**Journal of Innovations in Pharmaceutical and Biological Sciences (JIPBS)**
ISSN: 2349-2759
Available online at https://jipbs.com/index.php/journal

Review article

# A review on comparative study between metformin and hesperidin in the management of diabetic complications

**Rohit Chettri[1]*, Sairashmi Samanta, Sushil Gurung, Royan Chhettri**

*M. Pharmacy Student, Department of Pharmacology, Krupanidhi College of Pharmacy, Bengaluru, Karnataka, India.*

Received on: 27/07/2024, Revised on: 09/09/2024, Accepted on: 24/09/2024, Published on: 30/09/2024.

***Corresponding Author: Rohit Chettri,** M. Pharmacy Student, Department of Pharmacology, Krupanidhi College of Pharmacy, Bengaluru, Karnataka, India.
Phone No: +91-9382318267.
Email id: coolat30degree@gmail.com



**Key words:** Diabetes, Hesperidin, Metformin, Diabetic complications.

Vol. 11 (3): 08-20, Jul-Sep, 2024.

DOI: http://doi.org/10.56511/JIPBS.2024.11302

**Abstract**

Diabetes mellitus (DM) is a highly widespread condition that has a significant negative influence on global health. Typically, they give rise to microvascular and macrovascular challenges like neuropathy, gastropathy, cardiac myopathy, retinopathy, nephropathy etc as well as to an array of comorbidities like depression, cognitive decline, Alzheimer's disease etc. Apart from the use of oral hypoglycemic agent in regulating blood glucose levels that has a role in the development of diabetic complication, flavonoids have been a major research attraction in targeting diabetic complications. Hesperidin a plant-based flavone glycoside found abundantly in citrus fruits has gained a lot of attention in medical research with its anti-diabetic, antioxidant and hypolipidemic potential being formulated with novel approaches in diabetological research. This review article not only aims at contrasting the roles of hesperidin and metformin with a systematic approach in various diabetic complications along with associated comorbidities but also provides justifying information for carrying out a study to determine the effectiveness of combinational strategy between the two in fighting of various diabetic complications and to modulate the progression of the disease.

## Introduction

Diabetes mellitus (DM), an endocrinological disorder that stems from altered glucose metabolism and poorly managed hyperglycemic state over prolonged period of time. The branching of this typical endocrinological disorder is divided mainly into two types Type I DM (IDDM) resulting in inadequate release of insulin in response to glucose & Type II DM (NIDDM) resulting in insulin resistance where the insulin becomes unresponsive [1]. In developing countries like India, the prevalence of type-2 DM is flaring and is expected to rise from 25.2 million to 35.7 million cases by the year 2045 [2]. Insulin Resistance with improper glycemic control comes with a wide range of complications in the vasculature system categorized as micro (nephropathy, neuropathy & retinopathy) & macro (coronary heart failure, peripheral artery disease and stroke) vascular complications [3]. These complications moreover minimize the life quality and hastens the occurrence of disability & discomfort [4]. Sedentary lifestyle and obesity have been the major risk associated with the development of DM more common in developed and developing nations [5]. Still the etiopathological mechanism has not been well established for understanding the development of DM as is thought to be occurring from multiple factors [6-8]. Research studies has successfully demonstrated the effectiveness of use of oral hypoglycemic drugs in conjugation with lifestyle modulation in reversing type 2 DM associated complications by controlling hyperglycemic state in diabetic patients [9, 10]. But the use of oral hypoglycemic agents comes with a greater disadvantage of inducing hypoglycaemia that may be fatal in some cases thus in the present field of endocrinological research much

greater emphasis is being laid on discovering plant based bioactive compounds for delaying or preventing diabetes associated complications. For example, regular consumption of food rich in flavonoids like *Emblica officinalis gaertn* fruit can effectively delay the occurrence of diabetic complications as proven recently at our very own institute [11]. Flavonoids are plant-based phytochemical found at a diverse range in pant and its product such as tea, coffee, fruits, vegetables etc. and are well acknowledged for their antineoplastic, antibacterial, antifungal, antihyperglycemic, antiparasitic, neuron preserving, cardio-protective & anti-inflammatory activity [12]. Hesperidin (PubChem CID:10621) a bioflavonoid found abundantly in citrus fruits and peels is found to effectively improve plasma glucose levels & insulin levels moreover their anti-oxidative properties enhance its therapeutic importance in ameliorating diabetes-associated complications when used as a dietary supplement [13]. Metformin a well-known insulin sensitizer is used as 1st drug of choice in management of type 2 DM which has an effective control over high blood glucose levels and also gives a prominent fall in HbA1c levels which are the major precursors for development of advanced glycosylated end products (AGEs) that triggers the synthesis of free radicles as well as activates downstream signaling pathways for development of diabetic complications (Figure 1) [14, 15]. In this review article we went through a systematic review with a series of literatures on comparing the effectiveness of plant based flavonoid hesperidin for DM associated secondary complications in contrast to metformin a standard oral hypoglycemic agent used in type-2 DM.

## Hesperidin, metformin & secondary complications of diabetes mellitus

Insulin Resistance/Type 2 DM is a complex metabolic condition caused by prolonged high blood sugar levels, leading to changes in how the body processes glucose and fats, as well as dysfunction of the beta cells in the pancreas that contribute to the development of diabetes-related complications [16]. Based upon preclinical and human studies polyphenols such as flavonoids impart an important role in regulating metabolic alteration related to an effective management of diabetic complications [17]. Flavonoids are polyphenolic natural products produced by plant commonly found in fruits, herbs, vegetables, flowers and seeds [18]. Till date more than ten thousand different flavonoids have been discovered and have been well acknowledged for their therapeutic properties [19]. The biosynthesis of flavonoids are known to be brought from phenylpropanoid pathway in plants [20]. Flavonoids (Figure 2) are classified into 7 subtypes structure as anthoxanthins, flavanones, flavanonols, flavans, chalchones, anthocyanidins, and isoflavonoids are the different subgroups of flavonoids [21].

## A common link to diabetic complication

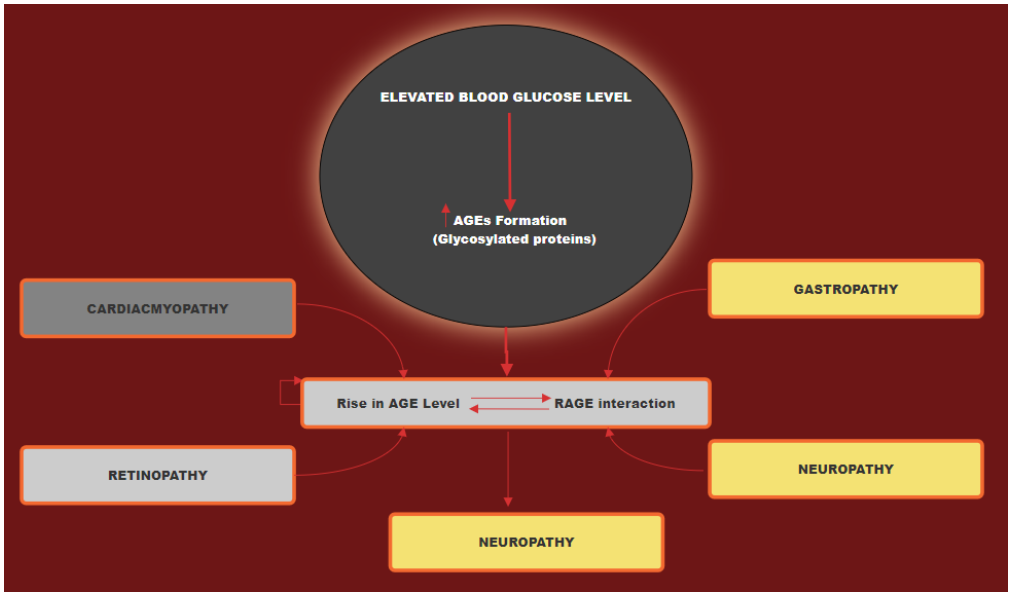


**Figure 1. A diagrammatic representation explaining the influence of hyperglycemia in development of diabetic complications. Hyperglycemia is associated with the progression of Insulin resistance (IR) which in turn promotes glycosylaton of proteins (AGEs) that acts as source for generation of free radicles to induce oxidative stress induced damage to the cellular structure moreover increased level of AGEs promotes greater interaction with its receptor (RAGE) that signals downstream cascade to promote the development of diabetic complications [Source data: *Mengstie MA et al.* 2022] [14].**

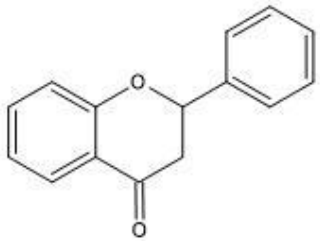

**Figure 2. Chemical structure of Flavonoid.**

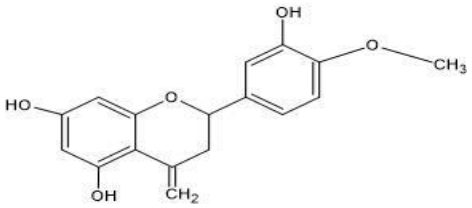

**Figure 3. Chemical structure of Hesperidin.**

Among the diverse group of flavonoids hesperidin (hesperetin 7-rutinoside) is a flavanone (Figure 3) found abundantly in citrus fruits such as in peels of *Citrus sinensis* (orange), *Citrus limon* (lemon), *Citrus paradise* (Grapefruit) etc [22].

