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Tangeretin-a special polymethoxyflavones: An insight into its pharmacological and therapeutic effects on diabetes

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Abstract

With global diabetes complication growing rapidly at an alarming rate each year, there is an increasing need to find suitable therapeutics for its management, regulation, and treatment which is cost-effective, safe, and naturally available. Continued dependence only on the available synthetic drug is not a solution. Therefore, there is a need to find suitable natural adjuncts to help manage diabetes. Flavonoids are a class of compounds that have been utilized for therapeutic purposes for generations due to their wide and varied pharmacological properties. One such important naturally available flavonoid is tangeretin belonging to a special class of methylated flavonoids found mostly only in citrus fruits. It is reported to possess a lot of pharmaceutic activities, and thus in this brief review, we elucidate its specific importance in the attenuation of diabetic and diabetes-related complications to get a better understanding of its physiological mechanism of action in the context relating to diabetes.

Keywords: Diabetes; Flavonoid; Natural Product; Tangeretin; Polymethoxyflavones; Therapeutics

1. Introduction

Every living thing needs energy. The main energy source for living things is glucose. It is broken down into a sequence of metabolic steps to generate ATP, which is required to fuel energy-demanding functions. It is crucial for both aerobic and anaerobic cellular respiration [1]. Human glucose reserves are maintained in the liver and muscle tissues by polymer glycogen and controlled by insulin and glucagon hormones, which are both made in the pancreatic Islet of Langerhans, with insulin produced by β-cells (levels are higher during energy-rich states) and glucagon by α-cells (levels are higher during fasting) [2]. The regulation of such a complex system of glucose homeostasis is very important because when there is a defect in the regulation and management of glucose homeostasis, it leads to an adverse complication and causes a major metabolic syndrome known as diabetes.

2. Diabetes: The antagonist

Diabetes, also called diabetes mellitus (DM), is a serious chronic condition characterized by elevated blood glucose levels caused by the body's inability to produce any or enough of the hormone insulin or to effectively use the insulin it does produce [3]. High rates of morbidity and death are mostly caused by the prevalence of diabetes mellitus and its consequences, which have become a danger to world health. It is anticipated that by 2045, there will be up to 700 million diabetes individuals worldwide [4]. The cost of management and treatment of diabetes also is very high and puts a lot of economic burdens not only on the patients and their families but also on the nation as a whole. Thus, a lot of effort and costs are required for the management and treatment of diabetes, incurring a lot of social and economic adverse implications. Now, much more than ever, there is an urgent need to find a solution for its treatment as with each growing

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year, it is not only affecting the aged and adults but there is also an increased risk of diabetes prevalence among the young due to a variety of reasons starting from a sedentary lifestyle, to food habits, environmental factors, genetics and so on and so forth. Numerous organs, including the peripheral nerves, kidneys, heart, liver, peripheral nerves, retina, and central nervous systems, are damaged and rendered dysfunctional as a result of diabetes-related chronic hyperglycemia [5]**.** Thus, there is a growing emphasis on identifying and targeting novel natural products that not only can combat, prevent and manage the growing rate of diabetes, but at the same time do not cause the risk of adverse effects on health when administered to the body for a longer duration of treatment if needed for the patient or that can be supplemented as a suitable adjunct to existing therapeutics available in the market.

