Phenolic Compounds as Preventive and Therapeutic Agents in Diabetes-Related Oxidative Stress, Inflammation, Advanced Glycation End-Products Production and Insulin Sensitivity

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Diabetes mellitus and its complications represent an extremely concerning health problem across the world. The extraordinary worldwide increase of the disease incidence highlights a challenging need for the development of new, safe, effective, and affordable therapeutic approaches. This complex disease, characterized by high blood sugar levels, involves numerous pathogenic processes in its etiology. Even though the molecular mechanisms behind are not clear, it is broadly recognized that oxidative stress, the accumulation of advanced glycation end-products (AGEs) and inflammation are implicated in the development, the progression and the related complications of the disease. In this regard, phenolic compounds represent a valuable therapeutic perspective. Thus, this review is focused on the role of phenolic compounds in diabetes-related oxidative stress, AGEs production and inflammation. In particular, we summarized recent results of *in vitro* and *in vivo* studies concerning antioxidant and antiglycative properties of phenolic compounds and also the modulation of activity on inflammation and inflammation-related pathways relevant in diabetes, namely arachidonic acid, nuclear factor-κB, mitogen-activated protein kinases and phosphatidylinositol 3-kinase/protein kinase B signaling pathways, were described. Highlighting thus the anti-diabetic potential of phenolic compounds in the development of preventive or therapeutic strategies for the management of diabetes and its related complications.

Keywords: phenolic compounds; diabetes mellitus; advanced glycation end products; inflammation; oxidative stress

Introduction

Diabetes Mellitus (DM) is a complex and heterogeneous metabolic disorder characterized by the dysregulation of glucose metabolism resulting from anomalies in insulin secretion, action, or both. The majority of cases of DM fall into two broad categories: Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM) [1]. Albeit in smaller proportions than the overall incidence, DM has been reported in various other forms related to gestational hormonal environment, genetic abnormalities, infections, and certain drugs [2]. T1DM is one of the most common metabolic disorders occurring in childhood. It is a chronic autoimmune disease in which the pancreatic insulin-producing β-cells are selectively destroyed by the immune system, leading to a decrease in insulin secretion and the development of hyperglycaemia. In a small subset of cases, no autoantibodies are detected, and the cause of β-cells destruction is unknown [3]. T2DM is

the most common form of DM accounting for more than 90% cases of diabetes. It is characterized by insulin deficiency due to pancreatic β-cell dysfunction and the loss of insulin sensitivity in target organs and tissues, such as the liver, skeletal muscles, and adipose tissues [4]. The impairment of pancreatic β-cells is a common trait in the pathogenesis of both T1DM and T2DM, although the pathways involved are different. While in T1DM β-cell failure is principally immune-mediated, in T2DM the progressive loss in mass and function of β-cells is mostly caused by metabolic stress, such as the hyperproduction of reactive oxygen species (ROS), endoplasmic reticulum stress, mitochondrial damage and inflammation [5]. β-cells are located inside the pancreas grouped in clusters known as Langerhans islets, their main function is insulin secretion in response to blood glucose levels. Glucose blood levels in healthy individuals are closely regulated and the disruption of glucose metabolism can lead to hypoglycaemia
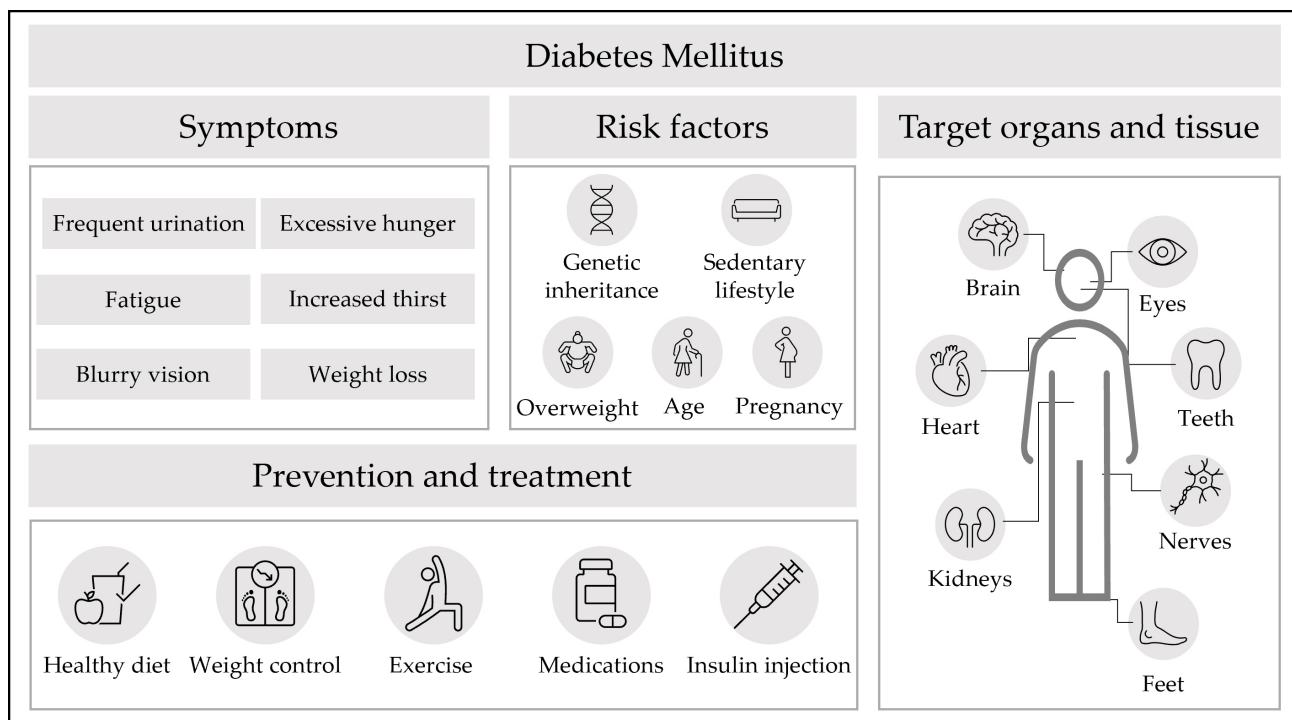
Fig. 1. Main features of Diabetes Mellitus (DM). DM, a complex metabolic disorder, is characterized by the dysregulation of glucose metabolism. This figure summarizes the main symptoms, risk factors, target organs and systems of DM and the main prevention and treatment approaches (drawn with MS Office 365 ProPlus Power Point, Microsoft, Redmond, WA, U.S.).

