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Review

The Potential Role of Gossypetin in the Treatment of Diabetes Mellitus and Its Associated Complications: A Review

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Abstract: Type 2 diabetes mellitus (T2DM) is a metabolic disorder caused by insulin resistance and dysfunctional beta (β)-cells in the pancreas. Hyperglycaemia is a characteristic of uncontrolled diabetes which eventually leads to fatal organ system damage. In T2DM, free radicals are continuously produced, causing extensive tissue damage and subsequent macro-and microvascular complications. The standard approach to managing T2DM is pharmacological treatment with anti-diabetic medications. However, patients' adherence to treatment is frequently decreased by the side effects and expense of medications, which has a detrimental impact on their health outcomes. Quercetin, a flavonoid, is a one of the most potent anti-oxidants which ameliorates T2DM. Thus, there is an increased demand to investigate quercetin and its derivatives, as it is hypothesised that similar structured compounds may exhibit similar biological activity. Gossypetin is a hexahydroxylated flavonoid found in the calyx of *Hibiscus sabdariffa*. Gossypetin has a similar chemical structure to quercetin with an extra hydroxyl group. Furthermore, previous literature has elucidated that gossypetin exhibits neuroprotective, hepatoprotective, reproprotective and nephroprotective properties. The mechanisms underlying gossypetin's therapeutic potential have been linked to its anti-oxidant, anti-inflammatory and immunomodulatory properties. Hence, this review highlights the potential role of gossypetin in the treatment of diabetes and its associated complications.

Keywords: gossypetin; diabetes mellitus; flavonoid

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1. Introduction

Approximately 90% of all cases of diabetes are type 2 diabetes mellitus (T2DM) [1]. The global prevalence of T2DM in adults was 536.6 million in 2021, and by 2045, 783.2 million people are expected to have the condition, according to the International Diabetes Federation (IDF) (Figure 1) [2,3]. The response to insulin is diminished in T2DM, which is characterised as insulin resistance [4]. It has been demonstrated that macro- and microvascular complications such as atherosclerosis, stroke, kidney failure and non-alcoholic fatty liver disease (NAFLD) are associated with diabetes mellitus (DM) [5,6]. Oxidative stress has been demonstrated to be an essential component in the pathophysiology of these complications [7]. Unfortunately, conventional medical treatments for T2DM exhibit unfavourable side effects, such as adverse reactions in the gastrointestinal tract and damage to the kidneys and liver [8].

There has been increased global interest currently to identify anti-oxidant compounds that are pharmacologically potent with little or no side effects [9]. As the primary source of anti-oxidants, flavonoids have emerged as an effective tool to combat against oxidative stress [10]. According to previous studies, one of the most prevalent flavonols derived from plants is quercetin, which has demonstrated various anti-diabetic effects, along with reduced side effects [11,12]. Thus, due to the notable therapeutic activities of quercetin, it has gained considerable interest [11]. Moreover, there exists an extensive reserve of phytochemicals that remain unexplored but may possess similar therapeutic properties to

quercetin [13,14]. It has been demonstrated that similarly structured compounds exhibit similar biological activity [13]. Moreover, research has demonstrated that the number and location of hydroxyl groups in flavonoids affect their anti-oxidant activity [15]. Gossypetin is a flavonoid that is found in the calyx of *Hibiscus sabdariffa* [16]. Interestingly, gossypetin has been shown to exhibit a similar structure to quercetin with an extra hydroxyl group, which may suggest more potent anti-oxidant activity [17]. Relevant to this review, studies have demonstrated the anti-oxidant, anti-inflammatory, nephroprotective, neuroprotective and hepatoprotective properties of gossypetin, all without any discernible toxicity [18–20]. Gossypetin has been demonstrated to be an effective dual-targeting agent that activates AMP-activated protein kinase (AMPK) and reduces oxidative stress, in contrast to conventional anti-diabetic medications that target one pathological mechanism [21]. In addition, the *Hibiscus* species is easily accessible and offers an inexpensive source of gossypetin [22]. The aim of the present review is to elucidate the potential role of gossypetin in the treatment of diabetes and its associated complications.

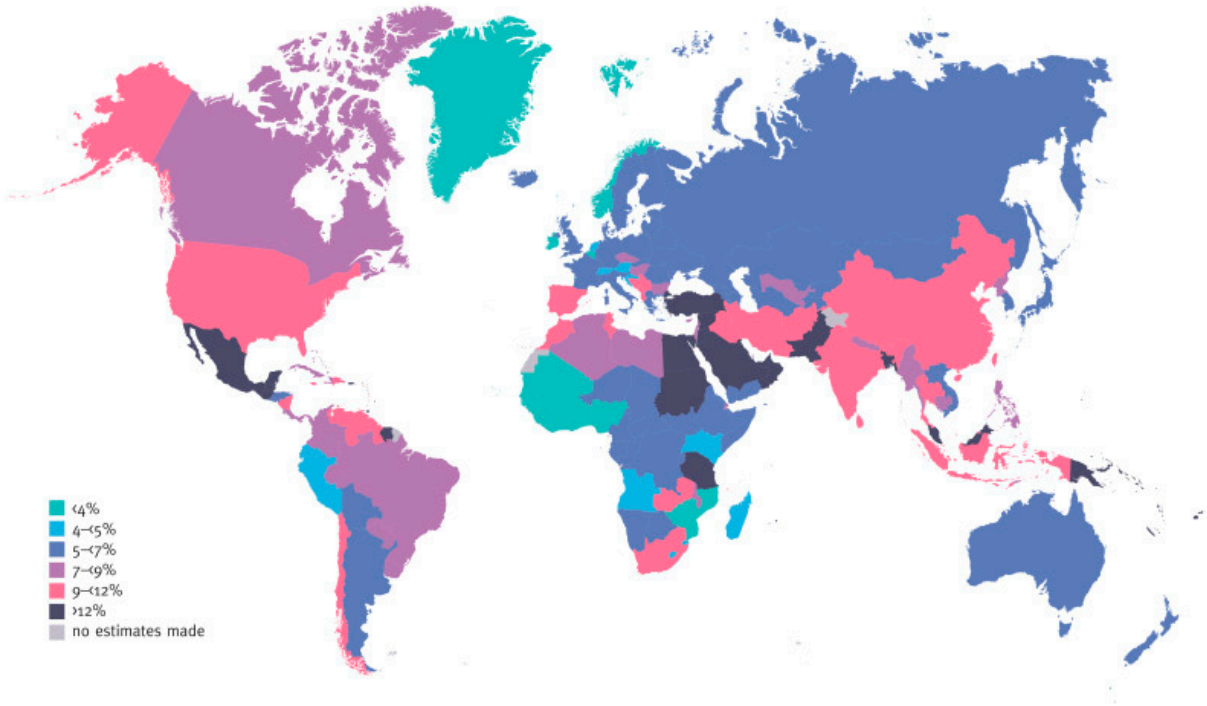

Figure 1. Estimated age-adjusted comparative prevalence of diabetes in adults (20–79 years) in 2021 Adapted with permission from International Diabetes Federation, 2013 [3].

1.1. Type 2 Diabetes Mellitus Complications

Type 2 diabetes (T2DM) is a chronic metabolic disease that is rapidly becoming more prevalent across the world [23]. It is characterised by insulin resistance and dysfunction in the β-cells in the pancreas [24]. The pathophysiology and progression of this metabolic disorder is associated with hyperglycaemia-induced reactive oxygen species (ROS) production and oxidative stress [7]. Oxidative stress under hyperglycaemic conditions is caused by an imbalance between the production of ROS and the cellular anti-oxidant system [7]. This leads to the development of diabetes [7]. Peroxisomes, phagocytic cells and the endoplasmic reticulum all produce reactive oxygen species (ROS), with the mitochondrial electron transport chain (ETC) playing a major role [25]. Structural and functional changes in proteins, lipids and nucleic acids have been shown to be induced by the increased production of ROS [26]. Moreover, ROS alters multiple intracellular signaling pathways, which results in insulin resistance and decreased β-cell performance [7]. In addition, the generation of ROS induced by hyperglycaemia also plays a role in the development of the macro- and microvascular complications associated with diabetes (Figure 2) [5,6,27]. Furthermore,

it has been suggested that the generation of ROS through hyperglycaemia triggers several stress-sensitive signaling pathways, such as p-38 mitogen-activated protein kinases (MAPK), nuclear factor kappa B (NF-κB) and Jun amino-terminal kinases/stress-activated protein kinases (JNK/SAPK), which in turn accelerates the development of complications related to T2DM [27]. Furthermore, research has demonstrated that the development of microvascular diabetic complications is significantly influenced by pro-inflammatory cytokines [28,29]. Thus, clinical treatments may be developed from therapeutic approaches based on anti-oxidant and anti-inflammatory properties that have beneficial action against diabetic complications [30].

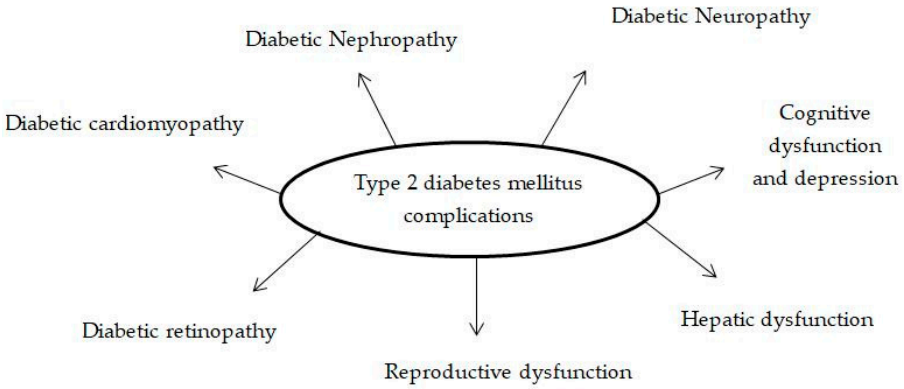

Figure 2. The complications associated with type 2 diabetes mellitus [5,6,27].