3. Flavonoids: A general overview

Insulin injection and oral anti-diabetic drug usage are currently the cornerstones of modern therapy for the management of diabetes mellitus. In the western market, sensitizers, secretagogues, analogs of insulin, α-glucosidase inhibitors, and other antidiabetic drugs are available and are used singly or in combination to enhance blood sugar management [6]**.** Sadly, the majority of them have noticeable side effects and can't stop diabetes problems from occurring. Pharmacologists are working tirelessly to find alternative treatment options for this metabolic disorder [7]**.** These alternative therapeutics include the uses of natural plant-based nutraceuticals, which includes flavonoids. Natural products are a vital component of the pharmaceutical industry and a key source for the development of novel lead compounds. The most frequent phenolic chemicals found in plants are flavonoids. On average, 400 mg/kg aglycone equivalent of flavonoids is ingested daily via food. They have reportedly shown a range of therapeutic promise in medicine and other biological processes [8]**.** The screening of natural chemicals, such as flavonoids, that may be useful for lowering the risk of metabolic syndrome has received a lot of interest recently as products from plant sources are often regarded to be less toxic and have fewer adverse effects than products from synthetic sources. Researchers have recently become interested in the screening of natural compounds, such as flavonoids, that may be useful in lowering the risk of metabolic syndrome because products derived from plants are typically thought to be less harmful and have adverse side effects than products derived from synthetic sources. Flavonoids are an important group of secondary metabolites in plants and are also good sources of natural antioxidants in human diets. They are a group of metabolites that are formed from plants and are very beneficial natural antioxidant sources for human diets. [9]**.** Flavonoids are found in a variety of fruits, vegetables, and seeds, as well as foods derived from them, such as cocoa, coffee, tea, soy-based foods, and red wine. Plants produce these flavonoids to protect themselves from microbial destruction, oxidation injury, and UV damage; they also produce the odours, colour, and taste of foods [10]. Due to their fundamental polyphenolic structure, which consists of two benzene rings connected by an oxygenated heterocyclic ring, flavonoids are categorized as phenolic substances. By directly interacting with proteins like important cellular receptors or signaling processes, flavonoids can influence a wide range of activities in different cells and organs [11,12]**.** Thus, identifying such kind of flavonoid compounds or their derivatives that can be effective for the treatment of diabetes is one important growing area of scientific studies and a crucial part of phytochemistry and natural product research.

4. Polymethoxyflavones: A special class of flavonoids

Polymethoxyflavones (PMFs) are a type of methylated flavonoid particularly abundant in citrus fruits, mainly in orange and mandarin peel. The term "polymethoxyflavone," also known as "PMF," is used to refer to flavones that have two or more methoxy groups attached to their fundamental benzo-pyrone (15-carbon, C6-C3-C6) structure with a carbonyl group at the C4 position [13]**.** Several *in vitro* and *in vivo* investigations conducted over the past few years have shown that PMFs are the primary bioactive flavonoids in citrus peel and also exhibit a variety of biological actions, such as anti-proliferative, anti-inflammatory, anti-angiogenic, and neuroprotective effects [14]**.** PMFs are virtually entirely found in citrus trees. Almost 105 million tonnes of citrus fruit are produced annually in the world, more than half of which are oranges. The generation of juice from around 34% of these items resulted in a by-product of peels of about 44% (4-5 billion lbs in the US) [14]**.** Citrus peel, such as orange peel, has been used traditionally in several parts of the world to treat conditions including ringworm infections, stomach upset, coughs, skin irritation, and discomfort in the muscles. It can also reduce blood pressure [14]**.** Due to their established wide range of biological activity, including anti-inflammatory [15]**,** anti-carcinogenic [16]**,** and anti-atherogenic properties 1[7], PMFs have attracted a lot of attention. With the increasing number of natural flavonoids whose potential antidiabetic activities are revealed, the mechanisms of action of these substances are carefully being elucidated.

5. Tangeretin: Sources and structure

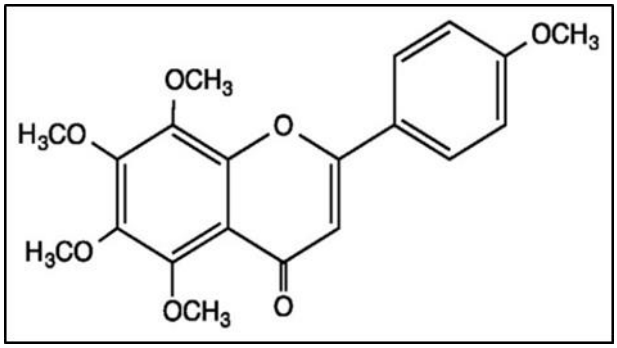

Figure 1 Structure of tangeretin (**Source: Pubchem**)

One such important flavonoid is tangeretin, a pentamethoxyflavone with methoxy groups at positions 4', 5, 6, 7, and 8. It has a molecular weight of 372.4 g/mol and a molecular formula of C20H20O7. Tangeretin is prevalent in the rinds of citrus fruits such as mandarin oranges.