Hesperidin as an anti-diabetic agent acts positively by regulating plasma glucose levels, glucose uptake and insulin secretion moreover also has an important role in diminishing the actions of AGEs which are proteins that undergo glycosylation in the systemic circulation during hyperglycemic state [23-25]. Many preclinical studies with positive results have been established with the use of Hesperidin a flavone glycoside in diabetic complications as discussed (Table 1). Hesperidin is generally considered safe, but one might experience side effects. Gastrointestinal issues like nausea or diarrhoea can occur, and allergic reactions such as skin rashes or itching are possible. It can also affect blood pressure, which may be a concern for those with cardiovascular conditions. Additionally, hesperidin might interact with medications like blood thinners or anticoagulants, potentially increasing bleeding risks [26]. Its bioavailability is relatively low due to poor water solubility and limited absorption in the digestive tract. Factors such as food intake, dosage, and individual gut microbiota can impact its absorption. Researchers are exploring various formulation techniques, including nano-carriers, to enhance hesperidin's absorption and effectiveness [27]. Genetic polymorphisms in enzymes like CYP3A4, UGT1A1, SULT1A1 and variations in drug transporters, such as P-glycoprotein (encoded by the ABCB1 gene) may influence hesperidin's bioavailability and clearance [28].

**Table 1. The potential underlying anti-diabetic mechanism of Hesperidin in Diabetic complications.**

| ***In vivo* / *In vitro* Models** | **Mechanism** | **Reference** |
|---|---|---|
| STZ Neuropathic rats | Negative regulation of ROS generation & release of inflammatory cytokines like TNF- α and IL-1β. | Visnagri 2014 [29] |
| STZ-nicotinamide mediated myocardial infarction | Lowers HbA1c, glucose, Low Density Lipoprotein, Total Cholesterol, Tri-Glyceride levels & blood pressure. | Kakadiya 2010 [30] |
| STZ Nephropathic rats | ↓TGF- β 1, 8-OHdG, serum urea & creatinine levels, MDA level, ↑ CAT and GPx. | Fatih 2017 [31] |
| HFD/STZ-induced type 2 diabetic rats | ↓oxidative stress, pro-inflammatory cytokines (TNF-α and IL-6). | Mahmoud 2012 [32] |
| STZ-induced type 1 diabetic rats | Activities glucose-6-phosphatase (G6Pase), glucokinase (GK), reduced blood glucose and normalized serum insulin levels. | Akiyama 2009 [33] |
| Diabetic Retinopathy- Retinal ganglion cell 5 (RGC-5) cell culture | anti-apoptotic agent (Bax & ↓ Bcl-2), down regulation of caspase-9 and caspase-3, restoration of mitochondrial function, activated p38 MAPK & inhibited phosphorylation of JNK. | Wayne 2017 [34] |
| STZ induced diabetic foot ulcers in rats | up-regulation of VEGF-c, Ang-1, Tie-2, TGF-β, Smad 2/3, reduced infiltration of inflammatory polymorphonuclear cells, ↑angiogenesis and vasculogenesis. | Li 2018 [35] |

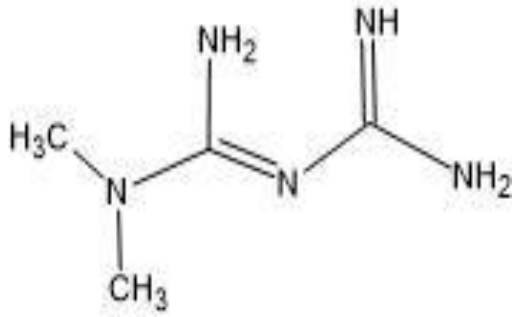


**Figure 4. Chemical structure of Metformin.**

**Figure 5. Galega Officinalis.**

Metformin (Figure 4) (1,1-dimethyl biguanide hydrochloride), a biguanide is a plant based anti-diabetic drug sourced from *Galega officinalis* (also known as goat's rue) (Figure 5) [36] the use of this oral hypoglycemic drug either as a monotherapy or in combination has been well known for effective management of DM, prior literatures have highlighted the potential benefits of both metformin and hesperidin in managing diabetic complications, with metformin primarily improving insulin sensitivity and hesperidin exhibiting antioxidant and anti-inflammatory properties [37, 38].

The anti-diabetic action behind this drug is mainly by increasing the sensitivity of insulin in response to glucose & by concealing hepatic glucose breakdown through AMPK mediated pathway [39]. On a molecular basis it supresses the genes that codes for enzymes involved in gluconeogenic pathway, such as glucose 6 phosphatase, phosphoenolpyruvate carboxykinase and pyruvate carboxylase resulting in suppression of gluconeogenesis [40], apart from regulating hepatic glucose production it also lowers blood glucose levels by up-regulating GLUT 4 transporters in the skeletal muscles, causing fall in glucose absorption from the intestines and stimulating glucagon-like-peptide-1 (GLP-1) thereby enhancing insulin action and lowering blood glucose levels [41-43]. The mechanistic role of metformin in diabetic complication is tabulated below. Use of metformin may occasionally lead to hypoglycemia, especially when combined with other glucose-lowering medications its rare but serious complications include lactic acidosis, particularly with potential long-term vitamin B12 deficiency [44]. It is contraindicated in individuals with severe renal impairment, liver disease, unstable heart failure, alcohol abuse, or those experiencing severe infections or dehydration [45].

### Diabetic nephropathy

One of the primary reasons for end-stage kidney failure is the onset of diabetes with poorly managed blood sugar levels resulting in diabetic nephropathy (DN), a prevalent complication of diabetes [52]. Diabetic nephropathy (DN) typically begins with hyperfiltration and albuminuria, progressing to renal function decline. However, in type 2 diabetes (T2DM), diabetic kidney disease (DKD) may present variably, with other kidney disorders and peripheral vascular disease often complicating the diagnosis [53].

**Table 2. The potential underlying anti-diabetic mechanism of metformin in Diabetic complications.**

| *In vivo* / *In vitro* Models | Mechanism | Reference |
|---|---|---|
| STZ induced Nephropathic rats | ↓LRG1 and TGFβ1/ALK1-induced renal angiogenesis, (IL-6), (TGF-β1) and (VEGF), serum urea & creatinine levels. | Mohammad 2023 [46] |
| STZ induced Neuropathic rats | ↓ TNF-α, reduction in Intraepidermal nerve fiber density (IENFD) is preserved. | Cao 2021 [47] |
| STZ induced Retinopathic rats | ↓ malondialdehyde, glutamate, tumor necrosis factor-α and vascular endothelial growth factor (VEGF) & ↓ retinal mRNA expression of NFkB, tumor necrosis factor-α and TLR4. | Suliman 2021 [48] |
| AKT-knockout mice-Cardiacmyopathy | ↓ Bax/Bcl-2 ratio, ↑ PK2, PKR1, and PKR2 expression & activation of AMPK/SIRT1. | Yang 2020 [49]<br>Jia 2021 [50] |
| Wound in STZ induced diabetic rats | ↑ PI3K/Akt, ↓ forkhead box O (FOXO). | Tombulturk 2022 [51] |

The determining characteristic feature of DN based on histopathological evaluation includes glomerular and tubular epithelial hypertrophy, increased basement membrane thickness and mesangial expansion with the accumulation of extracellular matrix (ECM) proteins [54]. Clinical symptoms include fall in GFR (glomerular filtration rate), glomerular hyperfiltration & increased urinary albumin excretion [55]. In this section we are going to have a comparative analysis between plant based bioflavonoid and metformin to modulate the progression or prevent the occurrence of DN. Hesperidin a potent therapeutic bioflavonoid is present in rich amount on the pigmented external layer of the peel and on the white soft middle portion of citrus fruit especially orange [56], AGEs are believed to play a role in the development of diabetic kidney disease through multiple mechanisms including the creation of oxidative stress and increased production of growth factors and cytokines [57]. According to a study conducted on rats with diabetes, treatment with hesperidin resulted fall in glycated hemoglobin (HbA1C) [58] precursors to AGEs. At the same time, it increased plasma insulin levels and elevated glycogen storage in the hepatic system and skeletal muscles of rats with resistance to insulin caused by diabetes [59, 60]. Another study also demonstrated a prominent fall in plasma glucose levels via influencing enzymes that regulate glucose, as well as restoring normal levels of lipids and adiponectin in rats with artificially induced Insulin dependent diabetes mellitus with STZ [61]. Also normalized the anti-oxidant status in tissue homogenate of diabetic rats. The renoprotective benefits of hesperidin is associated with regulation AGEs/its receptor (RAGE) transduction cascade [62]. Hypolipidemic activity of hesperidin is known to be exerted mainly through inhibition of HMG-CoA reductase and acyl-CoA: cholesterol acyltransferase (ACAT) and enhanced expression of the LDL receptor encoding gene which plays an important role in modulating the disease progression as Lipid nephrotoxicity is thought to be involved in the development of DN, also studies show hypercholesterolemia can exaggerate albuminuria in diabetic rats [63, 64]. The nephron protective effect of metformin on DN in type 2 diabetic rats is mainly brought in by its hypoglycemic, anti-oxidant, hypolipidemic & downregulation of inflammatory cytokines based on reports obtained from animal model of DN [65] very similar to hesperidin but in contrast to standalone treatment with hesperidin metformin is found to be more effective when given in combination than as a monotherapy. Thus, study can also be carried out to investigate the synergistic effect between the two then to be used as a monotherpy for delaying the progression or preventing the occurrence of DN. In conclusion, animal studies provide evidence that flavone glycoside hesperidin in contrast to metformin can be used as therapeutic agents in diabetic nephropathy and consumption of such food's rich in such class of flavonoids can successfully modulate the progression of disease.