1.2. Flavonoids

The majority of phytochemicals with anti-oxidant activity in plants are phenolics, which make up the largest class of phytochemicals [31]. Of all the phenolic compounds that occur naturally, flavonoids make up the largest group [32]. They are responsible for the different colours seen in leaves, seeds, bark, flowers and fruits [10]. The fundamental flavone skeleton of flavonoids is composed of 15 carbons and includes two benzene rings (A and B) connected by a three-carbon pyran ring (C) (Figure 3) [33,34]. The distinct subclasses of flavonoidal compounds are derived from variations in this fundamental structure (Figure 3) [10,34]. These include chalcones, anthocyanins, flavanones, isoflavones, flavones and flavanols [10]. These secondary metabolites have been the subject of recent research due to their potential to prevent metabolic disorders such as obesity and diabetes mellitus [35]. The research findings indicate that dietary flavonoids have the potential to enhance insulin sensitivity, improve dysregulated lipid metabolism and reduce oxidative stress in metabolic disorders [36]. The research has shown that quercetin, one of the most abundant flavonols found in plants, has potent anti-diabetic properties [37,38].

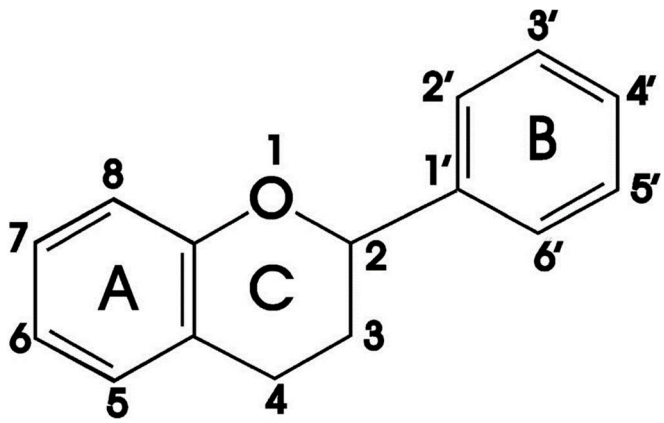

Figure 3. General structure of flavonoids. Adapted with permission from Ekalu and Habila, 2020 [34].

1.2.1. Quercetin

Quercetin is a flavonoid that is mainly found in citrus fruits, grapes, berries and broccoli [11]. It exhibits potent anti-oxidant properties [39]. Studies have indicated that quercetin is a beneficial natural substance that regulates important signaling pathways and acts on various diabetes targets [40]. Unlike the currently used therapeutics, quercetin improves both hyperglycaemia and its associated macrovascular and microvascular complications [12,37]. Quercetin increases the production of insulin, protects pancreatic beta-cells from oxidative stress and improves the cells' ability to defend against reactive oxygen species [37,41]. Diabetic complications including retinopathy, nephropathy and neuropathy have been shown to be induced by inflammation and oxidative stress [42,43]. Quercetin has been shown to prevent diabetic complications by blocking NF-κB cells, monocyte chemoattractant protein 1 (MCP-1) and intercellular adhesion molecule 1 (ICAM1) in T2DM patients (Figure 4) [44–48]. Moreover, quercetin has been shown to decrease nephropathy biomarker levels, such as creatinine, blood urea nitrogen (BUN) and 8-hydroxydeoxyguanosin [49,50]. Furthermore, the research has demonstrated that quercetin has a safer profile than conventional anti-diabetic medications that are marketed [37,51]. Additionally, a novel fermentation-based glycosylation technique using inexpensive substrates such as underutilised food waste can be used to produce quercetin on a large scale [37]. Furthermore, a study showed that similar structured compounds may exhibit similar biological activities [13]. There exists a large pool of unexplored compounds with similar therapeutic activities to quercetin [52].

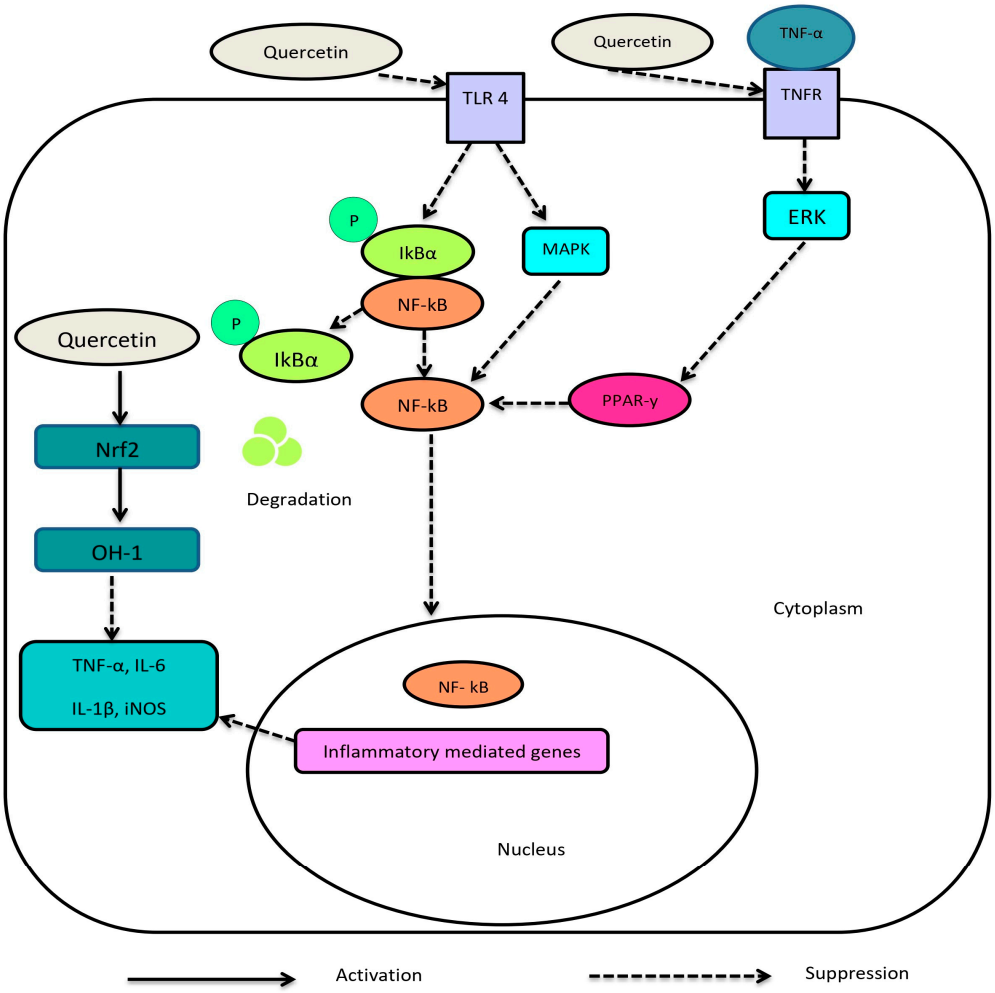

Figure 4. The potential molecular mechanism of quercetin on the NF-kB inflammatory pathway [44,45]. The activation of toll-like receptor (TLR) pathways encourages the production of pro-inflammatory

cytokines through the upregulation of transcription factors such as NF-κB [44,45]. Quercetin suppresses inflammatory cytokines production such as interleukin (IL)-6, tumour necrosis factor (TNF)-α and IL-1β via downregulating TLR4 [46,53]. Subsequently, repressed receptors yield targeted suppression of IκBα phosphorylation and mitogen-activated protein kinase (MAPK) expression and thereby inhibit nuclear transfer of the NF-κB [46,47]. Phosphorylation is represented as p in the above figure. In addition, quercetin may indirectly prevent inflammation by increasing peroxisome proliferator-activated receptor c (PPARγ) activity, thereby antagonising NF-κB [46,48]. In addition, TNF-α binds to TNF receptors, which causes the activation of extracellular signal-regulated kinase (ERK) [46]. Activated ERK inactivates PPARγ, therefore preventing nuclear translocation and the DNA binding of NF-κB [46,54]. This prevents the transcription of inflammatory mediators and triggers oxidative stress [46]. Quercetin activates nuclear factor erythroid 2-related factor 2 (Nrf2) and thereby contributes to increased heme oxygenase (HO)-1 levels, which are responsible for the downregulation of TNF-α [46]. Together, these block NF-kB-mediated induction of inflammatory cascades [46].

1.2.2. Gossypetin

Gossypetin (GTIN) is a natural derivative of well-known quercetin [55]. It has previously been noted that quercetin is beneficial against diabetes mellitus and its associated complications [21,37]. Gossypetin is hexahydroxyflavone and is found in the calyx of *Hibiscus sabdariffa* [16]. Tropical regions have made extensive use of these calyces as potential sources of medicinal phytochemicals [56]. Traditionally, these plant extracts were used to treat inflammation, jaundice and diabetes [57,58]. GTIN is a yellow pigment, with a chemical formula of C15H10O8, a molecular weight of 318.24 g/mol and a boiling point temperature of 679.30 °C @ 760.00 mmHg [59]. Since reducing agents exhibit anti-oxidant properties, an organic molecule's reducing power may serve as an indicator to evaluate its anti-oxidant activity [60]. The anti-oxidant actions of flavonoids are mediated by their functional hydroxyl groups, which chelate metal ions and scavenge free radicals [61]. The number and arrangement of hydroxyl groups in flavonoids also significantly influence their anti-oxidant properties [15]. The high anti-oxidant activity which gossypetin exhibits may be attributed to the presence of a carbonyl group at position C4, a double bond between C2 and C3 and the 3-OH and 4-OH groups in the B ring (Figure 5) [55,62,63]. Interestingly, gossypetin has a catechol moiety as a B-ring, similarly to quercetin [17]. In addition, gossypetin has three hydroxyl groups rather than two at positions 5, 7 and 8 in the A-ring (Figure 5) [17,55,63]. In gossypetin, the two subsequent hydroxyl groups at positions 7 and 8 function as another catechol-like center [17]. This suggests that gossypetin has three oxidisable redox active centers while quercetin only has two [17]. In addition, previous research showed that among 15 well-known flavonoids, including quercetin, gossypetin possessed the most potent reducing capacity [17]. This may suggest that gossypetin exhibits more potent anti-oxidant activity than quercetin. In addition, gossypetin may exhibit similar pharmacological properties to quercetin due to the structural similarity. Studies have shown that gossypetin exerts various pharmacological properties, including anti-oxidant, anti-atherosclerotic, anti-nephrotoxic, as well as reproprotective and hepatoprotective effects [18,21,55]. Gossypetin has been shown to exhibit therapeutic effects at doses as low as 10 mg/kg and 20 mg/kg in vivo [20,64]. Therefore, gossypetin may serve as a potential candidate in the treatment of diabetes and its associated complications.