5.1. Bioavailability of Tangeretin

The effects of absorption, distribution, metabolism, and excretion all determine bioavailability. Essentially, it refers to the quantity of medicine or nutrient that enters the tissue and blood circulation system [14]. Understanding bioavailability and the intimate connection between solubility, permeability, absorption, and potency is very important to fully understand the nature of the compound and its effect on the body. Unlike common flavonoids, which contain numerous hydrophilic hydroxyl groups, PMFs are hydrophobic and, as evidenced by the presence of many methoxy groups, may easily pass through the phospholipid's membrane. Tangeretin has a very high permeability (1.62×10^{-6} cm/s) and high solubility (19 µg/mL) [14]. In fact, tangeretin and the majority of PMF have high *in vitro* and *in vivo* bioactivities as well as bioavailability [14].

In a study conducted by Hung et al., 2019 [18] regarding the pharmacokinetics study of tangeretin in rats, they observed that upon oral administration of 50 mg/kg b.w. of tangeretin to rats, the Cmax (time taken by a drug to reach the maximum concentration) is 0.87 ± 0.33 µg/mL, Tmax (average rate of drug absorption) is 340.00 ± 48.99 min and t1/2 (rate of drug elimination) is 342.43 ± 71.27 min, respectively, and the calculated absolute oral bioavailability was 27.11%. Maximum tangeretin concentrations during tissue distribution happened 4 or 8 hours after oral treatment. The liver, kidney, and lung had the most tangeretin buildup, followed by the heart and spleen. Maximum tangeretin concentrations in the gastrointestinal tract were discovered in the small intestine and stomach at 4 hours, while tangeretin reached its peak concentrations in the rectum, colon, and cecum after 12 hours. During 48 hours of oral dosing, the concentrations of tangeretin that were eliminated in the urine and feces were only 0.0026% and 7.54%, respectively [18].

Parameters	Oral (50 mg/kg bw)	Intravenous (5 mg/kg bw)
T_{max} (min)	340.00 ± 48.99	–
C_{max} (µg/mL)	0.87 ± 0.33	1.07 ± 0.49
$t_{1/2}$ (min)	342.43 ± 71.27	69.87 ± 15.72
AUC (min · µg/mL)	213.78 ± 80.63	78.85 ± 7.39
AUC/Dose (min/L)	4.28 ± 1.61	15.77 ± 1.48
F (%)	27.11	

Figure 2 Pharmacokinetic parameter of tangeretin in rats (**Source: Hung et al., 2018** [18])

5.2. Metabolism and biotransformation of tangeretin

In an *in vitro* investigation, when tangeretin was treated with aroclor-induced rat liver microsomes, the main metabolites were identified as 5,4′-dihydroxy-6,7,8-trimethoxyflavone, 3′,4′-dihydroxy-5,6,7,8-tetramethoxyflavone and 4′-demethyltangeretin [19], while when rats were regularly gavage-fed tangeretin, the primary metabolites discovered in their urine and feces were 3′,4′-dihydroxy-5,6,7,8-tetramethoxyflavone and 4′-demethyltangeretin 20**.** The 4′-methoxy group of tangeretin's serves as the leading site for demethylation, whereas its 3′-position is more susceptible to hydroxylation or oxidation [19].

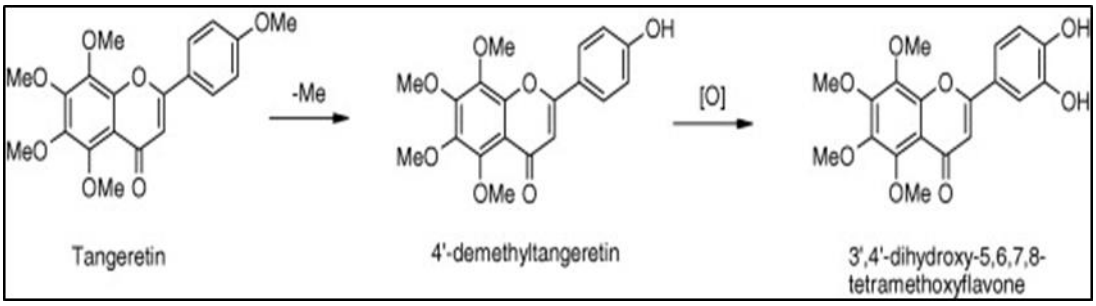

Figure 3 Biotransformation of tangeretin in rats (**Source: Li et al., 2009** [14])