(low blood glucose levels) or hyperglycaemia (high blood glucose levels) [6,7]. The principal consequences of uncontrolled diabetes include not only acute symptoms, like hyperglycemia with ketoacidosis, but also long-term conditions such as cardiovascular, gastrointestinal, and genitourinary, as well as retinopathy, nephropathy and abnormalities of lipoprotein metabolism [8,9], impacting both patient's quality of life and healthcare systems (Fig. 1). Moreover, the worldwide ever-growing spread of the disease makes DM even more concerning. Indeed, it is estimated that a total of 578 million people will be affected by diabetes in 2030 and this number is expected to increase to 700 million in 2045, representing 10.9% of the global population between 20 and 79 years [10]. DM, therefore, can be considered an epidemic metabolic syndrome and it is a critical health problem across the world. Several therapeutic approaches are used for controlling DM-related hyperglycemia, including insulin injection for T1DM patients or oral medications and lifestyle changes for T2DM patients [11]. However, the global burden of the disease makes novel therapeutical approaches necessary for DM prevention, treatment, and management. In this regard, natural products can be a valuable source of bioactive compounds with antidiabetic properties, especially for the prevention and treatment of T2DM.

Since ancient times, medicinal plants have been used as a remedy for several disorders including diabetes; recently, different research studies highlighted the anti-diabetic properties of natural products, principally related to the presence of bioactive compounds [12]. Among these, phenolic compounds are an important class of phytochemicals with anti-diabetic properties [13]. Polyphenols represent a large family of secondary metabolites, abundantly found in several plants and plant-based foods. According to the chemical structures, polyphenols are classified into different groups. The main groups are phenolic acids, stilbenes, flavonoids and lignans (Fig. 2). Phenolic acids can be further divided into two classes: hydroxycinnamic, abundant in edible plants, and hydroxybenzoic acids. Stilbenes are characterized by a 1,2-diphenylethylene basic structure and can be largely found in grapes and some berries, though their intake in a human diet is quite low. Flavonoids, the largest group of polyphenols, have a common basic structure consisting of two aromatic rings bound by a heterocyclic ring. Flavonoids, based on the variation in the heterocyclic ring structure, can be divided into six classes: flavones, flavanols, flavanones, isoflavones, flavanols, and anthocyanins. Lignans are formed by the dimerization of two cinnamic acid residues; the richest dietary source of lignans are seeds of the flax plant (*Linum usitatissimum*) [14]. Phenolic compounds can be found also in the form of esters, glycosides, or polymers, and in most cases, plants contain complex mixtures of phenolics with a differential distribution at tissue, cellular and sub-cellular levels. Increasing evidence has shown the beneficial role of phenolic compounds on human health, suggesting an inverse association between the risk of chronic diseases and

the consumption of polyphenol-rich foods. Several studies have shown that phenolic compounds, through their antioxidant properties, can protect cells against oxidative damage, therefore limiting the risk of degenerative diseases related to an oxidative status [15]. In this context, the aim of the present work is to summarize recent data on the anti-inflammatory properties of phenolic compounds and their relevance in DM, with a special emphasis on the target pathway for the modulation of the inflammatory signal.
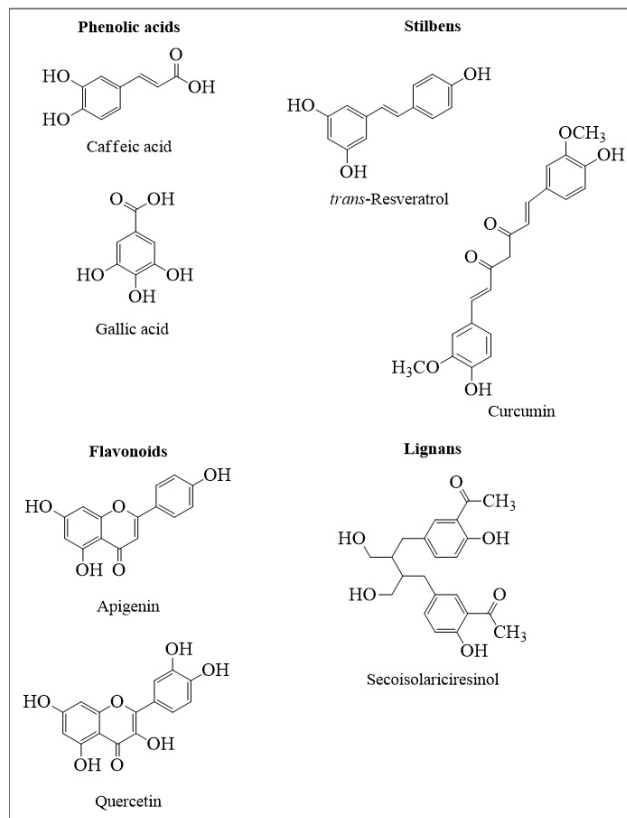

Fig. 2. Examples of different phenolic compounds chemical structures. Phenolic compounds can be classified according to the number of phenolic rings they contain and according to the structural elements that connect these rings together. The principal classes comprise phenolic acids, stilbenes, flavonoids and lignans (drawn with CambridgeSoft ChemDraw Ultra 12.0, PerkinElmer, Inc., Waltham, MA, U.S.).