**Diabetic neuropathy**

Diabetic neuropathy predominantly affects lengthier nerve fibers more severely than those that are shorter due to a proportional decrease in nerve conduction speed with increasing nerve length [66]. Hyperglycemia, along with metrics like fasting blood glucose (FBG), glycated hemoglobin (HbA1c), and disease duration, are the main risk factors for developing prediabetic neuropathy and diabetic peripheral neuropathy (DPN) in prediabetic and diabetic patients [67]. As a result, anomalous experiences of tremors, pain, pressure, and temperature perception are typically experienced in the lower limbs [68]. The predominant emphasis in examining morphological modifications in Diabetic neuropathy has been on the nerves in the extremities, specifically on phenomena such as axonal degeneration, demyelination, and Schwann cell ailments [69]. This section addresses the possible value of early treatment of peripheral neuropathy utilizing phytochemical methods or metformin in slowing the advancement of diabetic complication. Lim et al. studied ways hesperidin shields nerve cells against damage owing to elevated blood sugar levels. SH-SY5Y nerve cells subjected to excessive glucose promoted oxidative stress mediated dysfuntion. It substantially lowered reactive oxygen species generated by hyperglycemia & suppressed intracellular reactive oxygen species growth in dose-dependent manner. Hesperidin showed protection towards glucose-mediated DNA damage, decreased Endoplasmic Reticulum (ER) stress and demonstrated anti-apoptotic abilities hesperidin's powerful antioxidant capabilities shielded nerve cells against excessive glucose-mediated oxidative damage, ER stress, and cell death [70]. Research conducted by Bayir and colleagues on neuropathic rats induced with STZ revealed the ability of hesperidin to greatly reduce STZ-mediated pain stimulus and high blood sugar levels [71]. Moreover, histological study of sciatic nerve demonstrated decreased impairment with hesperidin therapy. Another investigation examined the curative abilities of hesperidin for its usage in reducing oxidative stress in STZ-induced DM in rats, therapy with hesperidin substantially alleviated these abnormalities, showing its extraordinary antioxidant action [72]. Research on metformin for diabetic neuropathy showed that metformin could reverse the low end threshold to pain stimuli and nociception in rats treated with fructose, suggesting that fructose's impact on pain is due to insulin resistance rather than high blood sugar [73]. One of the processes behind diabetic neuropathy is inflammation of the peripheral nerves. Metformin lowers inflammation [74] by activating AMPK to target inflammatory markers such as C-RP, IL-6, TNF-α [75]. For neuropathy caused by diabetes in STZ-induced diabetic mice, metformin raised motor nerve conduction velocity [76]. Part of the development of diabetic issue is merely linked to oxidative stress, AMPK can reduce oxidative stress and shield nerve cells from damage caused by oxidative stress by means of its activation [77]. However, metformin has been documented to cause inadequate

absorption of Vit B12 resulting in neurological issues (such as peripheral and autonomic neuropathy, painful neuropathy) [78] accelerating the development of diabetic neuropathy thus providing a more favourable relevance for alternate use of metformin with hesperidin. In the end, we have underlined in- vivo studies demonstrating the efficacy of hesperidin in comparison to metformin for having the possibility to be employed as alternative therapeutic or augmenting agent in diabetic neuropathy.

**Diabetic retinopathy**

Primary cause for blindness among diabetic patients is diabetic retinopathy (DR) mainly caused due to progressive damage in the cellular and vascular elements of the retina [79]. It is anticipated that worldwide incidence of Retinopathy caused by diabetes will experience a substantial increase in the coming decades, with an estimation of 130 million in 2030, and 161 million by the year 2045 [80]. It is seen that among the diverse type of diabetes, patients with Type 1 DM are very much susceptible to DR [81]. Diabetic retinopathy is strongly associated with longer diabetes duration, high blood sugar, and hypertension, with elevated HbA1c levels contributing to its progression [82]. The retinal lesions seen in diabetic retinopathy, including microaneurysms, hemorrhages, and hard exudates, mainly stem from damage to the retinal microvasculature [83]. Defects in the retinal layer was described by Singer *et al.* [84]. Shehata *et al.* made a study using Streptozotocin mediated DM in rats that indicated therapy with hesperidin lowered the thickness of different retinal layers based on morphometric analysis report [85]. Oxidative Imbalance is thought to a major reason behind development of DR [86]. The retina is additionally vulnerable to oxidative species because of its greater O2 demand, the substantial quantities of PUFA (poly unsaturated fatty acid) present in the structure, and continuous stimulation to light makes it more evident causing mitochondrial dysfunction and Endoplasmic Reticulum stress [87] which is ameliorated by the potential anti-oxidant capacity of hesperidin in preventing DR [88]. Roy *et al.* [89] have elucidated that malfunctioning mitochondria and stress within the endoplasmic reticulum are present in DR which was found to be alleviated by hesperidin therapy [90]. Kowluru et al. reported the association of retinal neuron apoptosis with mitochondrial dysfunction [91]. Metformin is postulated as safeguarding retinal cells from undergoing apoptosis triggered by Reactive Oxygen Species mainly by modulating MnSOD scavengers of oxidative species and down regulation of NOX which is triggered by elevated blood glucose level and increases oxidative stress [92]. Autophagy is frequently suggested as a dual-edged weapon in DR: Autophagy can assist cells in overcoming stressful circumstances during mild distress; yet, too much autophagy results in massive cell mortality and DR exacerbation [93]. Excessive autophagy has been associated with hyperglycemia which also leads to lysosomal dysfunction in turn releases large amount of vascular endothelial growth factor (VEGF) [94] a pro-angiogenic factor that tends to cause damage in the Blood Retina Barrier (BRB) [95] and MC (Müller cells) death which are involved in maintaining the normal retinal physiology in an animal model [96]. Thought to reduce VEGFR2's phosphorylation, metformin also induces VEGF-A mRNA splicing to VEGF120, hence lowering activity between VEGFR2 and VEGF-A. This stops angiogenesis thereby reversing the development of DR [97]. In a nutshell, evidence from in-vivo and molecular studies provide sufficient evidence for a beneficial effect of hesperidin in diabetic retinopathy in contrast to metformin which has profound positive effect on DR.

**Diabetic cardiovascular disease (CVD)**

It is widely recognized that DM increases the risks and mortality rates associated with heart diseases [98]. Individuals who have diabetes are more likely to develop cardiovascular disease, specifically heart failure, following a heart attack [99] than those without diabetes even prior to attaining enough blood sugar levels for a suspicion of diabetes, this risk rises gradually with elevated fasting blood sugar levels[100, 101]. A complex link between T2DM and CVD is thought to be associated common T2DM phenotypes include being overweight, lipid disorders, and high blood pressure all raise the likelihood of CVD in concert [102]. Cardiac dysfunction in diabetes mellitus is often asymptomatic and may not be detected until advanced stages of the disease [103]. A key feature of diabetic cardiomyopathy is left ventricular (LV) diastolic dysfunction, which often appears before clinically significant LV systolic dysfunction [104, 105]. In diabetes, excess fatty acid oxidation and hyperglycemia increase flux into the hexosamine biosynthetic pathway, leading to the production of UDP-GlcNAc. This promotes O-GlcNAcylation of proteins, which interferes with key cardiac functions like eNOS activity and SERCA2a expression. These disruptions impair calcium handling and cardiac relaxation. Oxidative stress further amplifies this pathway, contributing to cardiomyocyte dysfunction and apoptosis. Ultimately, this mechanism links hyperglycemia to diabetic heart complications [106]. This part of the article aims to underline the most recent findings on the relationship and comparative evaluation between Hesperidin and Metformin in diabetic heart ailments. Kosmas *et al.*, claims that dyslipidemia plays a key role in heart diseases, with LDL-C (low-density lipoprotein cholesterol) being the primary contributing factor. Additionally, elevated plasma triglyceride levels and reduced high-density lipoprotein cholesterol level also links metabolic syndrome (MetS) with cardiovascular ailments [107]. Based on study made by Rekha *et al.*, on diabetic myocardial infraction (DMI) rat model it showed that hesperidin successfully reduced LDL and increased HDL levels and also decreased cholesterol and TG (Triglyceride) in the blood and liver by blocking HMG-CoA reductase and