5.3. Mechanism of action of tangeretin against diabetes and its related complication

Tangeretin dramatically reduced plasma insulin, blood glucose, and glycosylated hemoglobin after being orally administered (100mg/kg b.w) to diabetic rats for 30 days. The altered activity of important enzymes involved in glucose metabolism was likewise dramatically recovered by oral tangeretin treatment. Glycolysis is a straightforward mechanism of glucose metabolism that plays a crucial role in controlling how much insulin is secreted and how each cell's metabolic processes work. Thus, enhancing glycolysis by targeting important metabolic and regulatory enzymes may be the key to managing diabetes and its complication [22]**.** Tangeretin increases the activity of various enzymes involved in glycolysis, such as hexokinase, and pyruvate kinase, and thus can be one of the therapeutic target pathways of tangeretin mechanism of action on diabetes [23]. For the maintenance of stable blood glucose concentrations, the coordinated regulation of cellular glucose absorption and endogenous glucose synthesis is essential. The primary cause of the elevated blood glucose levels seen in DM has increased gluconeogenesis, which results in increased glucose synthesis in the liver [24]**.** Inhibiting gluconeogenesis may therefore be the most effective way to reduce liver glucose synthesis. Tangeretin was shown to be crucial in controlling gluconeogenic enzymes, including fructose-1,6-bisphosphatase and glucose-6-phosphatase [23]**.** Decrease of glucose-6- phosphate dehydrogenase (G6PD) activity reduces glucose flux through the pentose phosphate pathway and hence reduces the synthesis of NADPH required as a cofactor for various antioxidant enzymes. By activating protein kinase A (PKA), hyperglycemia reduces G6PD function and increases intracellular oxidative stress, which causes inflammation and tissue damage [25]. Tangeretin oral administration is seen to increase the activity of G6PD in STZ-induced diabetic rats [23]. Tangertin oral administration also was able to activate glycogen synthase (an enzyme required for glycogen synthesis) in the liver of STZ-induced diabetic rats [23]**,** thus causing an increase in hepatic glycogen content, indicating tangeretin's ability to reduce hyperglycemia by modulating glycogen synthase enzyme activity [23]**.** Elevated lactate dehydrogenase (LDH) levels found in diabetic experimental mice are linked to reduced glucose-stimulated insulin production, which suggests that increased LDH activity disrupts normal insulin secretion and glucose metabolism in pancreatic cells [27]**.** However, giving tangeretin oral administration to diabetic rats caused the LDH activity to return to a normal level [23]**.** Also, when compared to untreated diabetic animals, the histopathological study of diabetic rats treated with tangeretin revealed a much higher rate of pancreatic β-cell regeneration in the islets of langerhans [23]**.**

The most well-known target protein for signaling molecules linked to diabetes is AMP-activated protein kinase (AMPK). When AMPK is activated, the glucose transporter 4 (GLUT-4) is moved from the cytosol to the plasma membrane, whereby GLUT-4 helps in glucose uptake from the blood into various tissue like adipose tissue and muscles [28]**.** A significant finding of the study by Kim et al. [29] is that tangeretin increased the activation of AMPK pathways in the muscles of mice and in C2C12 myotubes cells, resulting in an increase in glucose absorption as well as a reduction in obesity-induced glucose intolerance. Adipokines, including leptin and resistin, which were increased in obese mice, were reduced by tangeretin supplementation [29]**.** Another *in-vitro* experiment investigated by Onda et al. [30], shows that tangeretin significantly increased glucose ([3H]-deoxyglucose) uptake in 3T3-F442A murine adipocytes cells in a concentration-dependent manner and the possible mechanism of its anti-diabetic action maybe partly exerted via the signaling pathways including phosphatidyl inositol 3 kinases (PI3K), AKT1/2, and the protein kinase A (PKA) in insulin