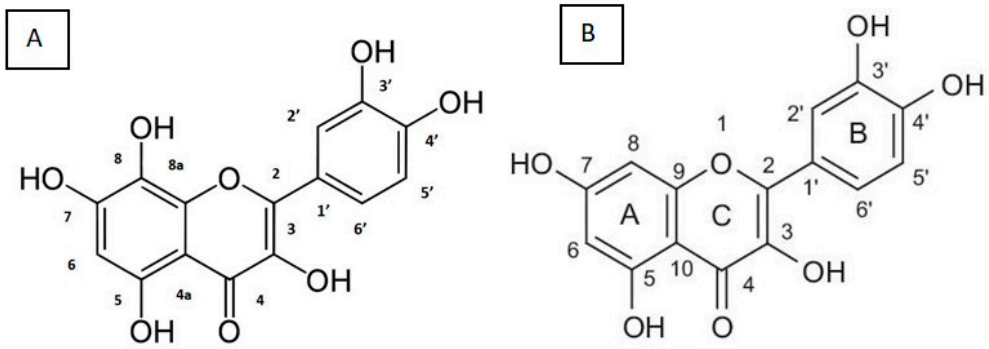

Figure 5. Structure of (**A**) gossypetin (GTIN) and (**B**) quercetin. Adapted with permission from Khan et al., 2013 and Zheng and Chow, 2009 [55,63].

1.3. Pharmacological Action of Gossypetin

As mentioned above, diabetes mellitus causes numerous micro- and macrovascular complications in affected patients [5,65]. Gossypetin may serve as an appropriate candidate for the prevention and treatment of diabetes mellitus complications. In the below section, we discuss the therapeutic potential of gossypetin for the treatment of inflammation, oxidative stress, kidney dysfunction, liver dysfunction, cognitive dysfunction, atherosclerosis and reproductive dysfunction (Figure 6) [18,19,62,66,67].

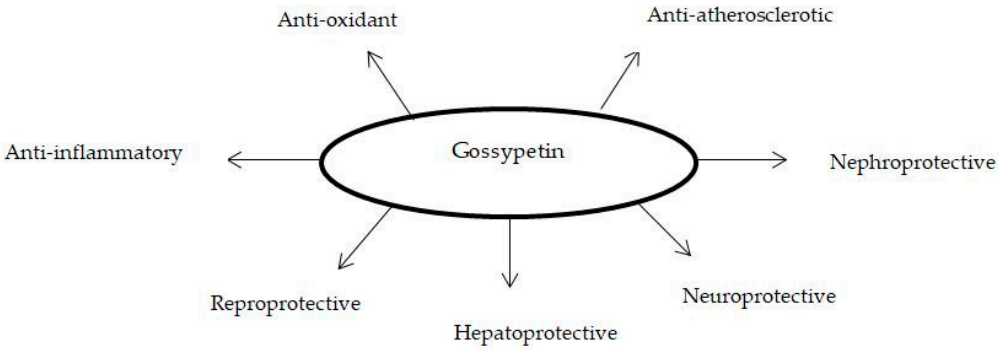

Figure 6. The reported pharmacological importance of gossypetin [18,19,62,66,67].

1.3.1. Anti-Oxidant and Anti-Inflammatory Effects of Gossypetin

The oxidative stress caused by ROS and free radicals has been shown to be linked with numerous complications in T2DM [68]. The cellular alterations that result in diabetic complications have been demonstrated to be caused by increased oxidative stress and inflammation, which are both a cause and an effect of diabetes [68]. Radiation promotes the production of hydroxyl radicals, which leads to lipid peroxidation and significant biological damage [69]. It is responsible for the development of inflammation through nitric acid (NO) production [69]. In a previous study, hepatocytes were treated with 20 mM and 40 mM GTIN for one hour before exposure to 5 Gy radiation [55]. The treatment with 20 mM of GTIN offered more effective protection against damage to supercoiled DNA than 40 mM of quercetin after exposure to 5 Gy radiation [70]. According to the study, GTIN significantly protected against radiation-induced DNA damage and inflammation directly and indirectly by scavenging ROS and NO [55]. The study demonstrated the anti-oxidant potential of GTIN, evidenced by the high ferric-reducing anti-oxidant power (FRAP) value [55]. FRAP denotes the total anti-oxidant pool [71]. GTIN contains a pair of parahydroxyls at positions 5 and 8 and two pairs of orthohydroxyls [55]. It is therefore oxidisable because it can form two o-quinone intermediates and one p-quinone intermediate, which aids in scavenging free radicals [55]. Moreover, it was found that GTIN inhibited free-radical-mediated DNA strand breakage and decreased radiation-mediated oxidative stress in the study's ex vivo model [55]. According to the study, GTIN terminates a radical chain reaction by reacting

with radicals, transforming them into more stable compounds [55]. In addition, in the study's ex vivo model, it was made evident that gossypetin exhibited the most potent anti-oxidant activity at a dosage of 50 mM [70]. It was also suggested that exposure to 50 mM gossypetin exhibits therapeutic effects against DNA damage at even a higher radiation dose exposure between 5 Gy and 20 Gy [55]. The aforementioned studies have demonstrated the anti-inflammatory and anti-oxidant properties of gossypetin in the management of radiation-induced oxidative stress (Figure 7) [55,70,72,73]. Taken together, gossypetin may alleviate oxidative-stress-induced diabetic complications due to its potent anti-oxidant and anti-inflammatory potential.

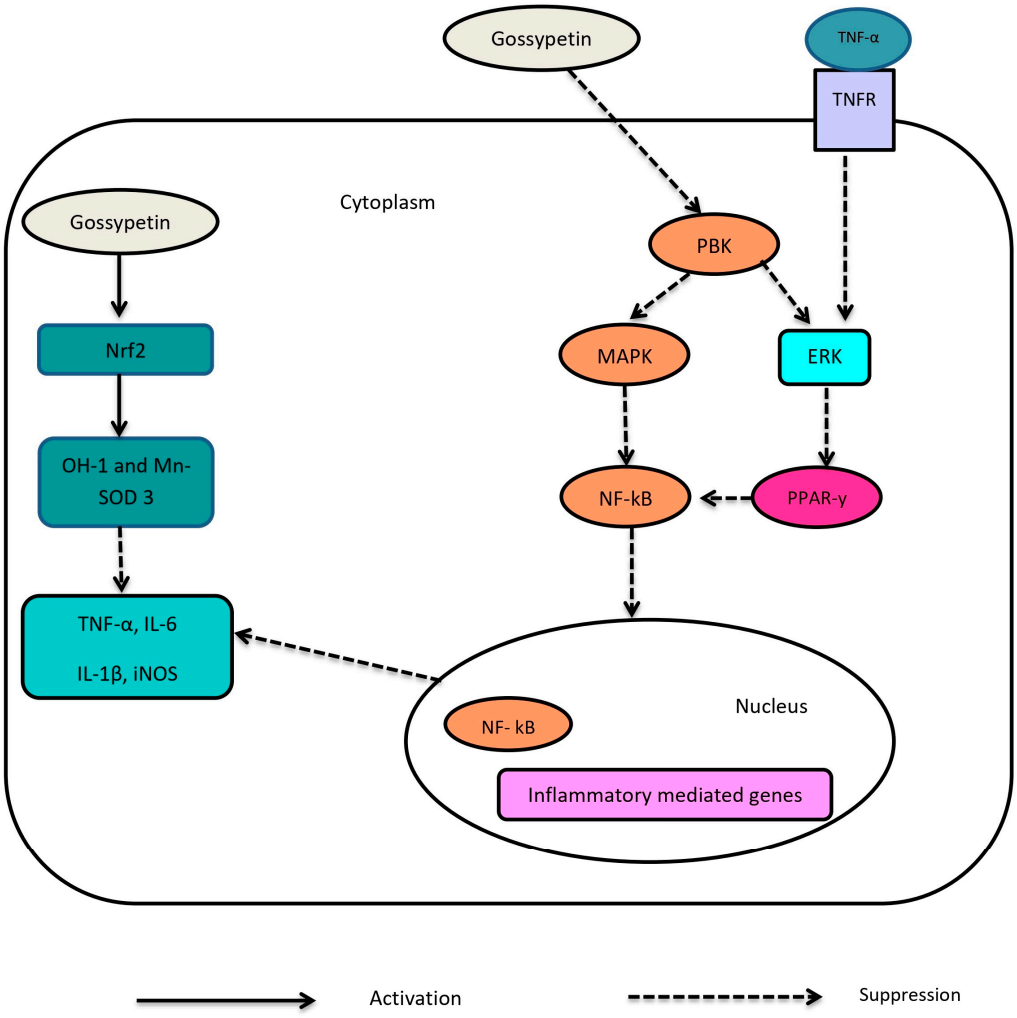

Figure 7. The potential molecular mechanism of gossypetin on the NF-kB inflammatory pathway [55,73]. It is shown that gossypetin inhibits PDZ-binding kinase (PBK) phosphorylation, which is involved in the regulation of p38 MAPK and ERK1/2 kinases [73]. Consequently, MAPK and ERK are inhibited by gossypetin [55,73]. The downregulation of MAPK inhibits NF-kB activation and translocation into the nucleus [55,73]. As a result, there is a downregulation in the transcription of inflammatory mediators. In addition, the downregulation of ERK inhibits PPAR-y, thereby antagonising NF-kB [55,73]. Furthermore, gossypetin has been shown to stimulate Nrf2, thereby activating OH-1 and superoxide dismutase (SOD)-3 [73]. This promotes anti-oxidant and anti-inflammatory properties.

