactive oxygen species (ROS) production, and increase AMP-activated protein kinase (AMPK)³⁸.

Anti-Diabetic: Diabetes is a metabolic disorder leading to an increased blood glucose level (BGL) because of decreased insulin release and/or insulin resistance. Insulin resistance is caused by many factors, including a high-fat diet, cell dysfunction, decreased glucose uptake, decreased insulin sensitivity and metabolism, increased lipoprotein level, and increased oxidative stress⁴.

Mechanism of Action: Quercetin has antidiabetic effects through various molecular mechanisms such as improving insulin sensitivity and glucose metabolism, reducing insulin resistance, decreasing oxidative stress in diabetic animal models by promoting pancreatic β -cell function in in-vivo studies and acts on multiple targets of diabetes by activating AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor- γ (PPAR- γ) and reducing blood glucose levels³⁹.

These various benefits are attributed to several mechanisms, Inhibition of glucosidase and amylase enzymes, Preservation of β -cell mass and functionality, and Stimulation of GLUT4 expression and translocation. Glucose transporter type 4 (GLUT4) is responsible for the uptake of blood glucose into muscle cells. Dietary polyphenols capable of inducing translocation of GLUT4 may promote glucose uptake in skeletal muscle cells and upregulation of estrogen receptor- α , subsequently increasing the phosphorylation of the phosphatidylinositol-3-kinase/Akt (PI3K/Akt) signaling pathways may be a potential compound for preventing or ameliorating diabetes. Its antioxidant and anti-inflammatory effects reduce oxidative stress and inflammation while modulating insulin signaling and glucose metabolism to improve insulin sensitivity⁴⁰.

Furthermore, quercetin has improved plasma insulin levels and lowered blood glucose in the streptozotocin (STZ)-induced diabetes model by maintaining β -cells, thereby enhancing the effect of serum insulin¹⁹. The most common substances inducing diabetes in the rat are alloxan and streptozocin (streptozotocin, STZ). STZ is taken up by pancreatic β -cells via glucose transporter GLUT2. The main cause of STZ-induced β -cell death is the alkylation of DNA by the nitrosourea moiety. Various studies confirm that quercetin significantly reduced the blood glucose level of

diabetic rats in 8–10 days at the two doses used. The blood glucose level of the diabetic animals treated with quercetin reached normal values thereby producing an increase in the number of pancreatic islets, probably increasing insulin release in STZ-diabetic rats and inducing the

hepatic glucokinase enzyme. The plasma glucose lowering property and its beneficial effects on the correction of glucose tolerance test and on lowering plasma cholesterol and triglycerides could also be probably attributed to its ability to regenerate pancreatic β -cells and to increase insulin release⁴¹.

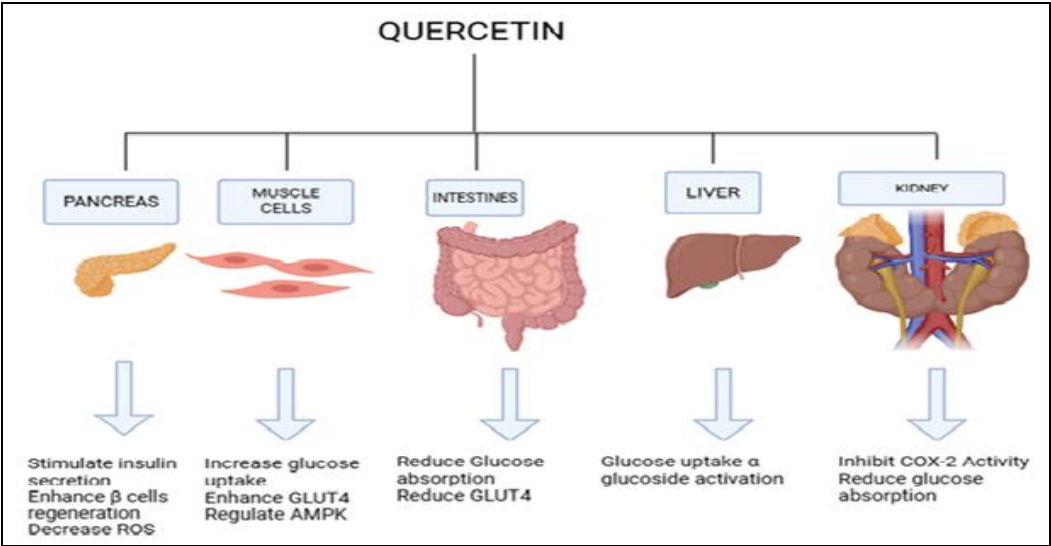


FIG. 4: MECHANISM OF QUERCETIN AS ANTI-DIABETIC

Various other preclinical studies report quercetin alone or in combination has been reported to improve glucose uptake and decrease oxidative stress and thereby insulin resistance. Quercetin and RS (resveratrol) alone lowered blood glucose levels in diabetic mice and rats. Individual treatment of QE and RS has also been shown to have

ameliorative effects on type 2 diabetes in both *in-vitro* and *in-vivo* studies. Quercetin has been shown to effectively lower plasma glucose levels and improve other diabetic-related parameters, such as liver gluconeogenesis and serum lipid parameters. RS treatment was also reported to exhibit anti-diabetic activity in type 2 diabetes-induced mice.