target tissues [30]. In db/db obese diabetic mice (genetically diabetic leptin receptor-mutated), intragastric injection of tangeretin (50 mg/kg) also improved glucose homeostasis and hepatic insulin sensitivity by triggering the activation of important downstream pathways in the insulin signaling system, such as the levels of p-AKT (Thr-473), and p-GSK3b (Ser9) and inhibiting the MEK-ERK1/2 pathway. As a result of blocking the MEK-ERK1/2 pathway in hepatocytes, the findings imply that tangeretin may be a potential insulin action enhancer [31]. Thus, the MEK-ERK1/2 pathway may also be another potential therapeutic target pathway for the attenuation of hyperglycemia by tangeretin. Tangeretin appears to be a viable therapeutic option for treating insulin resistance since it inhibits the release of monocyte chemoattractant protein 1 (MCP-1), an insulin-resistance factor, in 3T3-L1 adipocytes and at the same time, it also induces the secretion of adiponectin, which is an insulin-sensitizing factor [32]. Tangeretin significantly decreased the production of cytokines such as tumour growth factor-1 (TGF-1), interleukin-6 (IL-6), interleukin-1 (IL-1) and vascular endothelial growth factor (VEGF) in human retinal pigment epithelium (RPE) cells that are increased to exceeding levels under high glucose (HG) environment, suggesting that tangeretin may be useful in the management of diabetic retinopathy [33]. When diabetic nephropathy progresses, high glucose (HG) levels can promote the proliferation and hypertrophy of mesangial cells (MCs) [34]**.** To evaluate tangeretin's impact on oxidative stress and extracellular matrix (ECM) development, Chen et al. 2018, created an *in vitro* model of a high glucose-generated environment in human MCs. The findings demonstrated that HG stimulation enhanced MCs' proliferation, but tangeretin pretreatment considerably decreased HG-induced MCs proliferation. The ERK pathway is crucial for developing diabetic nephropathy (MCs). Activation of the ERK signaling pathway by high glucose-stimulated mesangial cells is inhibited by tangeretin, which is another significant conclusion from this study [35]. The overall mechanism by which tangeretin prevents high glucose from causing extracellular matrix to build up in human glomerular mesangial cells involves reducing the buildup of reactive oxygen species (ROS) and malondialdehyde (MDA), increasing anti-oxidant activities, preventing the increased expression of fibronectin (FN) and collagen IV in HG-stimulated MCs, and partially by suppressing the ERK signaling pathway [35]**.** These findings highlighted the promise of tangeretin as a therapy for diabetic nephropathy, one of the most common diabetic complications and a major cause of morbidity and mortality that contributes to end-stage renal disease [36]**.** In another study, Wu et al. [37] **c**onducted an experiment to see whether tangeretin exerted protective effects in 5/6 nephrectomized (5/6Nx) Sprague–Dawley (SD) rats. The results of the trial show that tangeretin treatment for 30 days straight at various dosages (50, 100, and 200 mg/kg b.w.) considerably reduced proteinuria, urea, and ROS levels, ultimately enhancing renal architecture and function. By modifying TNF-α/NF**-**κB signaling, tangeretin has been shown to reduce inflammatory cell infiltrate and inflammatory mediators, which may have significantly restored renal function and had nephroprotective effects in 5/6 Nx rats, and also aided in improving chronic kidney disease (CKD)-associated cognition and memory. Overall, this research supports tangeretin's role as a strong nephroprotective agent in kidney disease and renal failure.

One of the most frequent consequences of diabetes mellitus is heart-related complications, and diabetes mellitus itself is a risk factor for heart complications. Nakamura et al*.* [38] and Sundaram et al. [39] extensively studied tangeretin's antioxidant, anti-inflammatory, and cardioprotective properties to get detailed insights into the therapeutic mechanisms involved in its effect on cardiomyopathy. Tangeretin (100 mg/kg b.w/day) given orally to diabetic rats for 30 days was able to reverse the changes in their heart weight and body weight. Tangeretin's insulinotropic effect reduced the activity of vital liver enzymes involved in lipid metabolism, which resulted in a drop in the plasma and cardiac lipid profiles such as a decrease in HMG-CoA reductase (which under diabetic condition is significantly increased), increase in lecithin-cholesterol acyltransferase (LCAT); important for HDL metabolism and lipo-lipoprotein (LPL) activity. Also, it increased the expression of GLUT-4 in the heart tissues of diabetic rats. Glutathione peroxidase (GPX), superoxide dismutase (SOD), glutathione reductase (GR), and catalase (CAT) activities were all improved by tangeretin therapy in diabetic rats, which can be concluded from the decrease in oxidative biomarkers such as thiobarbituric acid reactive species (TBARS). Also, it resulted in a substantial decrease in cardiac marker enzymes such as lactate dehydrogenase (LDH), creatine phosphokinase (CPK), and aspartate aminotransferase (AST), as well as inflammatory cytokines, including IL-6 and TNF-α in the plasma and heart tissues. In conclusion, the findings imply that tangeretin therapy has positive effects on controlling diabetes and the cardiovascular risk it entails [39]. In cardiac dysfunction in diabetics, anomalies in Na^+/K^+-ATPase and Ca^{2+}-ATPase activities are well characterized [40]. Decreased calcium homeostasis was reported in diabetic cardiomyopathy and other complications of diabetes mellitus [40]**,** and also decreased Na^+/ K^+-ATPase activity plays a major role in many of the complications of diabetes and in the development of diabetic vascular complications [41]**.** Tangeretin treatment in diabetic rats, however, increased the activities of Ca^{2+}-ATPase and Na^+/K^+-ATPase in diabetic rats [39]. Thus, the current study by Sundaram et al. [39] shows that tangeretin increases the activities of membrane-bound ATPases and mineral metabolism by reducing cellular oxidative stress, proinflammatory cytokine levels in the blood, and cardiac markers, and also by improving lipid profiles in the heart of STZ-induced diabetic rats. In conclusion, the findings imply that tangeretin therapy is helpful in controlling diabetes and the cardiovascular risk that succeeds it.