1.3.2. Anti-Atherosclerotic Effects of Gossypetin

One of the main complications of DM is atherosclerosis, which is caused by endothelial dysfunction, inflammation and oxidative stress [74]. According to previous studies, increased low-density lipoprotein (LDL) oxidation has been linked to hyperinsulinaemia and impaired glucose tolerance in T2DM [75,76]. Oxidised low-density lipoprotein (ox-LDL)

induces damage to the vascular endothelial cells, which is a major factor in the development of atherosclerosis [77]. In T2DM, oxidative stress promotes the onset of vascular smooth muscle (VSMC) dysfunction [78]. Plaque formation results from VSMCs' progressive proliferation and migration from the vascular media to the neointima during the pathogenesis of atherosclerosis [78]. According to a previous study, starved rat aortic VSMCs were treated with 0, 1, 5, 10, 25, 50, 100 and 250 μM GTIN for 48 h [66]. The research findings indicated that GTIN inhibits the dysfunction of VSMCs through various mechanisms, including the suppression of cell proliferation, cell cycle progression, migration, matrix degradation and oxidative stress [66]. It was concluded that GTIN may demonstrate protective effects against VSMC dysfunction, which may delay atherosclerotic pathogenesis [20,66]. According to another study, gossypetin demonstrated protective effects against endothelial damage both in vitro and in vivo [20]. In the in vitro model, cells were treated with 0.1, 0.5, 1.0, 2.0 and 5.0 μM for 24 h [20]. In the study's in vivo model, New Zealand white rabbits were fed on a high-fat diet for 10 weeks to induce atherosclerosis and treated with 10 mg/kg gossypetin [20]. The results showed that in the in vitro model, gossypetin inhibited ox-LDL uptake, lipid-laden foam cell formation and promoted cholesterol efflux in a dose-dependent manner [20]. Furthermore, treatment with gossypetin has been shown to decrease liver injury markers and improve the lipid profile [20]. It was stated that numerous signals may have been involved in this process and the mechanisms are likely to be complex [20]. Gossypetin may have a major role in atheroprotection through upregulating autophagy [20]. Gossypetin inhibits oxidised low-density lipoprotein (ox-LDL) by activating peroxisome proliferator-activated receptor (PPAR)-α and inhibiting PPAR-γ, which promotes macrophage cholesterol clearance and delays atherosclerosis [20]. These studies have highlighted the anti-atherosclerotic property of gossypetin in the treatment of endothelial dysfunction [20,66]. Taken together, gossypetin may alleviate atherosclerosis in T2DM due to its anti-oxidant potential and ability to target endothelial dysfunction.

1.3.3. Nephroprotective Effects of Gossypetin

Oxidative stress and inflammation play a major role in the development of renal dysfunction in T2DM [43,79]. A previous study has demonstrated that in a nephrotoxicity model, kidney function was significantly improved in Sprague-Dawley rats administered 30 mg/Kg GTIN intraperitoneally for 30 days [18]. Anti-oxidant enzyme activities were significantly increased by GTIN supplementation, which was also associated with a reduction in ROS and malondialdehyde (MDA) levels [18]. Higher creatinine clearance was linked to an improved glomerular filtration rate, which was reflected by a reduction in urea, creatinine, kidney injury molecule-1 (KIM-1) and neutrophil-gelatinase-associated lipocalin (NGAL) levels after GTIN supplementation [18]. Urea and creatinine are used to monitor renal function [80]. The breakdown of phosphocreatine, which is catalysed by creatine kinase, produces creatinine, which is then eliminated from the kidney via glomerular filtration [81]. Any damage to the renal tissues caused by oxidation increases the levels of urea and creatinine while decreasing creatinine clearance [81]. Additionally, urine normally does not contain the transmembrane protein KIM-1, but its presence suggests damage to the proximal tubules [81]. The results of the study showed that GTIN treatment reduced the levels of inflammatory markers such as interleukin-10 and tumour necrosis factor-α (TNF-α) [18]. The results were corroborated by previous studies which suggested that flavonoids may be responsible for suppressing inflammation [82,83]. It was suggested that the free radical scavenging and anti-inflammatory properties of GTIN may be directly related to its renoprotective effects [18]. Taken together, gossypetin may serve as a novel compound in the treatment of diabetic nephropathy due to its ability to decrease the levels of renal injury biomarkers, oxidative markers, apoptotic markers and inflammatory markers and alleviate damage to the architecture of renal tissue. In addition, the anti-oxidant and anti-inflammatory properties of gossypetin may ameliorate diabetic nephropathy by targeting oxidative stress and inflammation.

1.3.4. Neuroprotective Effects of Gossypetin

Cognitive function is compromised by the oxidative stress and inflammation caused by the high blood glucose concentrations in the brain as a result of T2DM [84,85]. In a previous study, stress was used to induce memory and spatial learning deficits in mice [64]. Furthermore, long-term unpredictable stress leads to adverse consequences, such as neuropsychiatric conditions including dementia, depression and anxiety [86]. In this study, five weeks of exposure to different stressors were followed by four weeks of intraperitoneal administration of gossypetin at doses of 5, 10 and 20 mg/kg [64]. The behaviour pattern significantly improved following gossypetin administration, according to the results [64]. It has been found that mice exposed to 10 and 20 mg/kg of gossypetin had significantly lower levels of corticosterone and oxidative stress [64]. The main cause of synaptic loss and cognitive deficits is oxidative stress, which is accelerated by high cortisol levels [87]. Moreover, gossypetin administration was found to increase the levels of serotonin, norepinephrine and brain-derived neurotrophic factor (BDNF) [64]. A crucial molecule in the plastic changes linked to memory and learning is known as BDNF [88]. In patients with T2DM, lower levels of BDNF have been linked to cognitive impairment [89,90]. Another study found that at doses of 5 and 20 mg/kg po, respectively, gossypetin demonstrates significant anti-anxiety and anti-depressant activity in mice [91]. Diabetes promotes an increase in the renin–angiotensin–aldosterone system (RAAS) both locally and systemically in the brain [92]. Pro-inflammatory processes are induced in the brain by elevated RAAS activation [93]. One factor influencing the decreased synthesis and release of BDNF is neuroinflammation [94]. Reduced BDNF levels have been linked to the development of depression by promoting neuronal damage [95]. Furthermore, a previous study showed that gossypetin administration in vitro and in vivo decreased several of the hallmarks associated with Alzheimer's disease (AD), including microgliosis and astrogliosis [67]. In the study's in vitro model, the primary microglial cells were treated with 25 μM gossypetin for 24 h [67], and mice were intragastrically administered 10 mg/kg gossypetin daily for 13 weeks [67]. The results demonstrated that gossypetin reduced the formation of various types of beta-amyloid (Aβ) protein plaques, which delayed the progression of AD [67]. Interestingly, cognition and memory function was reversed to the same level as the control group after treatment with gossypetin [67]. Insulin resistance contributes to the development of Alzheimer's disease by promoting the build-up of Aβ proteins [96,97]. Taken together, gossypetin may serve as a novel compound in the treatment of cognition impairments in T2DM due to its ability to reduce oxidative stress and inflammation, decrease cortisol levels and increase BDNF levels.

1.3.5. Hepatoprotective Effects of Gossypetin

Systemic lipid and glucose homeostasis is maintained largely in part by the liver [98]. Studies have demonstrated that non-alcoholic fatty liver disease (NAFLD), fibrosis, cirrhosis and aberrant glycogen deposition are all associated with T2DM [99,100]. It has been demonstrated that oxidative stress and inflammation play a significant role in the development of liver dysfunction in T2DM patients [100,101]. Previous studies on drug development for nonalcoholic steatohepatitis (NASH) were based on the one-hit hypothesis [21,102]. However, the development of therapeutic agents that target one specific mechanism to improve NASH has failed [102,103]. As a result, the "multiple-hit hypothesis", which takes into account focusing on multiple factors concurrently to improve the effectiveness of therapeutic agents, has become the new paradigm in NASH drug development [21,104]. It has been suggested that targeting oxidative stress and metabolic dysfunction may be an approach to prevent NASH since these factors promote the development of fibrosis and inflammation [105]. According to a previous study, gossypetin reduced hepatic steatosis, lobular inflammation and liver fibrosis in mice induced with NASH for four weeks at a dose of 20 mg/kg/day [21]. According to the study, gossypetin directly acted as an antioxidant in both the in vitro and in vivo models, reducing the oxidative stress caused by hydrogen peroxide and palmitate [21]. It supports previous studies which have shown that

anti-oxidants have the ability to alleviate NASH [21,106]. Furthermore, the study revealed that gossypetin induced higher AMPK phosphorylation compared to the other flavonoids, including quercetin [21] Acetyl-CoA carboxylase 1 (ACC), an essential enzyme for fatty acid synthesis that controls hepatic insulin resistance, is phosphorylated by AMPK [21]. According to the study, mice treated with gossypetin exhibited increased AMPK activation, which reduced liver steatosis [21]. Taken together, gossypetin may serve as a novel therapeutic compound in the treatment of NASH and NAFLD due to its double targeting action against oxidative stress and AMPK phosphorylation.

1.3.6. Reproprotective Effects of Gossypetin

Male reproductive dysfunction in T2DM has been demonstrated to be exacerbated by oxidative stress, which promotes changes in hormone levels, apoptosis in germ cells and a decline in semen quality [107,108]. An organic substance known as paraquat (PQ) has been shown to promote major damage to the male reproductive system [19,109]. In a previous study, male reproductive dysfunction was induced by PQ exposure through the production of free radicals [19]. In the study, adult male Sprague-Dawley rats were administered with gossypetin at doses of 5 mg/kg and 30 mg/kg for 56 days [19]. Gossypetin was found to improve PQ-induced reproductive dysfunctions in the study [19]. Gossypetin reduced the levels of reactive oxygen species (ROS) and malondialdehyde (MDA) while increasing the activities of glutathione reductase (GSR), catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) [19]. Gossypetin also enhanced sperm viability, motility, as well as the quantity of hypo-osmotic tail-swelled spermatozoa and epididymal sperms [19]. In addition, it decreased sperm morphological abnormalities [19]. Gossypetin alleviated the luteinising hormone (LH) and follicle-stimulating hormone (FSH) reductions induced by PQ [19]. Additionally, gossypetin significantly increased the level of testosterone by upregulating the expression of steroidogenic enzymes, indicating that it has androgenic properties [19]. Gossypetin downregulated the gene expression of apoptotic markers such as caspase-3 and upregulated the gene expression of anti-apoptotic markers [19]. Taken together, gossypetin may serve as a novel compound in the treatment of male reproductive dysfunction in T2DM due to its anti-oxidant, androgenic and anti-apoptotic properties.