Phenolic Compounds, Nitrosative/Oxidative Stress, Inflammation, and Insulin Resistance

The terms nitrosative stress and oxidative stress are referred to an increase of reactive nitrogen species (RNS) and reactive oxygen species (ROS) respectively. ROS/RNS are recognized for playing a double role, as they can be either beneficial or detrimental to living systems [16]. Among RNS, nitric oxide (NO) acts as a crucial oxidative signaling molecule. However, an overproduction of RNS causes the

so-called nitrosative stress. Moreover, during inflammatory processes the immune system cells trigger an oxidative burst, under these conditions NO and superoxide (O_2^-) can react producing the peroxynitrite anion ($OONO^-$), which is a free radical that can determine DNA damage, lipid oxidation and is implicated in several diseases, such as diabetes and diabetic complications. A growing body of evidence has highlighted the key role of NO, $OONO^-$, and its downstream effectors, such as the nuclear enzyme poly (Adenosine diphosphate (ADP)-ribose) polymerase-1 (PARP-1), in the pathogenesis of diabetes and diabetic complications. In particular, NO is one of the main effectors of β-cells death; while, PARP-1 controls the expression of several inflammatory mediators, which aid the progression of diabetic cardiovascular complications [16,17]. ROS include both oxygen-centered radicals, like $O_2^\bullet$ or hydroxyl ($OH^\bullet$) radicals, and other non-radical oxygen derivatives, like hydrogen peroxide (H_2O_2) and singlet oxygen (O_2) [18]. ROS formation takes place continuously in the cells and is controlled by an integrated cellular enzymatic system that maintains the oxidative equilibrium [19]. Oxidative stress, chronic inflammation, and insulin resistance have a consistent connection with each other that leads to DM. ROS can trigger the activation of stress-sensitive signaling pathways, such as nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) that, in turn, phosphorylate other targets like insulin receptor (IR) and insulin receptor substrate (IRS). The phosphorylation of IRS, under physiological condition, is an event capable to terminate the insulin signal. Thus, chronic activation of stress-sensitive kinases, in response to oxidative stress and inflammation, leads to the pathological condition of insulin resistance [20]. The use of antioxidants to suppress the chronic activation of these pathways might lead to novel therapeutic approaches to prevent or delay the occurrence of oxidative stress-induced insulin resistance and phenolic compounds could play a role in protecting cells against the degenerative effects of ROS. Their antioxidant and anti-inflammatory activities have been mainly attributed to the chemical structure and arise from their ability in scavenging free radicals [19], but also to the inhibition of enzymes involved in ROS production and the upregulation of antioxidant defenses. Several phenolic compounds have shown antioxidant effects, among these epigallocatechin-3-gallate, gallic acid, oleuropein, resveratrol and curcumin appear to be good antioxidants, since they are able to reduce ROS production and enhance antioxidant defense [21]. Besides, the antioxidant properties of phenolic compounds can protect pancreatic β-cells from hyperglycaemia-induced oxidative stress. ROS formation in β-cells is promoted by the catabolism of glucose and free fatty acids. β-cells are particularly susceptible to oxidative stress because of their very low antioxidant capacity, therefore hyperglycemia-induced oxidative stress plays a pivotal role in the development of diabetes [22]. Reports are available of a number of phenolic com-

pounds, isolated or partially purified from plants, able to protect β-cells: as shown by Martín *et al.* [23], a cocoa phenolic extract rich in flavonoids, was able to protect Ins-1E pancreatic β-cells against the oxidative stress induced by tert-butylhydroperoxide (t-BOOH) [23]. Moreover, an extract obtained from *Crassocephalum crepidioides* rich in gallic acid and quercetin was able to significantly decrease the intracellular ROS level and apoptosis in pancreatic INS-1 cells treated with alloxan [24]. Moreover, Yin *et al.* [25], reported that a phenolics-rich chestnut (*Castanea mollissima*) extract protected β-cells in streptozotocin (STZ)-induced diabetic rats through the reduction of oxidative stress, the enhancement of the antioxidant system, and the inhibition of lipid peroxidation. Taken together, these data suggest that phenolic compounds can efficiently attenuate oxidative stress and might have a potential as anti-diabetic agents.

Phenolic Compounds and Advanced Glycation End-Products (AGEs)

Elevated glucose levels, which arise in diabetic people, enhance several important biochemical mechanisms, such as the formation of advanced glycation end-products (AGEs) [26]. Besides, the increased levels of AGEs and its precursors methylglyoxal (MGO), which characterize conditions of hyperglycemia, hyperlipidemia and enhanced oxidative stress, typical for obesity, underline the role of AGEs in the pathogenesis of obesity and insulin resistance [27]. The formation of AGEs, which derives from nonenzymatic glycation of macromolecules (such as proteins, lipids, and nucleic acid) with reducing sugar, is induced by the Maillard reaction (MR) and is a slow process that occurs under physiological conditions in the body [28]. The slow formation of Schiff bases, the early formation of unstable AGE precursors that may underlie Amadori rearrangement, and the formation of irreversible late AGEs represent the three steps of the glycation process [29]. In addition to endogenous production, various environmental factors, including high-carbohydrate diets, high-temperature cooking, cigarette smoke, and a sedentary lifestyle can increase AGEs formation [30]. Additionally, food high in lipids and proteins have the highest levels of dietary AGEs (dAGEs). Due to their harmful effects, dAGEs are also called glycotoxins [31]. During the Amadori products formation, these undergo chemical modifications, some dicarbonyl compounds such as glyoxal (GO), methylglyoxal (MGO), and deoxyglucosones (3-DG) are formed by several pathways. These compounds are highly reactive and represent a crucial step in AGEs generation since they can lead to the formation of hydroxyl compounds [32]. AGEs, through their chief signaling receptor, the receptor for advanced glycation end products (RAGE), enhance the production of ROS and trigger inflammatory signaling cascades. Thus, AGEs have significant roles in diabetes and