Liu et al. [42], demonstrated that tangeretin inhibited cell death in STZ-induced INS-1 cells by enhancing Bcl-2 activity, an anti-apoptotic protein, and lowering Bax activity, a pro-apoptotic protein. Tangeretin's ability to decrease oxidative stress by reducing NF-κB activation and raising the activities of SOD, GPx, and CAT may be partially responsible for its antiapoptotic properties. Also, tangeretin increased the ability of the cells to secrete insulin by increasing insulin 1 and 2 genes and protein expression in STZ-induced INS-1 cells [42]**.** The administration of tangeretin (200 mg/kg) to obese mice on a high-fat diet (HFD) reduced blood sugar, total cholesterol, body weight, and adipocytokines such as leptin, IL-6, and adiponectin [29]**.**

In C57BL/6J mice with pre-existing obesity, Marina et al. [43] looked into the ability of tangeretin to restore metabolic damage brought on by a high-fat diet (HFD). The result shows that the blood serum glucose levels, leptin, resistin, and TBARS in these diabetic mice were considerably lower after four weeks of supplementation with 100 mg/kg b.w. of tangeretin than in the healthy control and non-supplemented HFD groups [43]**.**

Shin et al. 2017 examined the effects of tangeretin on inflammatory changes and glucose absorption in a coculture of RAW 264.7 cells (a mouse macrophage cell line) and 3T3-L1 adipocytes (a mouse adipocyte cell line), whereby they observed that tangeretin (100 μM) treatment reduced the expression of interleukin IL-6, TNF-α and IL-1, inducible nitric oxide synthase, and cyclooxygenase-2 as well as the synthesis of nitric oxide, and also increase in glucose absorption in the coculture was observed. According to these results, tangeretin lowers inflammation caused by obesity in adipose tissue, which then alleviates insulin resistance [44]**.**

Diabetes is brought on by both improper glucose metabolism and impaired lipid physiology. Hence, one strategy for managing diabetes is to target substances with strong antihyperlipidemic activity. By reducing blood triacylglycerols (TAG), low-density lipoprotein cholesterol (LDL-C), and very-low-density lipoprotein (VLDL) in hamsters with casein-induced hypercholesterolemia, tangeretin reduces the risk of diabetes-induced atherosclerosis [45]**.** In Hep G2 cells (hepatocellular carcinoma cell line), tangeretin treatment reduced apoB secretion, TAG synthesis, DAG acyltransferase activity, and stimulation of the peroxisome proliferator-activated receptor (PPAR) [46].