TABLE 3: VARIOUS MECHANISMS OF QUERCETIN AS ANTI-DIABETIC

Model	Mechanism of action	References
STZ	Decrease fasting blood glucose, blood urea nitrogen, and reactive oxygen species. Increase superoxide dismutase.	42
STZ	Increase activity of superoxide dismutase (SOD), catalase. Decreased NF- κ B and malondialdehyde (MDA) levels.	43
STZ	Elevating Protein Kinase B and Glycogen Synthase Kinase 3(GSK-3) phosphorylation, and upregulate Glucokinase protein expression and activates Sirtuin1.	44
Epigenetic regulation	Inhibit sirtuin6 (SIRT6) activity. Reduce oxidative stress, Preserve β cell mass, Protect β cells Inhibit α -glucosidase, Promote glycogen synthesis, and stimulate glucose uptake in muscle cells via the AMPK pathway.	39
<i>In-vitro</i> and <i>in-vivo</i> studies	Suppress α -glucosidase activates hexokinase and adenosine monophosphate-activated protein kinase (AMPK), increasing blood glucose uptake by hepatic cells. Gliclazide and quercetin combined administration normalized glucose homeostasis	45
Meta-analysis	Decrease serum glucose via modulating hepatic gene expressions. Reduce the blood glucose level by inhibiting α -glucosidase activity. Upregulate mitochondrial activity in animal modelsby controlling the production of ATP through inhibiting ATPase and hexokinase enzymes. Quercetin-induced AMPK activation downregulates the oxidative damage and augments the glucose uptake in mice. Quercetin scavenges ROS and increases the AMP/ATP ratio in beta cells.	46 39

Additionally, few studies have investigated the additive or synergistic effects of combined treatment of QE and RS by *in-vitro* or *in-vivo* approaches⁴⁷. Quercetin is an *in-vitro* inhibitor of aldose reductase and effectively blocks polyol accumulation in intact rat lenses that are incubated in a medium with a high concentration of sugar. Research suggests that elevated CYP2E1 protein levels in type 1 diabetes (T1DM) contribute to liver damage triggered by oxidative stress. Notably, a study in diabetic rats demonstrated that daily quercetin supplementation (50mg/kg) significantly Decreased CYP2E1 enzyme activity, Enhanced antioxidant defenses, and Restored balance between pro-oxidant and antioxidant processes⁴². In another study in diabetic rats, quercetin supplementation of 50mg kg/day was shown to inhibit cytochrome c and caspase-3 activity and to increase the level of anti-apoptotic protein.

It has been reported that quercetin can be used to prevent diabetic retinopathy by inhibiting oxidative stress and exerting neuroprotective effects. 11b-hydroxysteroid dehydrogenase type 1 (11b-HSD1), which mediates the glucocorticoid hormone in target tissues for insulin action, is considered to be a regulator in glucose homeostasis. In a study comparing oral antidiabetic effects of flavonoids, 3-hydroxyflavone, chrysin, and quercetin, the hypoglycemic and anti-diabetic effects of quercetin were found to be significant.

Besides, quercetin showed the most inhibitory effect against 11b-HSD1. For the pathophysiological treatment of type 2 diabetes (T2DM), it is necessary to reduce blood glucose levels and improve insulin release. It is known that quercetin inhibits carbohydrate absorption by inhibiting digestive enzymes responsible for carbohydrate hydrolysis and glucose carriers in different forms *in-vitro* and *ex-vivo*. Quercetin has also been reported to help reduce numbness and pain in patients with T2DM and neuropathy. Research showed that the effect of Quercetin on T2DM in skeletal muscle cells was through the adenosine monophosphate kinase (AMPK) pathway. It has been shown that the mechanism of quercetin, similar to that of oral antidiabetic drug metformin, may be a potential component in the treatment of T2DM. Furthermore, quercetin can decrease the production of glucose in hepatocytes

and increase insulin sensitivity by enhancing the expression of AMP-dependent protein kinase (AMPK) and sirtuin 1 (SIRT1) protein activation in duodenal mucosa. The concomitant administration of sitagliptin and quercetin decreased oxidative and inflammatory stress, hyperlipidemia, and blood glucose levels. In addition, the combination restored the function as well as the integrity of pancreatic β cells. In another study, quercetin enhanced the uptake of glucose in L6 myotubes, thus enhancing glucose utilization. In a study., quercetin caused a substantial escalation in antioxidant enzymes [glutathione, catalase (CAT), and glutathione-S-transferase], which increased GLUT4 expression and decreased hyperglycemia in diabetic mice, thus highlighting quercetin as a potential candidate for treating type 2 diabetes mellitus (T2DM).