1.4. Potential Use of Gossypetin in Diabetes Mellitus

The above section highlights the reported findings of gossypetin in the treatment of dysfunctions in the renal, cardiovascular, hepatic, reproductive and cognition systems [20,21,67]. Many of the complications that occur in diabetes are associated with oxidative stress [110,111]. An imbalance between the generation of reactive oxygen species (ROS) and the anti-oxidant system's capacity to neutralise these molecules results in oxidative stress [112]. Diabetes promotes oxidative stress due to a variety of mechanisms, such as increased oxygen radical production from glucose auto-oxidation, the production of glycated proteins and the glycation of anti-oxidant enzymes, which limits the capacity of anti-oxidants to neutralise free radicals [7,113]. Gossypetin may prevent diabetic complications due to its anti-oxidant, anti-apoptotic and anti-inflammatory actions [21,73]. Elevated blood glucose levels pose a challenge in the treatment of diabetes mellitus [114]. Consequently, therapies that lower blood glucose levels may help treat diabetes mellitus [114]. Previous studies have shown that diabetes is associated with the impairment of AMPK activity [115,116]. AMPK stimulates β-oxidation and fatty acid uptake while suppressing the synthesis of triglycerides, cholesterol and fatty acids [117]. Moreover, AMPK signaling reduces oxidative stress, inflammation and apoptosis [118]. Insulin resistance is inhibited and beta (β)-cell survival is promoted by AMPK activation [119]. AMPK activation has been shown in numerous studies to improve glucose uptake into the cells and reduce intracellular glucose production in diabetics [116,117]. In addition, metformin and rosiglitazone, the two main conventional medications used in diabetes, demonstrate their metabolic effects partially by activating AMPK [120]. This makes the pharmacological activation of AMPK a viable target for DM drug development and discovery [121]. Unfortunately, there

are negative side effects associated with these conventional anti-diabetic drugs [122,123]. Consequently, it is imperative to investigate natural medications derived from plants that treat diabetes and lack adverse side effects [124]. There is significant potential for managing diabetes mellitus and its complications with fewer side effects when natural products such as quercetin are used to activate and regulate the AMPK pathway [116,125]. It is well known that gossypetin is structurally similar to quercetin with an extra hydroxyl [20,126]. Therefore, gossypetin may exhibit similar anti-diabetic properties to quercetin. Interestingly, gossypetin has been shown to possess higher AMPK activity than quercetin [21]. For this reason, gossypetin may serve as a promising treatment for diabetes mellitus and its associated complications.

1.5. Conclusions

In this review, we highlighted the pharmacological properties of gossypetin and its potential in the treatment of diabetes and the associated complications. Our review of the literature demonstrated that gossypetin exhibited anti-oxidant, anti-inflammatory, nephroprotective, neuroprotective and hepatoprotective properties [21,67,126]. Gossypetin ameliorates many complications by targeting oxidative stress and inflammation [17,21]. Oxidative stress and inflammation play a critical role in the development of T2DM [68]. It is worthy to note that gossypetin offered better protection against DNA damage from oxidative stress than quercetin [70]. In addition, gossypetin possessed the highest AMPK activity in comparison to other flavonoids, including quercetin [21]. Consequently, gossypetin may serve as a potential candidate in the treatment of diabetes and its associated complications. Future studies should investigate the therapeutic potential of gossypetin in diabetes mellitus. Moreover, further studies are also required to establish the pharmacokinetic and safety profiles of gossypetin.

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References

1. Erzse, A.; Stacey, N.; Chola, L.; Tugendhaft, A.; Freeman, M.; Hofman, K. The direct medical cost of type 2 diabetes mellitus in South Africa: A cost of illness study. *Glob. Health Action* **2019**, *12*, 1636611. [CrossRef] [PubMed]
2. Yan, Y.; Wu, T.; Zhang, M.; Li, C.; Liu, Q.; Li, F. Prevalence, awareness and control of type 2 diabetes mellitus and risk factors in Chinese elderly population. *BMC Public Health* **2022**, *22*, 1382. [CrossRef] [PubMed]
3. Federation, I.D. At a Glance | 119(3) Mar 2011. *Environ. Heal. Perspect.* **2011**, *119*, a106–a109. [CrossRef]
4. Galicia-Garcia, U.; Benito-Vicente, A.; Jebari, S.; Larrea-Sebal, A.; Siddiqi, H.; Uribe, K.B.; Ostolaza, H.; Martín, C. Pathophysiology of Type 2 Diabetes Mellitus. *Int. J. Mol. Sci.* **2020**, *21*, 6275. [CrossRef] [PubMed]
5. Rangel, E.B.; Rodrigues, C.O.; De Sa, J.R. *Micro- and Macrovascular Complications in Diabetes Mellitus: Preclinical and Clinical Studies*; Hindawi: London, UK, 2019.
6. Chawla, A.; Chawla, R.; Jaggi, S. Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? *Indian J. Endocrinol. Metab.* **2016**, *20*, 546–551. [CrossRef] [PubMed]
7. Bhatti, J.S.; Sehrawat, A.; Mishra, J.; Sidhu, I.S.; Navik, U.; Khullar, N.; Kumar, S.; Bhatti, G.K.; Reddy, P.H. Oxidative stress in the pathophysiology of type 2 diabetes and related complications: Current therapeutics strategies and future perspectives. *Free Radic. Biol. Med.* **2022**, *184*, 114–134. [CrossRef] [PubMed]
8. Marín-Peñalver, J.J.; Martín-Timón, I.; Sevillano-Collantes, C.; Del Cañizo-Gómez, F.J. Update on the treatment of type 2 diabetes mellitus. *World J. Diabetes* **2016**, *7*, 354–395. [CrossRef]