ACAT (acyl-CoA: cholesterol acyltransferase) [108]. Metformin replicates certain advantages of cutting back calories such as enhancing responsiveness to insulin, and decreased levels of LDL and cholesterol, all without the need for calorie restriction. A recent meta-analysis report shows that in T2DM patients treatment with metformin prominently dropped the risk for CVD [109] through suppression of gluconeogenesis [110], activates 5' adenosine monophosphate-activated protein kinase (AMPK), which in turn enhances the functioning of endothelial nitric oxide synthase (eNOS) which has a direct impact on protecting the endothelium in individuals with T2DM [111], reduces plasma triglyceride, overall cholesterol, and LDL cholesterol levels, whereas serum HDL-C levels either increase or remain unchanged [98] which in turn are all the major factors for aggravating CVD. Hyperglycemia and CVD have both been investigated in numerous animal studies [112, 113]. The excessive production of Endothelin-1 (ET-1), a powerful constrictor of blood vessels made by heart cells which impacts heart contraction, is present in people with diseases associated with oxidative stress like obesity and T2DM, changes in the levels of ET-1 and its interaction proteins are seen as cardiovascular conditions progress [114]. Hesperdin's effect on a animal model of diabetic cardiomyopathy where the heart undergoes change at structural, functional, and regulatory levels showed suppression in endothelin (ET)-1 secretion mainly due to its anti-oxidant potential [115]. Metformin is though proven to inhibit the expression of endothelin 1 (ET-1) partially in cancer research made by Liu et al. thus can be hypothesised for its cardioprotective effect against diabetic cardiomyopathy [116]. Acute myocardial infarction (AMI) is a consequence of a fatal breakdown of heart tissue in the heart due to a blockage in the coronary arteries, leading to reduced blood flow though not much of studies have been carried out but hesperidin is known to carry out its protective effect mainly through SIRT1/Nrf2/HO-1 signaling pathway [117]. On the other hand, a study on the damage caused by Myocardial ischemia-reperfusion in rats sheds light on how metformin activates the AMPK/PGC1α pathway to protect against mitochondrial dysfunction. The activation of AMPK promotes PGC1α activity, leading to increased gene transcription of mitochondrial DNA and proteins, which reduces mitochondrial fission, decreases apoptosis in the ischemic myocardium, and lowers infract size, ultimately providing cardioprotective benefits [118]. In conclusion, several therapeutic strategies have been proposed, especially in vivo studies where hesperidin seems to have a potential to exceed the cardio-protective impact of metformin on treating cardiovascular disease in diabetes mellitus.

## Emerging diabetic complication

In the present scenario diabetic population still carry a great weight from the well-known classic problems. Development in the field of diabetological research have improved our knowledge and has shown clear relationships between DM and an array of comorbidities, including dementia, mood disorders, obstructive breathing during sleep and hepatic impairment [119]. Learning & memory impairment establishes an alarming complication of DM, but the underlying molecular mechanisms are still not clear, prolonged hyperglycemia are thought to alter the synaptic plasticity and neurotransmitter level such as DA (dopamine) & Serotonin (5HT) in the brain involved in cognitive function driven by glucotoxicity Pignalosa *et al.* [120]. One of the most promising treatment options for cognitive impairment and memory loss is flavonoids [121]. Hesperidin is one such flavonoid and many studies [122, 123] have been carried for ameliorating the cognitive decline mediated by DM with novel approaches. In a study DM was found to affect the hippocampus region of the brain involved in learning and memory by promoting inflammatory cytokines like IL-6, TNF-α, MDA, and ROS and decreasing IL-4, IL-10, SOD, and CAT. These reflect as impairment of cognitive functions which was found to be reversed by hesperidin [124]. A different research study replicated dementia in humans by conducting experiments on diabetic mice to investigate the impact of metformin. The study found that diabetes mellitus (DM) has a significant role in activating DRP1 through mitochondrial fission, which is linked to various neurodegenerative diseases. Metformin effectively prevented the activation of mitochondrial fission by modulating the AMPK signal pathway, thereby safeguarding the mitochondria and synaptic plasticity in the hippocampus of diabetic mice. [125]. Depression is another such complication that can be mediated by DM (Figure 6) with a very high occurrence rate in people with T1DM [126] Both the forced swimming and tail suspension tests, utilized for evaluating depression, have demonstrated the antidepressant properties of hesperidin. Hesperidin exhibited benefits for depression by enhancing mRNA levels of Glo-1 and its activity in the amygdala and hippocampal region of diabetic rats, thus reducing the production of AGEs and oxidative stress-related damage [127, 128]. The effectiveness of antidepressant drugs in treating depressive disorders in individuals with type 2 diabetes mellitus (T2DM) has been largely unsuccessful due to non-compliance with the therapy. However, the use of the anti-diabetic drug metformin has provided valuable insights into the treatment of depressive disorders associated with T2DM by promoting growth of neurons (neurogenesis), spatial memory function, and protecting brain cells against oxidative imbalance [129]. The presumed antidepressant effect of metformin indicates that depressive disorders may be influenced by both oxidative stress and inflammation through different signaling proteins and channels, such as Nrf2, pro-inflammatory cytokines, and the AMPK/BDNF and NFκB pathways [130]. Metformin has been demonstrated to activate AMPK, which in turn enhances the synthesis of BDNF [131] as inadequate amounts of BDNF are linked to impaired synaptic plasticity, reduced numbers

of excitatory neurons leading to development of depressive disorder [132]. In this section based upon the evidence of existing comorbidity associated with DM recent papers has been reviewed taking in consideration to cognitive dysfunction and depressive disorders and the mechanistic role of hesperidin in contrast to metformin has been described. With increase in the advancement in the field of medical science and diabetological research, many comorbid conditions are being associated with DM and many are still under study though limited studies have been carried out for explaining the potential therapeutic role of flavonoids especially hesperidin in various emerging diabetic comorbidity with novel delivery approaches thus there is a need for further investigation and discovery of more potential flavonoids for its therapeutic implementation and latent complications that we may might be not aware of.

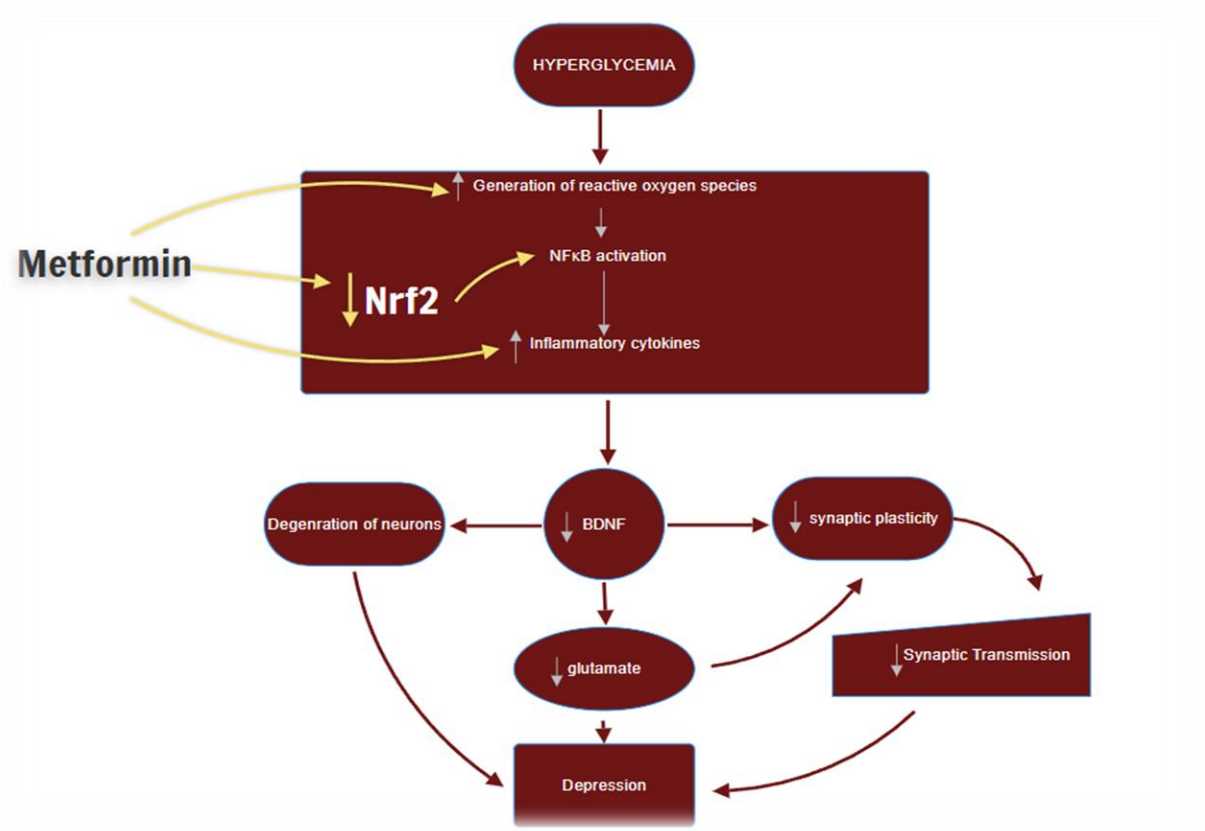


**Figure 6. A schematic representation on the role of metformin in ameliorating depressive disorders associated with DM. (Source data: Hamal et al. 2022 & Yang et al. 2020) [117,118].**