the related complications [26]. RAGE is normally expressed at low levels in different cell types, including inflammatory cells (monocytes, macrophages, and lymphocytes). In several pathological conditions, particularly in diabetes, the upregulation of RAGE is observed. RAGE, upon the activation with its ligands, initiates a 'feed forward' signaling loop that sustains an inflammatory environment which has an impact on the pathogenesis of both T1DM and T2DM and, over the time, in the development of their complications [26,33]. Among them, cardiovascular disease (CVD), which represents a significant cause of death, appear to be strongly related to AGEs. Indeed, Negrean *et al.* [34] observed that dAGEs impair vascular functions in T2DM patients, providing evidence that a high-dAGEs meal induced more acute deleterious effects than a low-dAGEs meal [35]. AGEs exert their pathological role by binding to different RAGE expressed on the cell surface, activating several signaling pathways. The AGE-RAGE interaction transduces signals through different pathways such as janus kinase-2-signal transducers and activators of transcription 1 (JAK-2-STAT 1), phosphatidylinositol 3-kinase-protein kinase B (PI3K-AKT), mitogen-activated protein kinases-extracellular signal-regulated kinase (MAPK-ERK), and nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase-ROS [36]. Several studies have shown that dAGEs can induce TNF-α secretion in human macrophage-like cells to generate more AGEs [37], leading to an increase in inflammatory response through macrophage activation [38,39]. AGEs can induce structural changes to several macromolecules, altering their function and leading to intracellular pathways that trigger inflammatory responses and endothelial cell damage [40,41]. Thus, the inhibition of AGE-RAGE or AGEs formation by natural compounds represents an alternative approach to prevent AGEs damage and pathological conditions related to their accumulation, such as diabetes and its complications [42]. Phenolic compounds can reduce the production of early products of the Maillard reaction in several ways: by covering protein glycation sites, regulating AGEs receptors, scavenging oxidative free radicals, trapping active di-carbonyl compounds and lowering blood glucose levels [43]. Different natural compounds are able to bind to proteins through hydrogen bonds or van der Waals forces, protecting the integrity of proteins and inhibiting non-enzymatic glycation which significantly modifies proteins structure thus altering proteins function [44]. Several studies have evidenced that different phenolic compounds hold antiglycation properties. Gallic acid is a phenolic compound significantly found in grape (*Vitis vinifera*), oak (*Quercus robur*) bark, green tea (*Camellia sinensis*) and, also, significant amounts of gallic acid have also been found in sumac (*Rhus coriaria*) [45]. Wu *et al.* [46], highlighted that gallic acid has a noteworthy inhibitory activity on glycation, indicating that this phenolic compound can prevent glucose-mediated protein modifications. Resvera-

trol inhibits the expression of RAGE by a mechanism involving peroxisome proliferator-activated receptor-gamma (PPAR-γ) and also interfering in the RAGE signaling cascade [47]. Additionally, (-)-Epigallocatechin gallate shows protective effects towards AGEs-induced injury not only through the anti-oxidative mechanism but also by interfering with pathways mediated by the AGEs-RAGE interaction [48]. Phenolics are able to trap active di-carbonyl compounds forming additional products and consequently exerting an important role in scavenging. For example, curcumin, by forming curcumin-MGO adducts, can directly capture MGO [49]. Thus, phenolic compounds appear to be promising candidates for the management of AGEs which can be indeed relevant in diabetes and diabetic complications.

Inflammation in Diabetes

Inflammation is our body's physiological response to infections or tissue damage. There are two primary categories of inflammation: acute and chronic. Acute inflammation arises within minutes, hours, and days, while chronic inflammation is a long-term response occurring over several months and even years. Inflammation is a self-limiting process, in which the anti-inflammatory mediators production closely follows the pro-inflammatory mediators production. This physiological process, in some cases, gets out of control and becomes harmful when the acute inflammation switches to chronic inflammation [50]. Notably, inflammation arising in organs like the liver or adipose tissue has a key role in the development of metabolic diseases, including diabetes [51]. Several studies provide evidence supporting the role of inflammation in both the initiation and progression of diabetes. Indeed, the activation of pro-inflammatory pathways in insulin target cells can contribute to insulin resistance and related metabolic disorders [52]. The connection between inflammation and diabetes has attracted increasing research interest in targeting inflammation to improve DM and DM-related disorders.

Inflammation in Type 1 Diabetes Mellitus

T1DM is a chronic disease in which insulin-producing pancreatic β-cells are destroyed selectively by the immune system. While it is unclear what the initiating factors are, it is known that in T1DM several immune cells cooperate in β-cell destruction [53]. Cells mediating both innate and adaptive immunity infiltrate Langerhans islets, leading to an aberrant inflammatory process called "insulitis", which is one of the main hallmarks of the pathogenesis of T1DM [54]. The infiltrating cells, mainly macrophages and T-lymphocytes, in tight cooperation, release pro-inflammatory cytokines, believed to be key factors in β-cell impairment. Macrophages, through the secretion of both Interleukin-1β (IL-1β) and Tumor Necrosis Factor-α (TNF-α) are crucial mediators in islet inflammation [52]. At the same time, T-lymphocytes appear to play a key role in T1DM progression; in particular, the T helper cell phenotype Th1 promotes diabetes progression through the secretion of interferon-γ (INF-γ) and the recruitment of cytotoxic CD^{8+} T lymphocytes [55]. The synergistic effect of IL-1β, TNF-α and INF-γ acts on β-cells through specific receptors and induces signal transduction pathways. These inflammatory molecules represent important factors in β-cell damage since they activate the transcription factor (NF-κB). Albeit a basal activity of NF-κB is essential for maintaining the β-cell normal function, its excessive activation can result in the upregulation of inducible nitric oxide synthase (iNOS), which determines an overproduction of NO, leading to β-cells cytotoxicity. Moreover, IL-1β activates c-Jun N-terminal kinase (JNK), a member of the (MAPKs), which plays an important role in the β-cell loss [55]. Therefore, multiple inflammatory pathways may contribute to the induction of impaired pancreatic β-cells survival in T1DM. In this context, the identification of compounds that target inflammation appears to be of pivotal importance, as they could aid in the management of T1DM.