9. Unuofin, J.O.; Lebelo, S.L. Antioxidant Effects and Mechanisms of Medicinal Plants and Their Bioactive Compounds for the Prevention and Treatment of Type 2 Diabetes: An Updated Review. *Oxidative Med. Cell. Longev.* **2020**, *2020*, 1356893. [CrossRef]
10. Panche, A.N.; Diwan, A.D.; Chandra, S.R. Flavonoids: An overview. *J. Nutr. Sci.* **2016**, *5*, e47. [CrossRef]
11. David, A.V.A.; Arulmoli, R.; Parasuraman, S. Overviews of biological importance of quercetin: A bioactive flavonoid. *Pharmacogn. Rev.* **2016**, *10*, 84.
12. Ansari, P.; Choudhury, S.T.; Seidel, V.; Rahman, A.B.; Aziz, M.A.; Richi, A.E.; Rahman, A.; Jafrin, U.H.; Hannan, J.; Abdel-Wahab, Y.H. Therapeutic potential of quercetin in the management of type-2 diabetes mellitus. *Life* **2022**, *12*, 1146. [CrossRef] [PubMed]
13. Dubey, R.; Prabhakar, D.P.; Gupta, J. Identification of Structurally Similar Phytochemicals to Quercetin with High SIRT1 Binding Affinity and Improving Diabetic Wound Healing by Using In silico Approaches. *Biointerface Res. Appl. Chem.* **2021**, *12*, 7621–7632.
14. Magar, R.T.; Sohng, J.K. A Review on Structure, Modifications and Structure-Activity Relation of Quercetin and Its Derivatives. *J. Microbiol. Biotechnol.* **2019**, *30*, 11–20. [CrossRef] [PubMed]
15. Banjarnahor, S.D.; Artanti, N. Antioxidant properties of flavonoids. *Med. J. Indones.* **2014**, *23*, 239–244. [CrossRef]
16. Huang, K.; Liu, Z.; Kim, M.-O.; Kim, K.-R. Anticancer effects of gossypetin from *Hibiscus sabdariffa* in oral squamous cell carcinoma. *J. Appl. Oral Sci.* **2023**, *31*, e20230243. [CrossRef] [PubMed]
17. Dutta, M.S.; Mahapatra, P.; Ghosh, A.; Basu, S. Estimation of the reducing power and electrochemical behavior of few flavonoids and polyhydroxybenzophenones substantiated by bond dissociation energy: A comparative analysis. *Mol. Divers.* **2022**, *26*, 1101–1113. [CrossRef] [PubMed]
18. Ijaz, M.U.; Alvi, K.; Khan, H.A.; Imran, M.; Afsar, T.; Almajwal, A.; Amor, H.; Razak, S. Gossypetin mitigates doxorubicin-induced nephrotoxicity: A histopathological and biochemical evaluation. *J. King Saud Univ.-Sci.* **2023**, *35*, 102830. [CrossRef]
19. Mustafa, S.; Anwar, H.; Ain, Q.u.; Ahmed, H.; Iqbal, S.; Ijaz, M.U. Therapeutic effect of gossypetin against paraquat-induced testicular damage in male rats: A histological and biochemical study. *Environ. Sci. Pollut. Res.* **2023**, *30*, 62237–62248. [CrossRef]
20. Lin, H.-H. In vitro and in vivo atheroprotective effects of gossypetin against endothelial cell injury by induction of autophagy. *Chem. Res. Toxicol.* **2015**, *28*, 202–215. [CrossRef]
21. Oh, E.; Lee, J.; Cho, S.; Kim, S.W.; Jo, K.W.; Shin, W.S.; Gwak, S.H.; Ha, J.; Jeon, S.Y.; Park, J.-H.; et al. Gossypetin prevents the progression of nonalcoholic steatohepatitis by regulating oxidative stress and AMP-activated protein kinase. *Mol. Pharmacol.* **2023**, *104*, 214–229. [CrossRef]
22. Jejurkar, G.; Chavan, M. Therapeutic benefits of gossypin as an emerging phytoconstituents of *Hibiscus* spp.: A critical review. *Future J. Pharm. Sci.* **2023**, *9*, 95. [CrossRef]
23. Khan, M.A.B.; Hashim, M.J.; King, J.K.; Govender, R.D.; Mustafa, H.; Al Kaabi, J. Epidemiology of Type 2 Diabetes—Global Burden of Disease and Forecasted Trends. *J. Epidemiol. Glob. Health* **2020**, *10*, 107–111. [CrossRef]
24. Saisho, Y. β-cell dysfunction: Its critical role in prevention and management of type 2 diabetes. *World J. Diabetes* **2015**, *6*, 109–124. [CrossRef] [PubMed]
25. Phaniendra, A.; Jestadi, D.B.; Periyasamy, L. Free radicals: Properties, sources, targets, and their implication in various diseases. *Indian J. Clin. Biochem.* **2015**, *30*, 11–26. [CrossRef] [PubMed]
26. Redza-Dutordoir, M.; Averill-Bates, D.A. Activation of apoptosis signalling pathways by reactive oxygen species. *Biochim. Biophys. Acta (BBA)-Mol. Cell Res.* **2016**, *1863*, 2977–2992. [CrossRef]
27. Yaribeygi, H.; Sathyapalan, T.; Atkin, S.L.; Sahebkar, A. Molecular Mechanisms Linking Oxidative Stress and Diabetes Mellitus. *Oxidative Med. Cell. Longev.* **2020**, *2020*, 8609213. [CrossRef] [PubMed]
28. Nguyen, D.V.; Shaw, L.C.; Grant, M.B. Inflammation in the pathogenesis of microvascular complications in diabetes. *Front. Endocrinol.* **2012**, *3*, 170. [CrossRef] [PubMed]
29. Devaraj, S.; Dasu, M.R.; Jialal, I. Diabetes is a proinflammatory state: A translational perspective. *Expert Rev. Endocrinol. Metab.* **2010**, *5*, 19–28. [CrossRef]
30. Kong, M.; Xie, K.; Lv, M.; Li, J.; Yao, J.; Yan, K.; Wu, X.; Xu, Y.; Ye, D. Anti-inflammatory phytochemicals for the treatment of diabetes and its complications: Lessons learned and future promise. *Biomed. Pharmacother.* **2021**, *133*, 110975. [CrossRef]
31. Tungmunnithum, D.; Thongboonyou, A.; Pholboon, A.; Yangsabai, A. Flavonoids and Other Phenolic Compounds from Medicinal Plants for Pharmaceutical and Medical Aspects: An Overview. *Medicines* **2018**, *5*, 93. [CrossRef]
32. Sun, W.; Shahrajabian, M.H. Therapeutic Potential of Phenolic Compounds in Medicinal Plants—Natural Health Products for Human Health. *Molecules* **2023**, *28*, 1845. [PubMed]
33. Dias, M.C.; Pinto, D.; Silva, A.M.S. Plant Flavonoids: Chemical Characteristics and Biological Activity. *Molecules* **2021**, *26*, 5377. [CrossRef] [PubMed]
34. Ekalu, A.; Habila, J.D. Flavonoids: Isolation, characterization, and health benefits. *Beni-Suef Univ. J. Basic Appl. Sci.* **2020**, *9*, 45. [CrossRef]
35. Shehadeh, M.B.; Suaifan, G.; Abu-Odeh, A.M. Plants Secondary Metabolites as Blood Glucose-Lowering Molecules. *Molecules* **2021**, *26*, 4333. [CrossRef] [PubMed]
36. Yi, X.; Dong, M.; Guo, N.; Tian, J.; Lei, P.; Wang, S.; Yang, Y.; Shi, Y. Flavonoids improve type 2 diabetes mellitus and its complications: A review. *Front. Nutr.* **2023**, *10*, 1192131. [CrossRef]
37. Dhanya, R. Quercetin for managing type 2 diabetes and its complications, an insight into multitarget therapy. *Biomed. Pharmacother.* **2022**, *146*, 112560. [CrossRef]
38. Aghababaei, F.; Hadidi, M. Recent Advances in Potential Health Benefits of Quercetin. *Pharmaceuticals* **2023**, *16*, 1020. [CrossRef]

39. Ozgen, S.; Kilinc, O.K.; Selamoğlu, Z. Antioxidant activity of quercetin: A mechanistic review. *Turk. J. Agric.-Food Sci. Technol.* **2016**, *4*, 1134–1138. [CrossRef]
40. Ghafouri-Fard, S.; Shoorei, H.; Sasi, A.K.; Taheri, M.; Ayatollahi, S.A. The impact of the phytotherapeutic agent quercetin on expression of genes and activity of signaling pathways. *Biomed. Pharmacother.* **2021**, *141*, 111847. [CrossRef]
41. Youl, E.; Bardy, G.; Magous, R.; Cros, G.; Sejalon, F.; Virsolvy, A.; Richard, S.; Quignard, J.F.; Gross, R.; Petit, P.; et al. Quercetin potentiates insulin secretion and protects INS-1 pancreatic β-cells against oxidative damage via the ERK1/2 pathway. *Br. J. Pharmacol.* **2010**, *161*, 799–814. [CrossRef]
42. Hammes, H.-P. Diabetic retinopathy: Hyperglycaemia, oxidative stress and beyond. *Diabetologia* **2018**, *61*, 29–38. [CrossRef] [PubMed]
43. Charlton, A.; Garzarella, J.; Jandeleit-Dahm, K.A.; Jha, J.C. Oxidative stress and inflammation in renal and cardiovascular complications of diabetes. *Biology* **2020**, *10*, 18. [CrossRef] [PubMed]
44. De Nardo, D. Toll-like receptors: Activation, signalling and transcriptional modulation. *Cytokine* **2015**, *74*, 181–189. [CrossRef] [PubMed]
45. Roy, A.; Srivastava, M.; Saqib, U.; Liu, D.; Faisal, S.M.; Sugathan, S.; Bishnoi, S.; Baig, M.S. Potential therapeutic targets for inflammation in toll-like receptor 4 (TLR4)-mediated signaling pathways. *Int. Immunopharmacol.* **2016**, *40*, 79–89. [CrossRef] [PubMed]
46. Wang, Y.; Tao, B.; Wan, Y.; Sun, Y.; Wang, L.; Sun, J.; Li, C. Drug delivery based pharmacological enhancement and current insights of quercetin with therapeutic potential against oral diseases. *Biomed. Pharmacother.* **2020**, *128*, 110372. [CrossRef] [PubMed]
47. Cheng, S.-C.; Huang, W.-C.; Pang, J.-H.S.; Wu, Y.-H.; Cheng, C.-Y. Quercetin inhibits the production of IL-1β-induced inflammatory cytokines and chemokines in ARPE-19 cells via the MAPK and NF-κB signaling pathways. *Int. J. Mol. Sci.* **2019**, *20*, 2957. [CrossRef] [PubMed]
48. Chuang, C.-C.; Martinez, K.; Xie, G.; Kennedy, A.; Bumrungpert, A.; Overman, A.; Jia, W.; McIntosh, M.K. Quercetin is equally or more effective than resveratrol in attenuating tumor necrosis factor-α–mediated inflammation and insulin resistance in primary human adipocytes. *Am. J. Clin. Nutr.* **2010**, *92*, 1511–1521. [CrossRef]
49. Lai, P.B.; Zhang, L.; Yang, L.Y. Quercetin ameliorates diabetic nephropathy by reducing the expressions of transforming growth factor-β1 and connective tissue growth factor in streptozotocin-induced diabetic rats. *Ren. Fail.* **2012**, *34*, 83–87. [CrossRef]
50. Yang, H.; Song, Y.; Liang, Y.N.; Li, R. Quercetin Treatment Improves Renal Function and Protects the Kidney in a Rat Model of Adenine-Induced Chronic Kidney Disease. *Med. Sci. Monit.* **2018**, *24*, 4760–4766. [CrossRef]
51. Yi, H.; Peng, H.; Wu, X.; Xu, X.; Kuang, T.; Zhang, J.; Du, L.; Fan, G. The Therapeutic Effects and Mechanisms of Quercetin on Metabolic Diseases: Pharmacological Data and Clinical Evidence. *Oxidative Med. Cell. Longev.* **2021**, *2021*, 6678662. [CrossRef]
52. Salehi, B.; Machin, L.; Monzote, L.; Sharifi-Rad, J.; Ezzat, S.M.; Salem, M.A.; Merghany, R.M.; El Mahdy, N.M.; Kılıç, C.S.; Sytar, O.; et al. Therapeutic Potential of Quercetin: New Insights and Perspectives for Human Health. *ACS Omega* **2020**, *5*, 11849–11872. [CrossRef] [PubMed]
53. Xiong, G.; Ji, W.; Wang, F.; Zhang, F.; Xue, P.; Cheng, M.; Sun, Y.; Wang, X.; Zhang, T. Quercetin inhibits inflammatory response induced by LPS from Porphyromonas gingivalis in human gingival fibroblasts via suppressing NF-κB signaling pathway. *BioMed Res. Int.* **2019**, *2019*, 6282635. [CrossRef] [PubMed]
54. Krajka-Kuźniak, V.; Baer-Dubowska, W. Modulation of Nrf2 and NF-κB signaling pathways by naturally occurring compounds in relation to cancer prevention and therapy. Are combinations better than single compounds? *Int. J. Mol. Sci.* **2021**, *22*, 8223. [CrossRef] [PubMed]
55. Khan, A.; Manna, K.; Bose, C.; Sinha, M.; Das, D.K.; Kesh, S.B.; Chakrabarty, A.; Banerji, A.; Dey, S. Gossypetin, a naturally occurring hexahydroxy flavone, ameliorates gamma radiation-mediated DNA damage. *Int. J. Radiat. Biol.* **2013**, *89*, 965–975. [CrossRef] [PubMed]
56. Riaz, G.; Chopra, R. A review on phytochemistry and therapeutic uses of *Hibiscus sabdariffa* L. *Biomed. Pharmacother.* **2018**, *102*, 575–586. [CrossRef] [PubMed]
57. Da-Costa-Rocha, I.; Bonnlaender, B.; Sievers, H.; Pischel, I.; Heinrich, M. *Hibiscus sabdariffa* L.—A phytochemical and pharmacological review. *Food Chem.* **2014**, *165*, 424–443. [CrossRef] [PubMed]
58. González-Stuart, A. Multifaceted therapeutic value of roselle (*Hibiscus sabdariffa* L.—Malvaceae). In *Nutrients, Dietary Supplements, and Nutriceuticals Cost Analysis Versus Clinical Benefits*; Humana Press: Totowa, NJ, USA, 2011; pp. 215–226. [CrossRef]
59. Har Bhajan, S.; Bharati, K.A. 6-Enumeration of dyes. In *Handbook of Natural Dyes and Pigments*; Har Bhajan, S., Bharati, K.A., Eds.; Woodhead Publishing: Delhi, India, 2014.
60. Shahidi, F.; Zhong, Y. Measurement of antioxidant activity. *J. Funct. Foods* **2015**, *18*, 757–781. [CrossRef]
61. Kumar, S.; Pandey, A.K. Chemistry and biological activities of flavonoids: An overview. *Sci. World J.* **2013**, *2013*, 162750. [CrossRef]
62. Puthanveedu, V.; Muraleedharan, K. Study on structural detailing of gossypetin and its medicinal application in UV filtering, radical scavenging, and metal chelation open up through NCI, TD-DFT, QTAIM, ELF, and LOL analysis. *Comput. Theor. Chem.* **2023**, *1225*, 114126. [CrossRef]
63. Samant, N.P.; Gupta, G.L. Gossypetin-based therapeutics for cognitive dysfunction in chronic unpredictable stress-exposed mice. *Metab. Brain Dis.* **2022**, *37*, 1527–1539. [CrossRef]
64. Zheng, Y.; Chow, A. Production and characterization of a spray-dried hydroxypropyl-β-cyclodextrin/quercetin complex. *Drug Dev. Ind. Pharm.* **2009**, *35*, 727–734. [CrossRef] [PubMed]