## Conclusion

Cellular and preclinical research have demonstrated that the plant-based flavonoid hesperidin and oral hypoglycemic medication metformin has the ability to combat diabetic complications. Research also indicates that both medicinal products to some extent share a similar molecular approach in effectively controlling the course of the disease. This information thus provides a strong rationale for implementing a novel formulation & combination strategy in a well-designed trial for patients with diabetic complications. These strategies thus may also help reduce the dosage and use of alternative oral hypoglycemic agents (OHA) that can cause significant hypoglycemia when used over a long period of time at standard therapeutic doses.

## Acknowledgement

The authors report no acknowledgements.

## Competing interests

The authors report no conflict of interest.

## Funding statement

The author has no relevant financial or non-financial interest to disclose.

## Ethics approval and consent to participate

This study does not involve experiments on animals or human subjects.

## Data availability

All data generated or analyzed during this study are included in this published article.

### References

1. Mukhtar Y, Galalain A, Yunusa U. A modern overview on diabetes mellitus: a chronic endocrine disorder. European Journal of Biology. 2020 Nov; 5(2):1-4.

2. Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. Indian journal of ophthalmology. 2021; 69(11): 2932-8.
3. Mezil SA, Abed BA. Complication of diabetes mellitus. Annals of the Romanian Society for Cell Biology. 2021; 25(3): 1546-56.
4. Wong E, Backholer K, Gearon E, Harding J, Freak-Poli R, Stevenson C, Peeters A. Diabetes and risk of physical disability in adults: a systematic review and meta-analysis. The lancet Diabetes & endocrinology. 2013; 1(2): 106-14.
5. Gonzalez Ramirez G, Bolaños Muñoz L. Relationship of sedentary lifestyle with obesity and comorbidities. InPhysical Activity and bariatric surgery 2023 Apr 20 (pp. 3-16). Cham: Springer International Publishing.
6. Conget I. Diagnosis, classification and cathogenesis of diabetes mellitus (in Spanish). Rev Esp Cardiol. 2002; 55: 528-35.
7. Skyler JS, Bakris GL, Bonifacio E, Darsow T, Eckel RH, Groop L, Groop PH, Handelsman Y, Insel RA, Mathieu C, McElvaine AT. Differentiation of diabetes by pathophysiology, natural history, and prognosis. Diabetes. 2017; 66(2): 241-55.
8. Unger R, Orci L. The essential role of glucagon in the pathogenesis of diabetes mellitus. The Lancet. 1975; 305(7897): 14-6.
9. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, Horton ES, Castorino K, Tate DF. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. Diabetes care. 2016; 39(11): 2065–2079.
10. Eckstein ML, Williams DM, O'Neil LK, Hayes J, Stephens JW, Bracken RM. Physical exercise and non-insulin glucose-lowering therapies in the management of Type 2 diabetes mellitus: a clinical review. Diabetic Medicine. 2019; 36(3): 349-58.
11. Kumar NP, Annamalai AR, Thakur RS. Antinociceptive property of Emblica officinalis Gaertn (Amla) in high fat diet-fed/low dose streptozotocin induced diabetic neuropathy in rats. NIScPR. 2009; 47(09): 737-42.
12. Ullah A, Munir S, Badshah SL, Khan N, Ghani L, Poulson BG, Emwas AH, Jaremko M. Important flavonoids and their role as a therapeutic agent. Molecules. 2020; 25(22): 5243.
13. Jamal A, Brettle H, Jamil DA, Tran V, Diep H, Bobik A, van der Poel C, Vinh A, Drummond GR, Thomas CJ, Jelinic M. Reduced Insulin Resistance and Oxidative Stress in a Mouse Model of Metabolic Syndrome following Twelve Weeks of Citrus Bioflavonoid Hesperidin Supplementation: A Dose–Response Study. Biomolecules. 2024; 14(6): 637.
14. Mengstie MA, Chekol Abebe E, Behaile Teklemariam A, Tilahun Mulu A, Agidew MM, Teshome Azezew M, Zewde EA, Agegnehu Teshome A. Endogenous advanced glycation end products in the pathogenesis of chronic diabetic complications. Frontiers in molecular biosciences. 2022; 9: 1002710.
15. Adeshara KA, Bangar NS, Doshi PR, Diwan A, Tupe RS. Action of metformin therapy against advanced glycation, oxidative stress and inflammation in type 2 diabetes patients: 3 months follow-up study. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020; 14(5): 1449-58.
16. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. Diabetologia. 2003; 46: 3-19.
17. Serina JJ, Castilho PC. Using polyphenols as a relevant therapy to diabetes and its complications, a review. Critical Reviews in Food Science and Nutrition. 2022; 62(30): 8355-87.
18. Feliciano RP, Pritzel S, Heiss C, Rodriguez-Mateos A. Flavonoid intake and cardiovascular disease risk. Current Opinion in Food Science. 2015; (2): 92-9.
19. Shkondrov A, Krasteva I, Pavlova D, Zdraveva P. Determination of flavonoids in related Astragalus species (Sect. Incani) occurring in Bulgaria. Comptes rendus de l'Académie Bulg. des Sci. 2017; 70(3): 363-66.
20. Liu W, Feng Y, Yu S, Fan Z, Li X, Li J, Yin H. The flavonoid biosynthesis network in plants. International journal of molecular sciences. 2021; 22(23): 12824.
21. Shen N, Wang T, Gan Q, Liu S, Wang L, Jin B. Plant flavonoids: Classification, distribution, biosynthesis, and antioxidant activity. Food chemistry. 2022; 383: 132531.
22. Gattuso G, Barreca D, Gargiulli C, Leuzzi U, Caristi C. Flavonoid composition of citrus juices. Molecules. 2007; 12(8): 1641-73.
23. Tabassum S, Misrani A, Yang L. Exploiting common aspects of obesity and Alzheimer's disease. Frontiers in human neuroscience. 2020; 14: 602360.
24. Mirzaei A, Mirzaei A, Khalilabad SN, Askari VR, Rahimi VB. Promising influences of hesperidin and hesperetin against diabetes and its complications: a systematic review of molecular, cellular, and metabolic effects. EXCLI journal. 2023; 22: 1235-63.
25. Vinayagam R, Xu B. Antidiabetic properties of dietary flavonoids: a cellular mechanism review. Nutrition & metabolism. 2015; 12: 1-20.
26. Khorasanian AS, Fateh ST, Gholami F, Rasaei N, Gerami H, Khayyatzadeh SS, Shiraseb F, Asbaghi O. The effects of hesperidin supplementation on cardiovascular risk factors in adults: a systematic review and dose–response meta-analysis. Frontiers in Nutrition. 2023 ;10: 1177708.
27. Wdowiak K, Walkowiak J, Pietrzak R, Bazan-Woźniak A, Cielecka-Piontek J. Bioavailability of hesperidin and its aglycone hesperetin—compounds found in citrus fruits as a parameter conditioning the pro-health potential (neuroprotective and antidiabetic activity)—mini-review. Nutrients. 2022 ;14(13): 2647.
28. Chen Z, Zheng S, Li L, Jiang H. Metabolism of flavonoids in human: a comprehensive review. Current Drug Metabolism. 2014; 15(1): 48-61.
29. Mahmoud AM, Ashour MB, Abdel-Moneim A, Ahmed OM. Hesperidin and naringin attenuate hyperglycemia-mediated oxidative stress and proinflammatory cytokine production in high fat fed/streptozotocin-induced type 2 diabetic rats. Journal of Diabetes and its Complications. 2012; 26(6): 483-90.
30. Kakadiya J, Mulani H, Shah N. Protective effect of hesperidin on cardiovascular complication in experimentally induced myocardial infarction in diabetes in rats. Journal of basic and clinical pharmacy. 2010; 1(2): 85-91.
31. Li W, Kandhare AD, Mukherjee AA, Bodhankar SL. Hesperidin, a plant flavonoid accelerated the cutaneous wound healing in streptozotocin-induced diabetic rats: Role of TGF-ß/Smads and Ang-1/Tie-2 signaling pathways. EXCLI journal. 2018; 17: 399-419.
32. Kandemir FM, Ozkaraca M, Küçükler S, Caglayan C, Hanedan B. Preventive effects of hesperidin on diabetic nephropathy induced by streptozotocin via modulating TGF-β1 and oxidative DNA damage. Toxin reviews. 2018; 37(4): 287-93.
33. Mahmoud AM, Ashour MB, Abdel-Moneim A, Ahmed OM. Hesperidin and naringin attenuate hyperglycemia-mediated oxidative stress and proinflammatory cytokine production in high fat fed/streptozotocin-induced type 2 diabetic rats. Journal of Diabetes and its Complications. 2012 ; 26(6): 483-90.