Inflammation in Type 2 Diabetes Mellitus

T2DM is a complex metabolic disorder characterized by chronic insulin resistance and pancreatic β-cells mass and function losses. It represents 90% of all cases of diabetes and represents a serious public health concern worldwide. Obesity is often associated with an increased risk of T2DM, and both are known to have an inflammatory component. Several cytokines and inflammatory signaling pathways are involved in the development of T2DM and its complications. Insulin resistance is the decrease in insulin-stimulated glucose uptake. The mechanisms hypothesized to explain insulin resistance, such as oxidative stress, endoplasmic reticulum stress, lipotoxicity and glucotoxicity, can be associated with an inflammatory response. Pancreatic β-cells can compensate for insulin resistance by enhancing their mass and the insulin secretory activity. However, when the expansion of β-cells is no longer sufficient to produce adequate levels of insulin, overt T2DM develops [56]. The state of low-grade inflammation of both pancreatic islets and insulin target organs, such as the liver, adipose tissue, and muscle is a typical feature of T2DM. Macrophages take an active part in the onset and development of inflammation [57]. Macrophages in pancreatic islets, through the secretion of IL-1β, stimulate insulin secretion, to compensate insulin resistance and promote β-cell proliferation. However, an excessive or prolonged secretion of IL-1β, through the activation of different molecular pathways, leads to a decrease in β-cell mass and impairs their function [12]. The liver, adipose tissue, and muscle represent the principal sites of inflammation in T2DM. Macrophage infiltration in these tissues leads to the production of pro-inflammatory cytokines that promote insulin resistance by interfering with insulin signaling [58]. In this
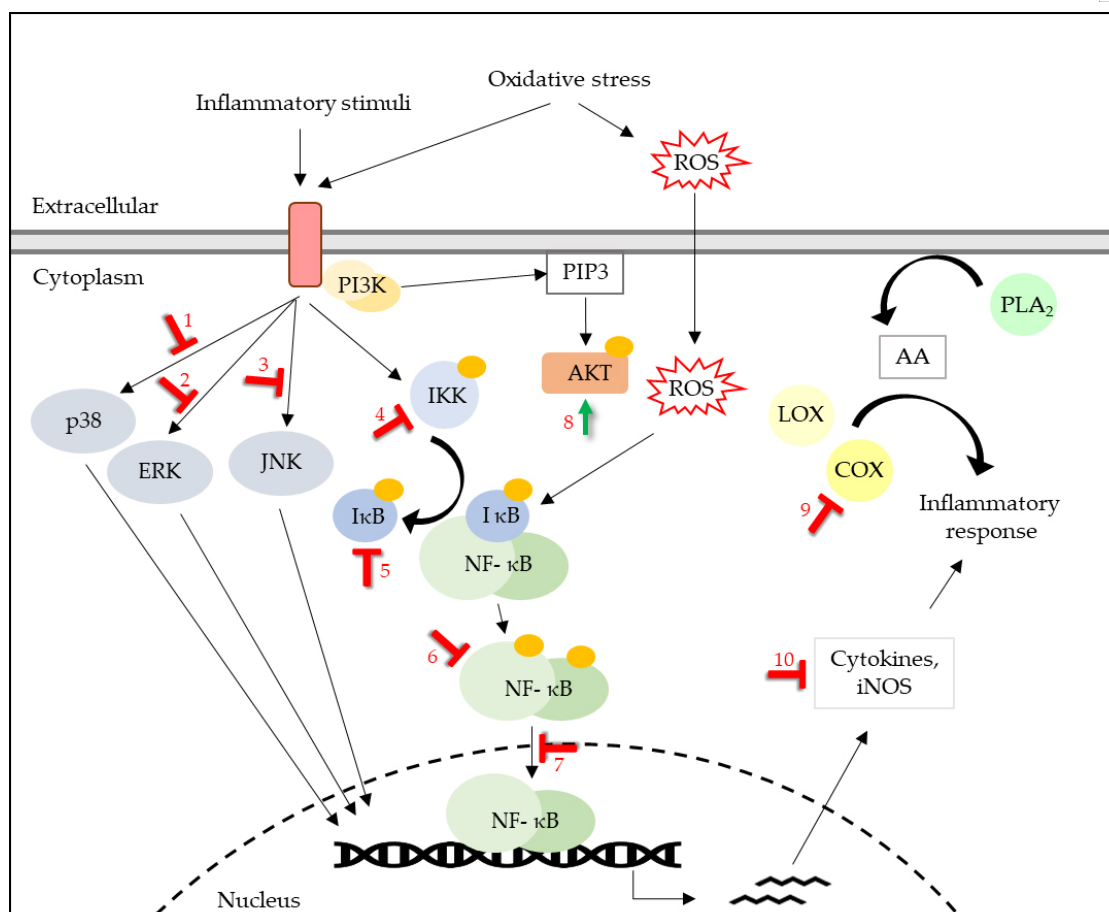
Fig. 3. Inflammation-associated signaling pathways modulated by phenolic compounds. Phenolic compounds, widely distributed in plants, have many therapeutic effects due to both their antioxidant capacity, and their modulation capacity across a broad range of inflammation-associated signaling pathways. This figure summarizes the inflammatory signaling pathways modulated by different phenolics and their action on inflammatory mediators production. Red bars indicate phenolic compounds targets. Numbers indicate examples of reviewed phenolic compounds acting on the corresponding target. 1: quercetin [59]; 2: punicalagin [60]; 3: ellagic acid [61]; 4: piceatannol [62]; 5: carnosol [63]; 6: morin [64]; 7: kurarinone and kuraridin [65]; 8: epigallocatechin-3-gallate [66]; 9: oleocanthal [67]; 10: genistein [68]. AA, arachidonic acid; COX, cyclooxygenase; AKT, protein kinase B; ERK, extracellular signal-regulated kinase; IκB, inhibitor of κB; iNOS, inducible nitric oxide synthase; IKK, IκB kinase; JNK, c-Jun N-terminal kinase; LOX, lipoxygenase; NF-κB, nuclear factor-κB; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PI3K, phosphatidylinositol 3-kinase; PLA$_2$, phospholipase A$_2$; ROS, reactive oxygen species (drawn with MS Office 365 ProPlus Power Point, Microsoft, Redmond, Washington, U.S.).

scenario, the inhibition of inflammatory cytokines appears to be an important step for treating T2DM. Therefore, the anti-inflammatory effects of phenolic compounds may be of great importance.

Anti-Inflammatory Role of Phenolic Compounds on Specific Inflammatory Pathways

Natural compounds with anti-inflammatory capacity are gaining considerable attention. In particular, several research studies have shown that phenolics were able to modulate different cell signaling pathways associated with inflammation (Fig. 3, Ref. [59–68]) [69], thus prevent-

ing the development of inflammatory disorders [70]. The main pathways affected by polyphenols are represented by the arachidonic acid (AA) dependent pathway, NF-κB signaling pathway, MAPKs pathway and phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathway. Understanding the mechanistic effects of polyphenols on inflammatory-related signaling pathways is a crucial step for their future utilization in the prevention or treatment of inflammatory diseases, such as diabetes.

Phenolic compounds have multiple mechanisms of action related to their chemical structure. The structure-activity relationship explains an effect on specific pathways, in some cases [71]. Table 1 (Ref. [59–62,64–68,72–96]) summarizes the selected phenolics and enriched extra-

Table 1. Effect of phenolic compounds on inflammatory-related signaling pathways.