65. Folli, F.; Corradi, D.; Fanti, P.; Davalli, A.; Paez, A.; Giaccari, A.; Perego, C.; Muscogiuri, G. The role of oxidative stress in the pathogenesis of type 2 diabetes mellitus micro-and macrovascular complications: Avenues for a mechanistic-based therapeutic approach. *Curr. Diabetes Rev.* **2011**, *7*, 313–324. [CrossRef] [PubMed]
66. Lin, H.-H.; Hsieh, M.-C.; Wang, C.-P.; Yu, P.-R.; Lee, M.-S.; Chen, J.-H. Anti-atherosclerotic effect of gossypetin on abnormal vascular smooth muscle cell proliferation and migration. *Antioxidants* **2021**, *10*, 1357. [CrossRef] [PubMed]
67. Jo, K.W.; Lee, D.; Cha, D.G.; Oh, E.; Choi, Y.H.; Kim, S.; Park, E.S.; Kim, J.K.; Kim, K.-T. Gossypetin ameliorates 5xFAD spatial learning and memory through enhanced phagocytosis against Aβ. *Alzheimer's Res. Ther.* **2022**, *14*, 158. [CrossRef] [PubMed]
68. Oguntibeju, O.O. Type 2 diabetes mellitus, oxidative stress and inflammation: Examining the links. *Int. J. Physiol. Pathophysiol. Pharmacol.* **2019**, *11*, 45. [PubMed]
69. Fischer, N.; Seo, E.-J.; Efferth, T. Prevention from radiation damage by natural products. *Phytomedicine* **2018**, *47*, 192–200. [CrossRef] [PubMed]
70. Devipriya, N.; Sudheer, A.R.; Srinivasan, M.; Menon, V.P. Quercetin ameliorates gamma radiation-induced DNA damage and biochemical changes in human peripheral blood lymphocytes. *Mutat. Res.* **2008**, *654*, 1–7. [CrossRef]
71. Benzie, I.F.; Devaki, M. The ferric reducing/antioxidant power (FRAP) assay for non-enzymatic antioxidant capacity: Concepts, procedures, limitations and applications. *Meas. Antioxid. Act. Capacit. Recent Trends Appl.* **2018**, 77–106.
72. Mounnissamy, V.; Gopal, V.; Gunasegaran, R.; Saraswathy, A. Antiinflammatory activity of gossypetin isolated from *Hibiscus sabdariffa*. *Indian J. Heterocycl. Chem.* **2002**, *12*, 85–86.
73. Proença, C.; Rufino, A.T.; Santos, I.; Albuquerque, H.M.T.; Silva, A.M.S.; Fernandes, E.; Ferreira de Oliveira, J.M.P. Gossypetin Is a Novel Modulator of Inflammatory Cytokine Production and a Suppressor of Osteosarcoma Cell Growth. *Antioxidants* **2023**, *12*, 1744. [CrossRef]
74. Marchio, P.; Guerra-Ojeda, S.; Vila, J.M.; Aldasoro, M.; Victor, V.M.; Mauricio, M.D. Targeting early atherosclerosis: A focus on oxidative stress and inflammation. *Oxidative Med. Cell. Longev.* **2019**, *2019*, 8563845. [CrossRef] [PubMed]
75. Tangvarasittichai, S. Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus. *World J. Diabetes* **2015**, *6*, 456. [CrossRef] [PubMed]
76. Hirano, T. Pathophysiology of diabetic dyslipidemia. *J. Atheroscler. Thromb.* **2018**, *25*, 771–782. [CrossRef] [PubMed]
77. Khatana, C.; Saini, N.K.; Chakrabarti, S.; Saini, V.; Sharma, A.; Saini, R.V.; Saini, A.K. Mechanistic insights into the oxidized low-density lipoprotein-induced atherosclerosis. *Oxidative Med. Cell. Longev.* **2020**, *2020*, 5245308. [CrossRef] [PubMed]
78. Casella, S.; Bielli, A.; Mauriello, A.; Orlandi, A. Molecular pathways regulating macrovascular pathology and vascular smooth muscle cells phenotype in type 2 diabetes. *Int. J. Mol. Sci.* **2015**, *16*, 24353–24368. [CrossRef] [PubMed]
79. Jha, J.C.; Ho, F.; Dan, C.; Jandeleit-Dahm, K. A causal link between oxidative stress and inflammation in cardiovascular and renal complications of diabetes. *Clin. Sci.* **2018**, *132*, 1811–1836. [CrossRef] [PubMed]
80. Bamanikar, S.; Bamanikar, A.A.; Arora, A. Study of Serum urea and Creatinine in Diabetic and nondiabetic patients in a tertiary teaching hospital. *J. Med. Res.* **2016**, *2*, 12–15. [CrossRef]
81. Luft, F.C. Biomarkers and predicting acute kidney injury. *Acta Physiol.* **2021**, *231*, e13479. [CrossRef]
82. Leyva-López, N.; Gutierrez-Grijalva, E.P.; Ambriz-Perez, D.L.; Heredia, J.B. Flavonoids as cytokine modulators: A possible therapy for inflammation-related diseases. *Int. J. Mol. Sci.* **2016**, *17*, 921. [CrossRef]
83. Al-Khayri, J.M.; Sahana, G.R.; Nagella, P.; Joseph, B.V.; Alessa, F.M.; Al-Mssallem, M.Q. Flavonoids as potential anti-inflammatory molecules: A review. *Molecules* **2022**, *27*, 2901. [CrossRef]
84. Barone, E.; Di Domenico, F.; Perluigi, M.; Butterfield, D.A. The interplay among oxidative stress, brain insulin resistance and AMPK dysfunction contribute to neurodegeneration in type 2 diabetes and Alzheimer disease. *Free Radic. Biol. Med.* **2021**, *176*, 16–33. [CrossRef] [PubMed]
85. Rojas-Gutierrez, E.; Muñoz-Arenas, G.; Treviño, S.; Espinosa, B.; Chavez, R.; Rojas, K.; Flores, G.; Díaz, A.; Guevara, J. Alzheimer's disease and metabolic syndrome: A link from oxidative stress and inflammation to neurodegeneration. *Synapse* **2017**, *71*, e21990. [CrossRef]
86. Antonelli, M.C.; Pallarés, M.E.; Ceccatelli, S.; Spulber, S. Long-term consequences of prenatal stress and neurotoxicants exposure on neurodevelopment. *Prog. Neurobiol.* **2017**, *155*, 21–35. [CrossRef] [PubMed]
87. Bisht, K.; Sharma, K.; Tremblay, M.-È. Chronic stress as a risk factor for Alzheimer's disease: Roles of microglia-mediated synaptic remodeling, inflammation, and oxidative stress. *Neurobiol. Stress* **2018**, *9*, 9–21. [CrossRef] [PubMed]
88. Miranda, M.; Morici, J.F.; Zanoni, M.B.; Bekinschtein, P. Brain-derived neurotrophic factor: A key molecule for memory in the healthy and the pathological brain. *Front. Cell. Neurosci.* **2019**, *13*, 363. [CrossRef] [PubMed]
89. Ortíz, B.M.; Emiliano, J.R.; Ramos-Rodríguez, E.; Martínez-Garza, S.; Macías-Cervantes, H.; Solorio-Meza, S.; Pereyra-Nobara, T.A. Brain-derived neurotrophic factor plasma levels and premature cognitive impairment/dementia in type 2 diabetes. *World J. Diabetes* **2016**, *7*, 615. [CrossRef] [PubMed]
90. Gatckikh, I.V. Association of Serum BDNF with Severity of Cognitive Disorders in Patients with Type 2 Diabetes. *Pers. Psychiatry Neurol.* **2022**, *2*, 67–77. [CrossRef]
91. Gulsheen; Kumar, A.; Sharma, A. Antianxiety and antidepressant activity guided isolation and characterization of gossypetin from *Hibiscus sabdariffa* Linn. calyces. *J. Biol. Act. Prod. Nat.* **2019**, *9*, 205–214. [CrossRef]
92. Balogh, D.B.; Molnar, A.; Hosszu, A.; Lakat, T.; Hodrea, J.; Szabo, A.J.; Lenart, L.; Fekete, A. Antidepressant effect in diabetes-associated depression: A novel potential of RAAS inhibition. *Psychoneuroendocrinology* **2020**, *118*, 104705. [CrossRef]