Type II diabetes and other lifestyle-related illnesses can be brought on by rapid postprandial blood glucose increase. Sodium/glucose cotransporter 1 (SGLT1) plays a significant role in the uptake of glucose obtained from food choices [47]. In the small intestine, glucose is absorbed via the SGLT1 transporter. Additionally, SGLT1 is found in the distal proximal tubule in the kidney, where it aids in the reabsorption of glucose when tubular glucose amounts are elevated [48]. Thus, SGLT1 inhibition could greatly reduce postprandial blood glucose rise, which could help in glycemic control. In STZ-induced diabetic rodents and humans with diabetes cardiomyopathy, SGLT1 expression has been found to increase significantly. By blocking SGLT1, attenuation of apoptosis and onset of diabetes cardiomyopathy can be prevented [48]**.** In scientific research conducted by Satso et al., they were able to maintain and create a CHO cell line (Chinese Hamster Ovary cells; an epithelial-like cell line) that is capable of consistently expressing human SGLT1 and investigated how phytochemicals affect SGLT1 function. They found that out of all the phytochemicals studied, tangeretin and cardamonin were two phytochemicals that significantly reduced SGLT1 function. Also, they found that tangeretin suppresses not only glucose reabsorption but fructose uptake, too [49].

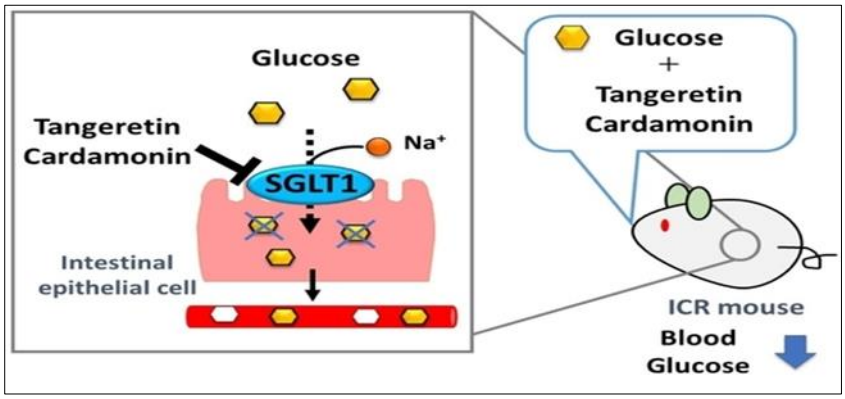

Figure 4 Inhibitory Effect of Tangeretin on Human Intestinal SGLT1 Activity *in vitro* and antihyperglycemic effect in mice *in vivo*. Source: **Satsu et al., 2021** [47].

Diabetic complications often accompany patients with dyslipidemia because an altered lipid profile often is one of the significant risk factors that can lead to diabetes [50], characterized by an elevated level of cholesterol, TG, LDL-C, VLDL-C, and diminished levels of HDL-C in the blood circulation. Dyslipidemia has been associated with an abnormal buildup of TG-rich lipoproteins (TGRLs) in the plasma. Lipoprotein lipase (LPL) is an enzyme that has the ability to break down TGRL particles, such as chylomicrons and VLDLs. Growing evidence suggests that elevated LPL activity can aid in the clearance of plasma TG; in contrast, LPL insufficiency or lack of its enzymatic activity causes TG to accumulate in the plasma and result in hypertriglyceridemia [51]. The lipid-modulating effects and underlying processes of tangeretin activity in hepatic cells were examined in research by Chen et al. 2021 [51]. Using bioinformatics and transcriptome studies and analyzing with the Gene Oncology database, they found that a collection of 13 differentially expressed genes (DEGs) connected to the control of lipoprotein lipase (LPL) activity was tightly regulated by tangeretin. Angiopoietin-like 3 (ANGPTL3), a key modulator of LPL enzymatic activity that regulates TGRL metabolism in plasma, was one of these DEGs that tangeretin substantially downregulated. Tangeretin was found to significantly reduce the mRNA and protein levels of ANGPTL3 in Huh-7 cells and HepG2 (hepatocellular carcinoma cell line). Also, Chen et al. (2021) demonstrated that tangeretin suppresses the gene and protein expression of hepatic ANGPTL3 by inhibiting the activity of LXRα, a crucial regulator for lipid homeostasis. Therefore, tangeretin reduces TG buildup in circulation by blocking the LXR-ANGPTL3 pathway, thus causing an increase in LPL catalytic activity and subsequently increasing TG breakdown in lipoproteins. Their results lend credence to the idea that tangeretin employs a lipid-reducing effect making it a viable phytochemical for dyslipidemia therapy or prevention [52].