Phenolic compounds or phenolic extracts	Biological assay	Results	References
Oleocanthal	*In vitro*: enzyme inhibition assay	Inhibited COX-1 and COX-2 activity	[67]
Isoliquiritigenin	*In vivo*: 1-methyl-4-phenylpyridinium (MPTP)-induced mice	Inhibited COX-2	[72]
	In vitro: LPS-treated RAW 264.7 macrophages	Down-regulated COX-2, iNOS and pro-inflammatory cytokines (IL-6, and TNF-α)	[73]
Aiphanol	*In vitro*: enzyme inhibition assay	Inhibited COX-1 and COX-2 activity	[74]
Naringenin	*In vivo*: alloxan-induced diabetic rats	Inhibited NO production	[75]
Fisetin	*In vitro*: LPS-stimulated macrophage-like cells	Down-regulated iNOS and NO release	[76]
Glycine max isoflavones (genistein, daidzein and glycitein)	*In vitro*: LPS-stimulated RAW 264.7 cells	Suppressed NO production	[77]
Genistein	*In vitro*: LPS-induced macrophages	Inhibited NO, IL-6 and iNOS production	[68]
	In vivo: alloxan-induced diabetic mice	Inhibited iNOS production	[78]
Caffeic acid phenethyl ester	*In vivo*: STZ-induced Wistar rats	Inhibited NO and iNOS production	[79]
Ferulic acid	*In vivo*: STZ-induced albino rats	Modulated NOS isoforms	[80]
Resveratrol	*In vitro*: pancreatic β cells	Suppressed iNOS and NO production	[81]
Hydroxytyrosol and tyrosol	*In vitro*: LPS-stimulated CaCo-2 cells	Inhibited NO release and iNOS expression	[82]
Piceatannol	*In vitro*: RAW 264.7 cells	Inhibited IKK-α and β phosphorylation	[62]
Morin	*In vitro*: high glucose-induced mouse neuroblastoma cell line (N2A)	Reduced the expression of phospho-p65	[64]
Kurarinone and kuraridin	*In vitro*: LPS-induced RAW 264.7 cells	Inhibited NF-κB p65 translocation	[65]
Quercetin	*In vitro*: 3T3-L1 adipocytes and RAW 264.7 macrophages	Inhibited ERK1/2, JNK and p38/MAPK	[59]
	In-silico study	Targeted MAPK	[83]
Punicalagin	*In vitro*: LPS-induced RAW 264.7 macrophages	Reduced pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) through the suppression of p38, ERK and JNK phosphorylation levels	[60]
Curcumin	*In-silico* study	High affinity towards p38	[84]
	In vitro: HepG2 cells	Inhibited JNK and p38 pathways	[85]
Rosmarinic acid	*In vivo*: HFD-STZ-induced T2DM Wistar albino rat model	Reduced blood glucose, AGEs, IL-1β, TNF-α, IL-6, p-JNK, p38 and NF-κB levels	[86]
Ellagic acid	*In vitro*: HAEC cells	Inhibited ERK activation and ROS production	[87]
	In vitro: LPS-induced bone marrow-derived dendritic cells	Inhibited JNK activity	[61]
Chrysin	*In vitro*: high glucose-stimulated chorioretinal endothelial cells	Down-regulated phosphorylated ERK, and AKT	[88]

Table 1. Effect of phenolic compounds on inflammatory-related signaling pathways.

Phenolic compounds or phenolic extracts	Biological assay	Results	References
Vitexin	*In vitro*: INS-1 pancreatic β-cells	Inhibited p38 activation	[89]
	In vitro: LPS-elicited RAW 264.7 macrophages	Down-regulated p-p38, p-ERK1/2 and p-JNK	[90]
Epigallocatechin-3-gallate	*In vitro*: L6 skeletal muscle cells	Enhanced the glucose uptake through PI3K/AKT	[66]
Baicalein	*In vitro*: HepG2 cells	Enhanced the glucose uptake through the regulation of InsR/IRS-1/PI3K/AKT	[91]
	In vivo: diabetic cardiomyopathy rats	Regulated the oxidative stress through PI3K/AKT	[77]
Oleuropein	*In vitro*: 3T3-L1 cells *In vivo*: high-fat diet-fed rats	Improved insulin sensitivity via PI3K/AKT	[92]
Ferulic acid	*In vivo*: STZ-induced Wistar rats	Improved diabetic cardiomyopathy and GLUT4 translocation by the activation of PI3K/AKT	[93]
Nobiletin	*In vitro*: murine 3T3-F442A adipocytes	Improved the glucose uptake via PI3K/AKT	[94]
Tangeretin	*In vitro*: murine 3T3-F442A adipocytes	Improved the glucose uptake via PI3K/AKT	[94]
Didymin	*In vitro*: HepG2 cell line	Improved glucose uptake, activation of IRS-1 and PI3K and AKT	[95]
Hesperetin	*In vitro*: HepG2 cell line	Reduced hepatic ROS overproduction and oxidative damage by PI3K/AKT	[96]

LPS, lipopolysaccharide; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α; MAPK, mitogen-activated protein kinase; AGEs, advanced glycation end-products; IRS, insulin receptor substrate; STZ, streptozotocin; GLUT4, glucose transporter type 4.

cts examined in the present review, in relation to the pathways on which they have been reported to exert an action and the biological assay used for the evaluation.