34. Liu WY, Liou SS, Hong TY, Liu IM. Protective effects of hesperidin (citrus flavonone) on high glucose induced oxidative stress and apoptosis in a cellular model for diabetic retinopathy. Nutrients. 2017; 9(12): 1312.
35. Li W, Kandhare AD, Mukherjee AA, Bodhankar SL. Hesperidin, a plant flavonoid accelerated the cutaneous wound healing in streptozotocin-induced diabetic rats: Role of TGF-ß/Smads and Ang-1/Tie-2 signaling pathways. EXCLI journal. 2018; 17: 399-419.
36. Hernández-Velázquez ED, Alba-Betancourt C, Alonso-Castro ÁJ, Ortiz-Alvarado R, López JA, Meza-Carmen V, Solorio-Alvarado CR. Metformin, a biological and synthetic overview. Bioorganic & Medicinal Chemistry Letters. 2023; 86: 129241.
37. Zhang Q, Hu N. Effects of metformin on the gut microbiota in obesity and type 2 diabetes mellitus. Diabetes, Metabolic Syndrome and Obesity. 2020; 13: 5003-14.
38. Ali AM, Gabbar MA, Abdel-Twab SM, Fahmy EM, Ebaid H, Alhazza IM, Ahmed OM. Antidiabetic potency, antioxidant effects, and mode of actions of Citrus reticulata fruit Peel hydroethanolic extract, hesperidin, and quercetin in nicotinamide/streptozotocin-induced Wistar diabetic rats. Oxidative medicine and cellular longevity. 2020; 2020(1): 1-21.
39. Fullerton MD, Galic S, Marcinko K, Sikkema S, Pulinilkunnil T, Chen ZP, O'neill HM, Ford RJ, Palanivel R, O'brien M, Hardie DG. Single phosphorylation sites in Acc1 and Acc2 regulate lipid homeostasis and the insulin-sensitizing effects of metformin. Nature medicine. 2013 Dec; 19(12): 1649-54.
40. Miller RA, Chu Q, Xie J, Foretz M, Viollet B, Birnbaum MJ. Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP. Nature. 2013; 494(7436): 256-60.
41. Kristensen JM, Treebak JT, Schjerling P, Goodyear L, Wojtaszewski JF. Two weeks of metformin treatment induces AMPK-dependent enhancement of insulin-stimulated glucose uptake in mouse soleus muscle. American Journal of Physiology-Endocrinology and Metabolism. 2014; 306(10): 1099-109.
42. Gu S, Shi J, Tang Z, Sawhney M, Hu H, Shi L, Fonseca V, Dong H. Comparison of glucose lowering effect of metformin and acarbose in type 2 diabetes mellitus: a meta-analysis. PLoS One. 2015; 10(5): 0126704.
43. Sokolova LK, Pushkarev VV, Cherviakova SA, Vatseba TS, Kovzun OI, Pushkarev VM, Tronko MD. The effect of metformin treatment on the level of GLP-1, NT-proBNP and endothelin-1 in patients with type 2 diabetes mellitus.2020; 16(8): 616-21.
44. Mohammad HM, Gouda SG, Eladl MA, Elkazaz AY, Elbayoumi KS, Farag NE, Elshormilisy A, Al-Ammash BB, Hegazy A, Abdelkhalig SM, Mohamed AS. Metformin suppresses LRG1 and TGFβ1/ALK1-induced angiogenesis and protects against ultrastructural changes in rat diabetic nephropathy. Biomedicine & Pharmacotherapy. 2023; 158: 114128.
45. Tombulturk FK, Todurga-Seven ZG, Huseyinbas O, Ozyazgan S, Ulutin T, Kanigur-Sultuybek G. Topical application of metformin accelerates cutaneous wound healing in streptozotocin-induced diabetic rats. Molecular Biology Reports. 2022; 49: 73–83.
46. Sweileh WM. Contraindications to metformin therapy among patients with type 2 diabetes mellitus. Pharmacy World & Science. 2007; 29: 587-92.
47. Infante M, Leoni M, Caprio M, Fabbri A. Long-term metformin therapy and vitamin B12 deficiency: an association to bear in mind. World journal of diabetes. 2021 ; 12(7): 916.
48. Cao XJ, Wu R, Qian HY, Chen X, Zhu HY, Xu GY, Sun YZ, Zhang PA. Metformin attenuates diabetic neuropathic pain via AMPK/NF-κB signaling pathway in dorsal root ganglion of diabetic rats. Brain Research. 2021; 1772: 147663.
49. Alomar SY, Barakat BM, Eldosoky M, Atef H, Mohamed AS, Elhawary R, El-Shafey M, Youssef AM, Elkazaz AY, Gabr AM, Elaskary AA. Protective effect of metformin on rat diabetic retinopathy involves suppression of toll-like receptor 4/nuclear factor-k B expression and glutamate excitotoxicity. International Immunopharmacology. 2021; 90: 107193.
50. Yang Z, Wang M, Zhang Y, Cai F, Jiang B, Zha W, Yu W. Metformin ameliorates diabetic cardiomyopathy by activating the PK2/PKR pathway. Frontiers in physiology. 2020; 11: 425.
51. Jia W, Bai T, Zeng J, Niu Z, Fan D, Xu X, Luo M, Wang P, Zou Q, Dai X. Combined administration of metformin and atorvastatin attenuates diabetic cardiomyopathy by inhibiting inflammation, apoptosis, and oxidative stress in type 2 diabetic mice. Frontiers in Cell and Developmental Biology. 2021; 9: 634900.
52. Samsu N. Diabetic nephropathy: challenges in pathogenesis, diagnosis, and treatment. BioMed research international. 2021; 2021(1): 1497449.
53. Sagoo MK, Gnudi L. Diabetic nephropathy: an overview. Diabetic nephropathy: methods and protocols. 2020: 1; 3-7.
54. Misra PS, Szeto SG, Krizova A, Gilbert RE, Yuen DA. Renal histology in diabetic nephropathy predicts progression to end-stage kidney disease but not the rate of renal function decline. BMC nephrology. 2020; 21: 285
55. Selby NM, Taal MW. An updated overview of diabetic nephropathy: Diagnosis, prognosis, treatment goals and latest guidelines. Diabetes, Obesity and Metabolism. 2020; 22: 3-15.
56. Chen Q, Wang D, Tan C, Hu Y, Sundararajan B, Zhou Z. Profiling of flavonoid and antioxidant activity of fruit tissues from 27 Chinese local citrus cultivars. Plants. 2020; 9(2): 196.
57. Peng P, Jin J, Zou G, Sui Y, Han Y, Zhao D, Liu L. Hesperidin prevents hyperglycemia in diabetic rats by activating the insulin receptor pathway. Experimental and Therapeutic Medicine. 2021; 21(1): 1-7.
58. Tan AL, Forbes JM, Cooper ME. AGE, RAGE, and ROS in diabetic nephropathy. InSeminars in nephrology 2007; 27(2): 130-143.
59. Ahmed OM, Mahmoud AM, Abdel-Moneim A, Ashour MB. Antidiabetic effects of hesperidin and naringin in type 2 diabetic rats. Diabetologia Croatica. 2012; 41(3): 53–67.
60. Akiyama S, Katsumata S, Suzuki K, Ishimi Y, Wu J, Uehara M. Dietary hesperidin exerts hypoglycemic and hypolipidemic effects in streptozotocin-induced marginal type 1 diabetic rats. J Clin Biochem Nutr. 2009; 46(1): 87–92.
61. Hanchang W, Khamchan A, Wongmanee N, Seedadee C. Hesperidin ameliorates pancreatic beta-cell dysfunction and apoptosis in streptozotocin-induced diabetic rat model. Life Sci. 2019; 235: 11685.
62. Wang Y, Wang LN, Xu GM, Wei DH. Hesperidin exerts the gestational diabetes mellitus via AGEs-RAGE signalling pathway. Int J Pharmacol. 2020; 15(5): 604–615.
63. Utsunomiya K, Ohta H, Kurata H, Tajima N, Isogai Y. The effect of macrophage colony-stimulating factor (M-CSF) on the progression of lipid-induced nephrotoxicity in diabetic nephropathy. Journal of Diabetes and its Complications. 1995; 9(4): 292-5.
64. Wilcox LJ, Borradaile NM, de Dreu LE, Huff MW. Secretion of hepatocyte apoB is inhibited by the flavonoids,