93. Gimenez, V.M.; Sanz, R.L.; Marón, F.J.M.; Ferder, L.; Manucha, W. Vitamin D-RAAS connection: An integrative standpoint into cardiovascular and neuroinflammatory disorders. *Curr. Protein Pept. Sci.* **2020**, *21*, 948–954. [CrossRef]
94. Lima Giacobbo, B.; Doorduin, J.; Klein, H.C.; Dierckx, R.A.; Bromberg, E.; de Vries, E.F. Brain-derived neurotrophic factor in brain disorders: Focus on neuroinflammation. *Mol. Neurobiol.* **2019**, *56*, 3295–3312. [CrossRef]
95. Colucci-D'Amato, L.; Speranza, L.; Volpicelli, F. Neurotrophic factor BDNF, physiological functions and therapeutic potential in depression, neurodegeneration and brain cancer. *Int. J. Mol. Sci.* **2020**, *21*, 7777. [CrossRef] [PubMed]
96. Nguyen, T.T.; Ta, Q.T.H.; Nguyen, T.T.D.; Le, T.T.; Vo, V.G. Role of insulin resistance in the Alzheimer's disease progression. *Neurochem. Res.* **2020**, *45*, 1481–1491. [CrossRef] [PubMed]
97. Sharma, V.K.; Singh, T.G. Insulin resistance and bioenergetic manifestations: Targets and approaches in Alzheimer's disease. *Life Sci.* **2020**, *262*, 118401. [CrossRef]
98. Jones, J.G. Hepatic glucose and lipid metabolism. *Diabetologia* **2016**, *59*, 1098–1103. [CrossRef] [PubMed]
99. Mu, W.; Cheng, X.-f.; Liu, Y.; Lv, Q.-z.; Liu, G.-l.; Zhang, J.-g.; Li, X.-y. Potential nexus of non-alcoholic fatty liver disease and type 2 diabetes mellitus: Insulin resistance between hepatic and peripheral tissues. *Front. Pharmacol.* **2019**, *9*, 1566. [CrossRef]
100. Mohamed, J.; Nafizah, A.N.; Zariyantey, A.; Budin, S. Mechanisms of diabetes-induced liver damage: The role of oxidative stress and inflammation. *Sultan Qaboos Univ. Med. J.* **2016**, *16*, e132. [CrossRef]
101. Masarone, M.; Rosato, V.; Dallio, M.; Gravina, A.G.; Aglitti, A.; Loguercio, C.; Federico, A.; Persico, M. Role of oxidative stress in pathophysiology of nonalcoholic fatty liver disease. *Oxidative Med. Cell. Longev.* **2018**, *2018*, 9547613. [CrossRef]
102. Ballestri, S.; Nascimbeni, F.; Romagnoli, D.; Lonardo, A. The independent predictors of non-alcoholic steatohepatitis and its individual histological features. Insulin resistance, serum uric acid, metabolic syndrome, alanine aminotransferase and serum total cholesterol are a clue to pathogenesis and candidate targets for treatment. *Hepatol. Res.* **2016**, *46*, 1074–1087.
103. Yang, K.; Chen, J.; Zhang, T.; Yuan, X.; Ge, A.; Wang, S.; Xu, H.; Zeng, L.; Ge, J. Efficacy and safety of dietary polyphenol supplementation in the treatment of non-alcoholic fatty liver disease: A systematic review and meta-analysis. *Front. Immunol.* **2022**, *13*, 949746. [CrossRef]
104. Myint, M.; Oppedisano, F.; De Giorgi, V.; Kim, B.-M.; Marincola, F.M.; Alter, H.J.; Nesci, S. Inflammatory signaling in NASH driven by hepatocyte mitochondrial dysfunctions. *J. Transl. Med.* **2023**, *21*, 757. [CrossRef] [PubMed]
105. Luangmonkong, T.; Suriguga, S.; Mutsaers, H.A.; Groothuis, G.M.; Olinga, P.; Boersema, M. Targeting oxidative stress for the treatment of liver fibrosis. *Rev. Physiol. Biochem. Pharmacol.* **2018**, *175*, 71–102. [PubMed]
106. Eslamparast, T.; Eghtesad, S.; Poustchi, H.; Hekmatdoost, A. Recent advances in dietary supplementation, in treating non-alcoholic fatty liver disease. *World J. Hepatol.* **2015**, *7*, 204. [CrossRef] [PubMed]
107. He, Z.; Yin, G.; Li, Q.Q.; Zeng, Q.; Duan, J. Diabetes mellitus causes male reproductive dysfunction: A review of the evidence and mechanisms. *In Vivo* **2021**, *35*, 2503–2511. [CrossRef] [PubMed]
108. Rato, L.; Oliveira, P.F.; Sousa, M.; Silva, B.M.; Alves, M.G. Role of reactive oxygen species in diabetes-induced male reproductive dysfunction. In *Oxidants, Antioxidants and Impact of the Oxidative Status in Male Reproduction*; Elsevier: Amsterdam, The Netherlands, 2019; pp. 135–147.
109. Chen, J.; Su, Y.; Lin, F.; Iqbal, M.; Mehmood, K.; Zhang, H.; Shi, D. Effect of paraquat on cytotoxicity involved in oxidative stress and inflammatory reaction: A review of mechanisms and ecological implications. *Ecotoxicol. Environ. Saf.* **2021**, *224*, 112711. [CrossRef] [PubMed]
110. Asmat, U.; Abad, K.; Ismail, K. Diabetes mellitus and oxidative stress—A concise review. *Saudi Pharm. J.* **2016**, *24*, 547–553. [CrossRef] [PubMed]
111. Pickering, R.J.; Rosado, C.J.; Sharma, A.; Buksh, S.; Tate, M.; de Haan, J.B. Recent novel approaches to limit oxidative stress and inflammation in diabetic complications. *Clin. Transl. Immunol.* **2018**, *7*, e1016. [CrossRef]
112. Pisoschi, A.M.; Pop, A. The role of antioxidants in the chemistry of oxidative stress: A review. *Eur. J. Med. Chem.* **2015**, *97*, 55–74. [CrossRef]
113. Thakur, P.; Kumar, A.; Kumar, A. Targeting oxidative stress through antioxidants in diabetes mellitus. *J. Drug Target.* **2018**, *26*, 766–776. [CrossRef]
114. Wang, P.; Fiaschi-Taesch, N.M.; Vasavada, R.C.; Scott, D.K.; Garcia-Ocana, A.; Stewart, A.F. Diabetes mellitus—Advances and challenges in human β-cell proliferation. *Nat. Rev. Endocrinol.* **2015**, *11*, 201–212. [CrossRef]
115. Entezari, M.; Hashemi, D.; Taheriazam, A.; Zabolian, A.; Mohammadi, S.; Fakhri, F.; Hashemi, M.; Hushmandi, K.; Ashrafizadeh, M.; Zarrabi, A.; et al. AMPK signaling in diabetes mellitus, insulin resistance and diabetic complications: A pre-clinical and clinical investigation. *Biomed. Pharmacother.* **2022**, *146*, 112563. [CrossRef] [PubMed]
116. Joshi, T.; Singh, A.K.; Haratipour, P.; Sah, A.N.; Pandey, A.K.; Naseri, R.; Juyal, V.; Farzaei, M.H. Targeting AMPK signaling pathway by natural products for treatment of diabetes mellitus and its complications. *J. Cell. Physiol.* **2019**, *234*, 17212–17231. [CrossRef] [PubMed]
117. Wang, Q.; Liu, S.; Zhai, A.; Zhang, B.; Tian, G. AMPK-mediated regulation of lipid metabolism by phosphorylation. *Biol. Pharm. Bull.* **2018**, *41*, 985–993. [CrossRef] [PubMed]
118. Marino, A.; Hausenloy, D.J.; Andreadou, I.; Horman, S.; Bertrand, L.; Beauloye, C. AMP-activated protein kinase: A remarkable contributor to preserve a healthy heart against ROS injury. *Free Radic. Biol. Med.* **2021**, *166*, 238–254. [CrossRef] [PubMed]
119. Coughlan, K.A.; Valentine, R.J.; Ruderman, N.B.; Saha, A.K. AMPK activation: A therapeutic target for type 2 diabetes? *Diabetes Metab. Syndr. Obes.* **2014**, *7*, 241–253. [PubMed]

120. Misra, P.; Chakrabarti, R. The role of AMP kinase in diabetes. *Indian J. Med. Res.* **2007**, *125*, 389–398.
121. Madhavi, Y.; Gaikwad, N.; Yerra, V.G.; Kalvala, A.K.; Nanduri, S.; Kumar, A. Targeting AMPK in diabetes and diabetic complications: Energy homeostasis, autophagy and mitochondrial health. *Curr. Med. Chem.* **2019**, *26*, 5207–5229. [CrossRef]
122. Babiker, A.; Al Dubayee, M. Anti-diabetic medications: How to make a choice? *Sudan. J. Paediatr.* **2017**, *17*, 11. [CrossRef]
123. Kumar, R.; Kerins, D.; Walther, T. Cardiovascular safety of anti-diabetic drugs. *Eur. Heart J.-Cardiovasc. Pharmacother.* **2016**, *2*, 32–43. [CrossRef]
124. Blahova, J.; Martiniakova, M.; Babikova, M.; Kovacova, V.; Mondockova, V.; Omelka, R. Pharmaceutical drugs and natural therapeutic products for the treatment of type 2 diabetes mellitus. *Pharmaceuticals* **2021**, *14*, 806. [CrossRef]
125. Francini, F.; Schinella, G.R.; Ríos, J.-L. Activation of AMPK by medicinal plants and natural products: Its role in type 2 diabetes mellitus. *Mini Rev. Med. Chem.* **2019**, *19*, 880–901. [CrossRef] [PubMed]
126. Hurtová, M.; Biedermann, D.; Osifová, Z.; Cvačka, J.; Valentová, K.; Křen, V. Preparation of Synthetic and Natural Derivatives of Flavonoids Using Suzuki–Miyaura Cross-Coupling Reaction. *Molecules* **2022**, *27*, 967. [CrossRef] [PubMed]