Inhibition of Arachidonic Acid Pathway

AA is an important constituent of cell membranes and modulates cell membrane fluidity. AA is released by membrane phospholipids through the action of phospholipase A_2 (PLA_2) and can be metabolized by cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 (CYP) enzymes, to produce metabolites involved in essential biological functions. COX enzymes, which generate prostanoids, exist in two different isoforms: COX-1 and COX-2. COX-1 is constitutively expressed in several cell types and is the major source of prostanoids for basal functions [97]; instead, COX-2 is an inducible enzyme, highly expressed in inflammatory cells such as macrophages after pro-inflammatory cytokines or lipopolysaccharide (LPS) stimulation [98]. However, both enzymes can contribute to the generation of homeostatic prostanoids, as well as to inflammation-related prostanoids [97]. LOX enzymes generate hydroxy acids and leukotrienes and have been found in several cells and tissues. Among their products, hydroxyeicosatetraenoic acids are able to induce inflammatory response [98]. CYPs belong to a large and complex family of enzymes able to generate a broad spectrum of products including hydroxyeicosatetraenoic acids [97]. Phenolic compounds have been found to inhibit these enzymes, thus exerting an important anti-inflammatory action. Oleocanthal, an olive phenolic compound, is mainly responsible for the stinging sensation in the throat typical of extra virgin olive oils. Notably, it shows functional similarities with the anti-inflammatory drug ibuprofen. Beauchamp et al. [67], found that oleocanthal, like ibuprofen, was able to inhibit COX-1 and COX-2 activities; moreover, oleocanthal inhibits these enzymes in a dose-dependent way and significantly more than ibuprofen at equimolar concentrations. In specific, (-)oleocanthal at a concentration of 100 µM inhibits COX-1 and COX-2 activity by 83.5% and 70.9% respectively, at 25 µM inhibits by 56.1% and 56.6% respectively, and at 7 µM inhibits by 24.6% and 14.5% respectively. Instead, ibuprofen at a concentration of 25 µM inhibits COX-1 and COX-2 activity by 17.8% and 12.7% respectively, and at 7 µM inhibits by 0% and 1.3% respectively [67]. Isoliquiritigenin is a flavonoid isolated from the roots of different Glycyrrhiza species, such as licorice (Glycyrrhiza glabra) and Mongolian licorice (Glycyrrhiza uralensis). Bai et al. [72], highlighted that this compound prevented the upregulation of COX-2 in 1-methyl-4-phenylpyridinium (MPTP)-induced mice. In another study, Kim et al. [73] evaluated the anti-inflammatory effects of isoliquiritigenin isolated from the roots of Glycyrrhiza uralensis in LPS-treated RAW 264.7 macrophages. Results showed that it was able to reduce the expression of COX-2 and iNOS at protein and mRNA

levels in a dose-dependent way. In the same study, it was found that isoliquiritigenin lowered the expression of TNF-α and IL-6 [73]. Aiphanol, a stilbenolignan isolated from the seeds of Aiphanes aculeata, showed a significant inhibitory activity against COX-1 and COX-2 with IC_{50} values respectively of 1.9 and 9.9 µM [74]. Morus alba, which belongs to the Moraceae family, is widely utilized for its anti-diabetic activity in traditional Chinese medicine. Research studies confirmed its antidiabetic potential, indeed, as evidenced by Zhou et al. [99], extracts from roots, twigs, leaves, and fruits of M. alba displayed significant hypoglycemic activity in the high-fat diet/STZ-induced T2DM mouse model. In particular, morusin, which represents the main compound identified from the roots extract, displayed a broad activity in reducing blood glucose levels [99]. Thus, the outcomes mentioned underline the role of phenolic compounds in the direct inhibition of this pathway (Fig. 3 and Table 1), demonstrating a potential therapeutic role in improving the inflammatory status relevant to diabetes.

Modulation of Nitric Oxide Synthase (NOS) Family

NO, a cellular signaling molecule fundamental in both physiological and pathological processes, is produced from L-arginine by the NOS enzymes family. The latter consist of three isoforms: endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS). Small amounts of NO, synthesized by eNOS and nNOS, are necessary for maintaining cell homeostasis. However, a substantial increase of NO, synthesized by iNOS, often occurs in inflammatory-related diseases, such as liver diseases, insulin resistance and obesity. Several phytochemicals have been shown to reduce NO production by iNOS. Among these, phenolic compounds appear to be very promising as anti-inflammatory agents and their effects on iNOS activity have been investigated [98]. Naringenin, mainly found in grapefruit (Citrus paradisi), tomato (Solanum lycopersicum) and orange (Citrus sinensis) possess several pharmacological activities, such as anti-inflammatory, anti-diabetic, and antioxidant effects [100]. Naringenin has been reported to reduce NO production in an alloxan-induced diabetes model in rats [75]. Fisetin belongs to the flavonoid family, it is widely found in several fruits and vegetables like strawberry (Fragaria ananassa), mango (Mangifera indica), and onion (Allium cepa). It is known for its antioxidant, anti-inflammatory, and anti-proliferative activities. Fisetin, at 20 or 30 µM, was found to be able to reduce the mRNA levels of iNOS and the release of NO in lipopolysaccharide (LPS)-stimulated macrophage-like cells [76]. As reported by Sheu et al. [77] soy isoflavones (genistein, glycitein and daidzein) were capable of suppressing NO production in LPS-stimulated RAW 264.7 cells. Among them, genistein showed a stronger suppressive effect on iNOS activity than the other isoflavones [77]. Similarly, Choi et al. [68] evidenced a broad and dose-dependent inhibition of NO and IL-6 production, iNOS protein and RNA expres-

sion of genistein in LPS-treated macrophages. In particular, authors evidenced that at a concentration of 50 μM genistein blocked the secretion of NO (83%) and IL-6 (91%) induced by LPS and that was also able to down-regulate the expression of iNOS with a dose-dependent behaviour (from 5 to 50 μM treatments) [68]. Moreover, another study in alloxan-induced diabetic mice aimed at the evaluation of genistein role during the early inflammatory stage of cutaneous wound healing, demonstrating that genistein improved wound healing rate. It was also reported a reduction of iNOS protein levels with an overall amelioration of both anti-inflammatory and antioxidant defence systems [78]. Caffeic acid phenethyl ester, which can be found in buds' resinous exudates of different species of Populus, mainly *Populus nigra*, is known for its biological properties, such as antioxidant, anti-inflammatory, and immunomodulatory activities. It acts on a number of biochemical pathways involved in the modulation of inflammation and oxidative stress. It was shown that caffeic acid phenethyl ester (10 μM kg^{-1} day^{-1}) significantly decreased the levels of NO induced by diabetes and suppressed the mRNA expression of inflammatory cytokines and iNOS in diabetic rats brain; thus, caffeic acid phenethyl ester might alleviate diabetes-induced complications in the brain, suppressing inflammation and restoring redox state of brain cells [79]. Ferulic acid, a phenolic acid isolated for the first time from *Ferula foetida* (Apiaceae) is widely distributed in vegetables and fruits and has a strong antioxidant and anti-inflammatory activity. Ferulic acid treatment was capable of improving the degenerative changes induced by diabetes of rat cerebellum thanks to its antioxidant effect and the capability to modulate NOS isoforms; indeed, the treatment with ferulic acid (10 mg/kg) attenuated the increase of iNOS but did not affect eNOS expression. Moreover, the authors observed an increase of nNOS, which can be related to the influence of ferulic acid on insulin levels [80]. Resveratrol is a phenolic compound mainly found in plant sources such as *Polygonum cuspidatum* and *Vitis vinifera*, known for its wide range of health properties, especially related to oxidative stress protection. Resveratrol, besides its strong antioxidant properties, has significant relevance against inflammatory-related disorders and diabetes. The beneficial effects of resveratrol seem to be due to the action on inflammatory cellular pathways and pro-inflammatory factors [101]. Lee *et al*. [81] highlighted the role of this phenolic compound in improving inflammatory injury in rat pancreatic islet cells exposed to cytokines. Resveratrol not only suppresses iNOS and decreases NO production but also restores the secretory function of islet cells [81]. Moreover, it was reported that resveratrol is active against LPS-induced inflammation in RAW 264.7 macrophages inhibiting both the formation of NO (IC$_{50}$ of 21.5 ± 3.2 μM) and iNOS (IC$_{50}$ of 18.8 nM) expression [97]. Hydroxytyrosol and tyrosol, two phenolic compounds present in Olive (*Olea europaea*) oil, have been extensively studied for their important ben-