naringenin and hesperetin, via reduced activity and expression of ACAT2 and MTP. Journal of lipid research. 2001; 42(5): 725-34.
65. Ravindran S, Kuruvilla V, Wilbur K, Munusamy S. Nephroprotective effects of metformin in diabetic nephropathy. Journal of cellular physiology. 2016; 232(4): 731-42.
66. Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, Malik RA, Maser RE, Sosenko JM, Ziegler D. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes care. 2005; 28(4): 956-62.
67. Elafros MA, Andersen H, Bennett DL, Savelieff MG, Viswanathan V, Callaghan BC, Feldman EL. Towards prevention of diabetic peripheral neuropathy: clinical presentation, pathogenesis, and new treatments. The Lancet Neurology. 2022; 21(10): 922-36.
68. Jung UJ, Choi MS, Lee MK, Jeong KS. The hypoglycemic effects of hesperidin and naringin are partly mediated by hepatic glucose-regulating enzymes in C57BL/KsJ-db/db mice. The Journal of nutrition. 2004; 134(10): 2499-503.
69. Said G. Diabetic neuropathy—a review. Nature clinical practice Neurology. 2007; 3(6): 331-40
70. Lim C, Zhen AX, Ok S, Fernando PD, Herath HM, Piao MJ, Kang KA, Hyun JW. Hesperidin protects SH− SY5Y neuronal cells against high glucose− induced apoptosis via regulation of MAPK signaling. Antioxidants. 2022; 11(9): 1707.
71. Bayir MH, Yıldızhan K, Altındağ F. Effect of hesperidin on sciatic nerve damage in STZ-induced diabetic neuropathy: modulation of TRPM2 channel. Neurotoxicity Research. 2023; 41(6): 638-47.
72. Ashafaq M, Varshney L, Khan MH, Salman M, Naseem M, Wajid S, et al. Neuromodulatory effects of hesperidin in mitigating oxidative stress in streptozotocin induced diabetes. Biomed Res Int. 2014; 2014: 249031.
73. Byrne FM, Cheetham S, Vickers S, Chapman V. Characterisation of pain responses in the high fat diet/streptozotocin model of diabetes and the analgesic effects of antidiabetic treatments. Journal of diabetes research. 2014; 2015(1): 752481.
74. Bierhaus A, Fleming T, Stoyanov S, Leffler A, Babes A, Neacsu C, Sauer SK, Eberhardt M, Schnölzer M, Lasitschka F, Neuhuber WL. Methylglyoxal modification of Nav1. 8 facilitates nociceptive neuron firing and causes hyperalgesia in diabetic neuropathy. Nature medicine. 2012; 18(6): 926-33.
75. Hasanvand A, Amini-Khoei H, Hadian MR, Abdollahi A, Tavangar SM, Dehpour AR, Semiei E, Mehr SE. Anti-inflammatory effect of AMPK signaling pathway in rat model of diabetic neuropathy. Inflammopharmacology. 2016; 24: 207-19.
76. Barber AJ, Lieth E, Khin SA, Antonetti DA, Buchanan AG, Gardner TW. Neural apoptosis in the retina during experimental and human diabetes. Early onset and effect of insulin. The Journal of clinical investigation. 1998; 102(4): 783-91.
77. Cao XJ, Wu R, Qian HY, Chen X, Zhu HY, Xu GY, Sun YZ, Zhang PA. Metformin attenuates diabetic neuropathic pain via AMPK/NF-κB signaling pathway in dorsal root ganglion of diabetic rats. Brain Research. 2021; 1772: 147663.
78. Singh AK, Kumar A, Karmakar D, Jha RK. Association of B12 deficiency and clinical neuropathy with metformin use in type 2 diabetes patients. Journal of Postgraduate Medicine. 2013; 59(4): 253-7.
79. Barber AJ, Lieth E, Khin SA, Antonetti DA, Buchanan AG, Gardner TW. Neural apoptosis in the retina during experimental and human diabetes. Early onset and effect of insulin. The Journal of clinical investigation. 1998; 102(4): 783-91.
80. Teo ZL, Tham YC, Yu M, Chee ML, Rim TH, Cheung N, Bikbov MM, Wang YX, Tang Y, Lu Y, Wong IY. Global prevalence of diabetic retinopathy and projection of burden through 2045: systematic review and meta-analysis. Ophthalmology. 2021; 128(11): 1580-91.
81. Ahmed H, Elshaikh T, Abdullah M. Early diabetic nephropathy and retinopathy in patients with type 1 diabetes mellitus attending Sudan childhood diabetes centre. Journal of Diabetes Research. 2020; 2020(1): 7181383.
82. Vujosevic S, Aldington SJ, Silva P, Hernández C, Scanlon P, Peto T, Simó R. Screening for diabetic retinopathy: new perspectives and challenges. The Lancet Diabetes & Endocrinology. 2020; 8(4): 337-47.
83. Antonetti DA, Silva PS, Stitt AW. Current understanding of the molecular and cellular pathology of diabetic retinopathy. Nature Reviews Endocrinology. 2021; 17(4): 195-206.
84. Song KH, Jeong JS, Kim MK, Kwon HS, Baek KH, Ko SH, Ahn YB. Discordance in risk factors for the progression of diabetic retinopathy and diabetic nephropathy in patients with type 2 diabetes mellitus. Journal of diabetes investigation. 2019 ; 10(3): 745-52.
85. Singer M, Ashimatey BS, Zhou X, Chu Z, Wang R, Kashani AH. Impaired layer specific retinal vascular reactivity among diabetic subjects. PLoS One. 2020; 15(9): e0233871.
86. Shehata AS, Mohamed DA, Hagras SM, El-Beah SM, Elnegris HM. The role of hesperidin in ameliorating retinal changes in rats with experimentally induced type 1 diabetes mellitus and the active role of vascular endothelial growth factor and glial fibrillary acidic protein. Anatomy & Cell Biology. 2021; 54(4): 465-78.
87. Soufi FG, Mohammad-Nejad D, Ahmadieh H. Resveratrol improves diabetic retinopathy possibly through oxidative stress - nuclear factor κB - apoptosis pathway. Pharmacol Rep. 2012; 64: 1505–14.
88. Qian H, Ripps H. Neurovascular interaction and the pathophysiology of diabetic retinopathy. Exp Diabetes Res. 2011; 2011: 693426.
89. Khan MS, Rehman MT, Ismael MA, AlAjmi MF, Alruwaished GI, Alokail MS, Khan MR. Bioflavonoid (hesperidin) restrains protein oxidation and advanced glycation end product formation by targeting AGEs and glycolytic enzymes. Cell Biochemistry and Biophysics. 2021; 79(4): 833-44.
90. Roy S, Trudeau K, Roy S, Tien T, F Barrette K. Mitochondrial dysfunction and endoplasmic reticulum stress in diabetic retinopathy: mechanistic insights into high glucose-induced retinal cell death. Current clinical pharmacology. 2013; 8(4): 278-84.
91. Kowluru RA, Mishra M. Oxidative stress, mitochondrial damage and diabetic retinopathy. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2015; 1852(11): 2474-83.
92. Cheng G, Lanza-Jacoby S. Metformin decreases growth of pancreatic cancer cells by decreasing reactive oxygen species: Role of NOX4. Biochemical and biophysical research communications. 2015; 465(1): 41-6.
93. Dehdashtian E, Mehrzadi S, Yousefi B, Hosseinzadeh A, Reiter RJ, Safa M, Ghaznavi H, Naseripour M. Diabetic retinopathy pathogenesis and the ameliorating effects of melatonin; involvement of autophagy, inflammation and oxidative stress. Life sciences. 2018; 193: 20-33.
94. Yi QY, Deng G, Chen N, Bai ZS, Yuan JS, Wu GH, Wang YW, Wu SJ. Metformin inhibits development of diabetic retinopathy through inducing alternative splicing of VEGF-A. American journal of translational research. 2016; 8(9): 3947–3954.