Quercetin was reported to promote SIRT1 expression in the pancreas, antioxidant defense mechanism, and normalized proinflammatory cytokine expression, thus decreasing the β cell dysfunction. Furthermore, another study reported a decrease in total cholesterol (TC), low-density lipoprotein (LDL), triglycerides (TG), oxidative stress, and an increase in insulin sensitivity observed after administration of quercetin to diabetic rats. Quercetin also showed pronounced effects in treating diabetic memory disorder in Wistar rats at a dose of 5/10 and 20mg/kg/day for 30 days⁴⁸.

Furthermore, quercetin extracted from *Phyllanthus emblica* L. fruit administered at a dose of 25, 50, or 75 mg/kg/bw daily for 28 days led to a substantial decrease in BGL and urine sugar levels in rats with streptozotocin (STZ)-induced diabetes. Quercetin treatment at a dose of 50mg/kg/bw for 14 days in rats also significantly improved dyslipidemia and reduced BGL. Similar effects were seen in another study where quercetin was administered at a dose of 10 and 15mg/kg/day for 2 weeks in rats, whereas quercetin supplementation at a dose of 15mg/kg/bw in Wistar Albino rats aided the regeneration of pancreatic β cells as well as increasing insulin release, resulting in a reduction in BGL. Quercetin reduced the risk of diabetic retinopathy and retinal edema when given to rats at a dose of 150mg/kg/day for 20 days. It was further reported that quercetin supplementation at a dose of

10mg/kg/bw to C57BL/6 J mice for 4 weeks was effective in treating diabetic nephropathy. Studies provide evidence that quercetin can protect diabetic erythrocytes from oxidation-induced damage through its strong antioxidant effect⁴⁹. Quercetin has various effects on Diabetic complications. It has demonstrated potential in reducing diabetic complications, including retinopathy, nephropathy, neuropathy, and cardiovascular diseases. A serious complication of DM, diabetic retinopathy (DR) is one of the leading causes of adult blindness and visual impairment. Recent studies have indicated that quercetin at 150 mg/kg improved retinopathy in STZ-induced rats by reducing the expression of monocyte chemoattractant protein-1 (MCP-1), matrix metalloproteinase-9 (MMP-9), and vascular endothelial growth factor (VEGF). Another major complication of DM, diabetic nephropathy is caused by long-term hyperglycemia which leads renal cells to secrete an array of pro-inflammatory and pro-fibrotic substances, resulting in cell hypertrophy and proliferation and the development of renal interstitial fibrosis⁴².

Reports have shown that quercetin deactivated the SphK1-S1P (sphingosine kinase-1) signaling pathway, and hence inhibited the development of renal fibrosis. Quercetin alleviates nephropathy by deactivating the SphK1-S1P signaling pathway. Additionally, quercetin enhances cognitive function and reduces brain energy metabolism impairment, and in STZ-induced rats, quercetin, with or without glibenclamide, provides cardioprotection by increasing endothelial cell receptors and nitric

oxide production⁴⁵. Another study performed with Type 2 diabetic women reported that quercetin supplements also lower systolic blood pressure. While these findings are promising, further clinical trials are necessary to fully understand quercetin's mechanisms of action and potential therapeutic applications¹².

Limitations and Challenges: Recently, anti-hyperglycemic research involving quercetin as a safe alternative has been extensively explored. One of the primary challenges in quercetin's application lies in its bioavailability and solubility. Using quercetin as pharmacologic therapy in the form of dietary supplementation may cause a few problems. Firstly, the bioavailability of quercetin is generally poor and it is affected by numerous factors. As per the biopharmaceutical classification system, quercetin is classified in class IV with poor water solubility, low permeation, and a short biological half-life⁵⁰. So there is negligible absorption of quercetin in the gastrointestinal tract. This limitation restricts the amount of quercetin that enters the circulation and reaches the target to overcome these challenges, numerous efforts have been made to enhance its solubility and, hence, bioavailability. Various delivery systems, such as lipid, polymeric, metallic, and inorganic-based nanoparticles, nano-emulsions, co-crystals, liposomes, micelles, inclusion complexes conjugate-based delivery systems, microspheres, and solid dispersion have been prepared to increase its solubility and bioavailability⁵¹.