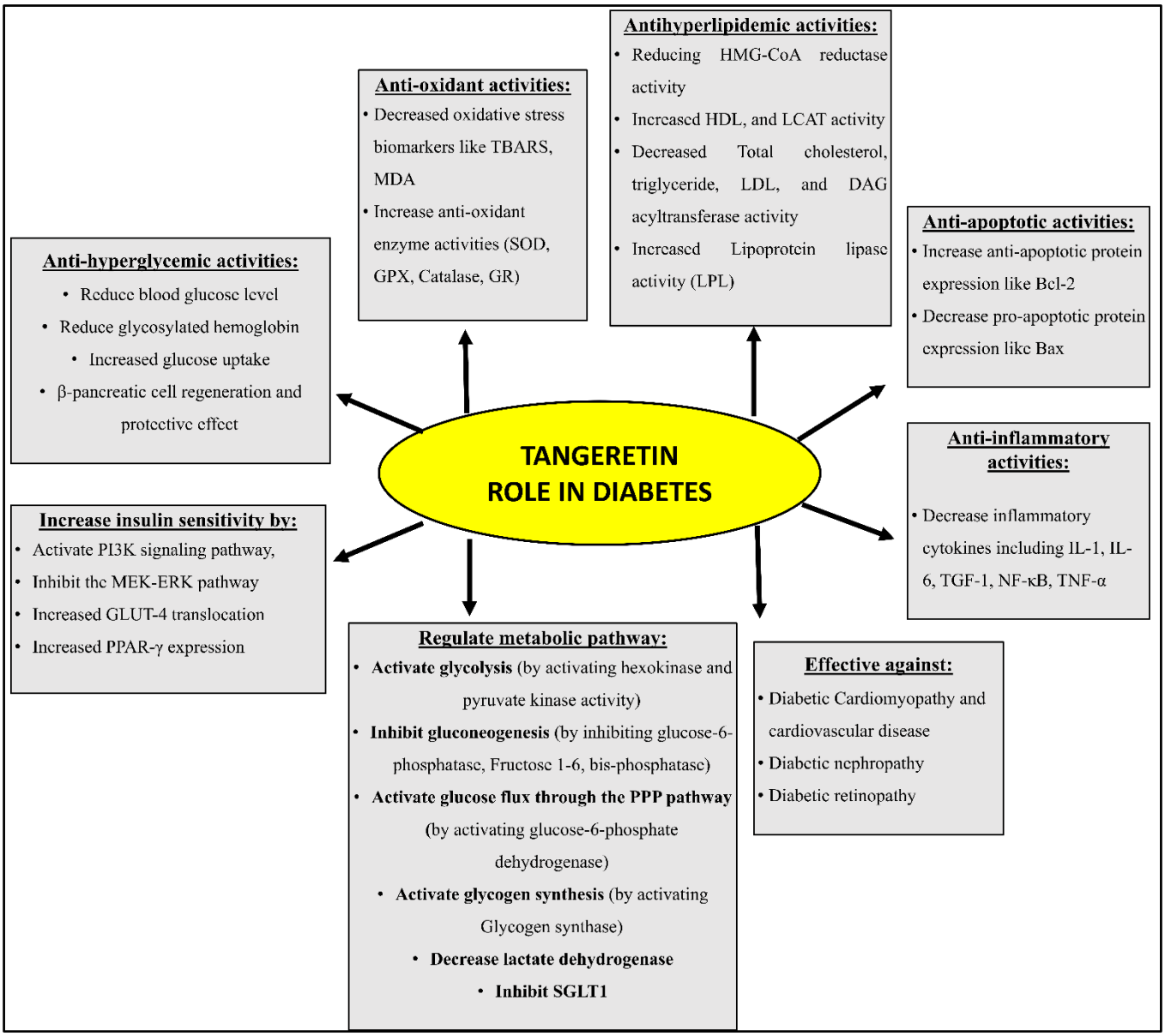

Figure 5 Tangeretin therapeutic role in attenuating diabetes: An overview

6. Conclusion

With so many pre-clinical studies showing such positive, consistent reliable and beneficial effect against diabetes and its related complication, tangeretin could serve as one of the most potent agents and find its uses and important in the development of a therapeutic and pharmaceutical product in clinical studies or as an adjunct to pre-existing drugs to enhance their anti-diabetic property or to provide a protective effect to their adverse side effect. Thus, tangeretin being a phytochemical compound found abundantly in nature, and which exhibits such great anti-diabetic activities in pre-clinical studies, can be used extensively for its usage as a therapeutic agent.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

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