95. Chen W, Yao X, Zhou C, Zhang Z, Gui G, Lin B. Danhong Huayu Koufuye prevents diabetic retinopathy in streptozotocin-induced diabetic rats via antioxidation and anti-inflammation. Mediators of Inflammation. 2017; 2017(1): 3059763.
96. Zhang E, Guo Q, Gao H, Xu R, Teng S, Wu Y. Metformin and resveratrol inhibited high glucose-induced metabolic memory of endothelial senescence through SIRT1/p300/p53/p21 pathway. PloS one. 2015; 10(12): e0143814.
97. Yi, Q.Y.; Deng, G.; Chen, N.; Bai, Z.S.; Yuan, J.S.; Wu, G.H.; Wang, Y.W.; Wu, S.J. Metformin inhibits development of diabetic retinopathy through inducing alternative splicing of VEGF-A. Am. J. Transl. Res. 2016; 8: 3947–3954.
98. Chiha M, Njeim M, Chedrawy EG. Diabetes and coronary heart disease: a risk factor for the global epidemic. International journal of hypertension. 2012; 2012(1): 697240.
99. Carrabba N, Valenti R, Parodi G, Santoro GM, Antoniucci D. Left ventricular remodeling and heart failure in diabetic patients treated with primary angioplasty for acute myocardial infarction. Circulation. 2004; 110(14): 1974-79.
100. Danaei G, Lawes CM, Vander Hoorn S, Murray CJ, Ezzati M. Global and regional mortality from ischaemic heart disease and stroke attributable to higher-than-optimum blood glucose concentration: comparative risk assessment. The Lancet. 2006; 368(9548): 1651-59.
101. Singh GM, Danaei G, Farzadfar F, Stevens GA, Woodward M, Wormser D, Kaptoge S, Whitlock G, Qiao Q, Lewington S, Di Angelantonio E. The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. PloS one. 2013; 8(7): e65174.
102. Kosmas CE, Rodriguez Polanco S, Bousvarou MD, Papakonstantinou EJ, Peña Genao E, Guzman E, Kostara CE. The triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) ratio as a risk marker for metabolic syndrome and cardiovascular disease. Diagnostics. 2023; 13(5): 929.
103. Boyer JK, Thanigaraj S, Schechtman KB, Pérez JE. Prevalence of ventricular diastolic dysfunction in asymptomatic, normotensive patients with diabetes mellitus. The American journal of cardiology. 2004 ; 93(7): `870-5.
104. Liu X, Yang ZG, Gao Y, Xie LJ, Jiang L, Hu BY, Diao KY, Shi K, Xu HY, Shen MT, Ren Y. Left ventricular subclinical myocardial dysfunction in uncomplicated type 2 diabetes mellitus is associated with impaired myocardial perfusion: a contrast-enhanced cardiovascular magnetic resonance study. Cardiovascular diabetology. 2018; 17: 1-2.
105. Jia G, Hill MA, Sowers JR. Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity. Circulation research. 2018; 122(4): 624-38.
106. De Geest B, Mishra M. Role of oxidative stress in diabetic cardiomyopathy. Antioxidants. 2022; 11(4): 784.
107. Rekha SS, Pradeepkiran JA, Bhaskar M. Bioflavonoid hesperidin possesses the anti-hyperglycemic and hypolipidemic property in STZ induced diabetic myocardial infarction (DMI) in male Wister rats. Journal of Nutrition & Intermediary Metabolism. 2019; 15: 58-64.
108. Zhang K, Yang W, Dai H, Deng Z. Cardiovascular risk following metformin treatment in patients with type 2 diabetes mellitus: Results from meta-analysis. Diabetes Research and Clinical Practice. 2020; 160: 108001.
109. Agius L, Ford BE, Chachra SS. The metformin mechanism on gluconeogenesis and AMPK activation: the metabolite perspective. International journal of molecular sciences. 2020; 21(9): 3240.
110. Ding Y, Zhou Y, Ling P, Feng X, Luo S, Zheng X, Little PJ, Xu S, Weng J. Metformin in cardiovascular diabetology: a focused review of its impact on endothelial function. Theranostics. 2021; 11(19): 9376.
111. Weng S, Luo Y, Zhang Z, Su X, Peng D. Effects of metformin on blood lipid profiles in nondiabetic adults: a meta-analysis of randomized controlled trials. Endocrine. 2020; 67: 305-17.
112. Kottaisamy CP, Raj DS, Prasanth Kumar V, Sankaran U. Experimental animal models for diabetes and its related complications—a review. Laboratory animal research. 2021; 37(1): 1-14.
113. Riehle C, Bauersachs J. Of mice and men: models and mechanisms of diabetic cardiomyopathy. Basic research in cardiology. 2019; 114(1): 1-22.
114. Chuang TY, Au LC, Wang LC, Ho LT, Yang DM, Juan CC. Potential effect of resistin on the ET-1-increased reactions of blood pressure in rats and Ca2+ signaling in vascular smooth muscle cells. Journal of Cellular Physiology. 2012; 227(4): 1610-18.
115. Hussein SA, Abdelmaksoud HF, Ismael TF. Hesperidin and Rosemary extract alleviates apoptosis and alterations of DNA methyltransferase and targeting microRNA in a rat model of diabetic cardiomyopathy. Benha Veterinary Medical Journal. 2022; 42(2): 31-6.
116. Toldo S, Marchetti C, Mauro AG, Chojnacki J, Mezzaroma E, Carbone S, Zhang S, Van Tassell B, Salloum FN, Abbate A. Inhibition of the NLRP3 inflammasome limits the inflammatory injury following myocardial ischemia–reperfusion in the mouse. International Journal of Cardiology. 2016; 209: 215-20.
117. Ma ZW, Jiang DY, Hu BC, Yuan XX, Cai SJ, Guo J. Mechanism of hesperidin improving myocardial ischemia/reperfusion injury in type 2 diabetic rats through SIRT1/Nrf2/HO-1 signaling pathway. Journal of Hainan Medical University. 2022; 28(8): 5-10.
118. Palee S, Higgins L, Leech T, Chattipakorn SC, Chattipakorn N. Acute metformin treatment provides cardioprotection via improved mitochondrial function in cardiac ischemia/reperfusion injury. Biomedicine & Pharmacotherapy. 2020; 130: 110604.
119. Tomic D, Shaw JE, Magliano DJ. The burden and risks of emerging complications of diabetes mellitus. Nature Reviews Endocrinology. 2022; 18(9): 525-39.
120. Pignalosa FC, Desiderio A, Mirra P, Nigro C, Perruolo G, Ulianich L, Formisano P, Beguinot F, Miele C, Napoli R, Fiory F. Diabetes and cognitive impairment: a role for glucotoxicity and dopaminergic dysfunction. International journal of molecular sciences. 2021; 22(22): 12366.
121. Li X, Zhao T, Gu J, Wang Z, Lin J, Wang R, Duan T, Li Z, Dong R, Wang W, Hong KF. Intake of flavonoids from Astragalus membranaceus ameliorated brain impairment in diabetic mice via modulating brain-gut axis. Chinese medicine. 2022; 17(1): 22.
122. Pradhan SP, Sahoo S, Behera A, Sahoo R, Sahu PK. Memory amelioration by hesperidin conjugated gold nanoparticles in diabetes induced cognitive impaired rats. Journal of Drug Delivery Science and Technology. 2022; 69: 103145.
123. Behera A, Pradhan SP, Tejaswani P, Sa N, Pattnaik S, Sahu PK. Ameliorative and Neuroprotective Effect of Core-Shell Type Se@ Au Conjugated Hesperidin Nanoparticles in Diabetes-Induced Cognitive Impairment. Molecular Neurobiology. 2023; 60(12): 7329-45.
124. Ahmed AS, Mona MM, Elsisy RA, Hantash EM. Hesperidin preserves cognitive functions and Hippocampus histological architecture in albino wistar rats subjected to stress through enhancement of brain-derived neurotrophic factor. Neurotoxicity Research. 2022; 40(1): 179-85.

125. Hu Y, Zhou Y, Yang Y, Tang H, Si Y, Chen Z, Shi Y, Fang H. Metformin protects against diabetes-induced cognitive dysfunction by inhibiting mitochondrial fission protein DRP1. Frontiers in Pharmacology. 2022; 13: 832707.
126. Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. Journal of affective disorders. 2012; 142: 8-21.
127. Souza LC, de Gomes MG, Goes AT, Del Fabbro L, Carlos Filho B, Boeira SP, Jesse CR. Evidence for the involvement of the serotonergic 5-HT1A receptors in the antidepressant-like effect caused by hesperidin in mice. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2013; 40: 103-9.
128. Bélanger M, Yang J, Petit JM, Laroche T, Magistretti PJ, Allaman I. Role of the glyoxalase system in astrocyte-mediated neuroprotection. Journal of Neuroscience. 2011; 31(50): 18338-52.
129. Hamal C, Velugoti LS, Tabowei G, Gaddipati GN, Mukhtar M, Alzubaidee MJ, Dwarampudi RS, Mathew S, Bichenapally S, Khachatryan V, Muazzam A. Metformin for the improvement of comorbid depression symptoms in diabetic patients: a systematic review. Cureus. 2022; 14(8): 1-14
130. Woo YS, Lim HK, Wang SM, Bahk WM. Clinical Evidence of antidepressant effects of insulin and anti-hyperglycemic agents and implications for the pathophysiology of depression—a literature review. International journal of molecular sciences. 2020; 21(18): 6969.
131. Fang W, Zhang J, Hong L, Huang W, Dai X, Ye Q, Chen X. Metformin ameliorates stress-induced depression-like behaviors via enhancing the expression of BDNF by activating AMPK/CREB-mediated histone acetylation. Journal of affective disorders. 2020; 260: 302-13.
132. Yang T, Nie Z, Shu H, Kuang Y, Chen X, Cheng J, Yu S, Liu H. The role of BDNF on neural plasticity in depression. Frontiers in cellular neuroscience. 2020; 14: 82.