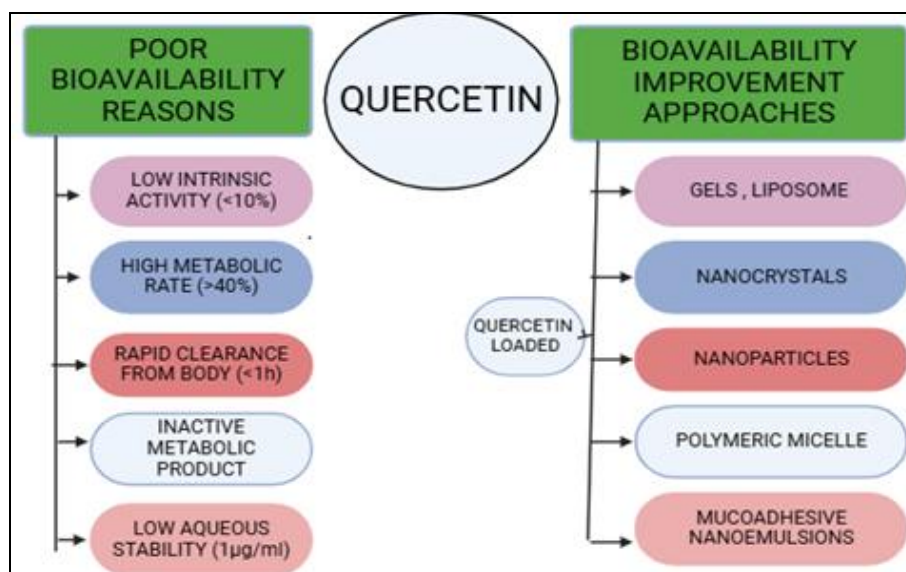


FIG. 5: QUERCETIN POOR BIOAVAILABILITY REASONS AND IMPROVEMENT APPROACHES

However, all these delivery systems have limitations in terms of their affordability, safety, efficacy, and stability. There is a need to develop an accurate *in-vivo* pharmacodynamic and pharmacokinetic picture. Therefore, randomized as well as controlled clinical studies on humans are required⁴⁸. Quercetin can affect the development of embryo, fetus, and placenta during pregnancy in animal models. Cytoprotective properties of the fetus were observed in numerous studies. It was shown that quercetin did not have teratogenicity and abortive effects on the fetus and it is generally recognized as safe⁵². Rodent models, for instance, have shown that while moderate doses of quercetin can be beneficial, excessive intake can lead to kidney and liver toxicity, highlighting the organ-specific vulnerability to quercetin's cytotoxic effects. Quercetin research within nanotechnology is promising due to its potential to enhance bioavailability and targeted delivery, overcoming traditional limitations like poor solubility and rapid metabolism. Nanotechnology-based systems aim to optimize quercetin's therapeutic use by reducing dosage and minimizing side effects.

CONCLUSION: Quercetin is a naturally occurring compound with anti-diabetic properties, and its therapeutic potential warrants further investigation. As a dietary supplement, quercetin may offer a safe and effective adjunctive treatment for diabetes management, particularly when used in conjunction with conventional therapies. In conclusion, more research is needed to determine the precise mechanism of quercetin on various disorders. Quercetin may be used to successfully prevent some of the clinical consequences of diabetes according to the findings reported in the current review. Future research will focus on QE's involvement in the management of diabetes and its negative effects. These cutting-edge techniques hold great promise for future drug development and personalized medicine, as they can be tailored to suit specific routes of administration, target tissues, and safety considerations. Future research will explore its role in managing diabetes and its related effects. Advancements in quercetin-rich foods, supplements, and pharmaceuticals may lead to a shift in healthcare, focusing on prevention and holistic well-being. Quercetin's versatile properties make it a hopeful solution for improved healthcare and disease management. As researchers continue

to explore the potential applications of quercetin, collaboration between pharmaceutical companies, academic institutions, and regulatory agencies will play a vital role in turning these promising findings into tangible medical breakthroughs. The future of quercetin in pharmaceuticals is undoubtedly bright. Most of the formulations are developed using biodegradable polymeric materials like natural polymers such as chitosan, and alginate and synthetic polymers such as poly-D,L-lactide (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(3-caprolactone) (PCL) to improve oral bioavailability of quercetin. With advancements in novel bioprocesses effective development and subsequent modifications of polymeric materials are also investigated in several reports. The ultimate goal is to exert the maximum bioavailability *in-vivo*, which can reduce the blood glucose level resulting in hypoglycemic condition for a long period in effective diabetes treatment. While the current evidence is promising, further studies are needed to fully elucidate the anti-diabetic effects of quercetin and to establish its therapeutic potential. Moreover, clinical trials are necessary to determine the optimal dosage and duration of quercetin supplementation for diabetic patients.

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