eficial effects. These molecules are well known for their antioxidant capacity; moreover, they can modulate molecular pathways involved in inflammatory process. Serreli *et al*. [82] evidenced that these compounds, tested both at a biologically relevant concentration (1 μM), inhibited NO release, acting as inhibitors of iNOS expression, in LPS-stimulated CaCo-2 cells. The literature data indicate that phenolics might significantly help to modulate NO over-production and NOS enzymes expression (Fig. 3 and Table 1), thus playing a key role in decreasing oxidative stress and chronic inflammation, both tightly linked to diabetes pathophysiology.

Modulation of NF-κB Pathway

NF-κB are highly conserved transcription factors that play key roles in immune reactions, inflammation, and cancer. NF-κB controls the expression of many genes related to inflammation [102]. NF-κB, a heterodimer formed by the p65 and p50 subunit, in its basal form is bound to the inhibitor IκB, which confines NF-κB into the cytoplasm. The phosphorylation of IκB, mediated by several stimuli such as TNF-α or IL-1, permits the release of NF-κB in the active form, which translocates into the nucleus. Subsequently, NF-κB induces the transcription of proinflammatory cytokines and other genes involved in transcription, apoptosis, and cell proliferation processes [18]. NF-κB is strongly connected to MAPK in the regulation of inflammatory responses. Several polyphenols downregulate NF-κB activation reducing inflammation [102]. Therapeutic approaches based on dietary phenolic compounds are gaining interest as alternative treatment choices against chronic inflammatory ailments thanks to their effectiveness and non-toxic nature [103]. For example, resveratrol administration to obese mice improved hyperinsulinemia via modulation of hypothalamic NF-κB inflammatory signaling [104]. The activation of the NF-κB pathway, at early stages, requires the phosphorylation of IκB kinase (IKK). The stilbene piceatannol, mainly present in grapes (*Vitis vinifera*) and passion fruit (*Passiflora edulis*) can inhibit IKK phosphorylation [105]. Islam *et al*. [62] demonstrated, in LPS-stimulated RAW 264.7 cells, that piceatannol (50 μM) inhibits IKK-α and β phosphorylation, which might stop successive IκB activation and degradation, and lastly NF-κB activation. After its activation, IKK phosphorylates IκB, which is then eliminated through the proteasome. Several phenolic compounds can inhibit IκB phosphorylation. Carnosol is a phenolic compound that derives from the oxidative degradation of carnosic acid. It is found in several herbs such as sage (*Salvia officinalis*) and rosemary (*Rosmarinus officinalis*). It was found to inhibit the degradation of IκB-α [63]. Moreover, the phosphorylation of the p65 subunit of the NF-κB complex and the consequent translocation to the nucleus are other crucial points in the activation of the NF-κB pathway. Morin is a flavonoid isolated from members of Moraceae family,

also found in Indian guava (*Psidium guajava*), onion (*Allium cepa*), and almond (*Prunus dulcis*). Morin has several pharmacological properties, such as anti-inflammatory, anti-cancer, antioxidant, and anti-diabetic properties. It has been reported that it is able to inhibit inflammatory responses through the downregulating NF-κB signaling pathway [106]. Bachewal *et al.* [64] explored the pharmacological effect of morin against mitochondrial ROS generation mediated by a metabolic excess and the corresponding effect on NF-κB pathway in STZ-induced diabetic rats and high glucose-induced mouse neuroblastoma cell line (N2A). Results on N2A cells showed that morin effectively counteracts NF-κB-mediated neuroinflammation by lowering ROS production. Moreover, the authors highlighted that high glucose-induced neuroinflammation in N2A cells significantly increased the phosphorylation of the p65 subunit (ser536) and the treatment with morin at a 20 mM dose decreased this inflammatory response by reducing the expression of phospho-p65 [64]. Furthermore, the inhibition of NF-κB translocation into the nucleus was reported for several compounds in association with an anti-inflammatory effect. Kurarinone and kuraridin are two flavonoids mainly present in *Sophora flavescens*. These compounds, known for their anti-inflammatory activities, were found to be active against NF-κB translocation; indeed, the treatment of LPS-stimulated RAW 264.7 cells with pure kurarinone and kuraridin, both at 20 and 40 μM, inhibited LPS-induced translocation of NF-κB p65 [65]. These observations underline the capacity of phenolic compounds to inhibit NF-κB signaling pathway at different crucial points (Fig. 3 and Table 1). Given that this pathway is considered the principal modulator of the inflammatory process, its inhibitors play a pivotal role in the development of new anti-inflammatory drugs, eventually also targeting diabetes pathophysiology.

Modulation of MAPK Pathway

MAPKs are highly conserved members of protein kinases which transduce signals involved in several cellular activities. They respond to several extracellular stimuli [70]. Aberrant conditions of MAPKs have been related to different inflammatory-related diseases, such as diabetes and obesity. The best-known MAPKs are the Extracellular signal-Regulated Kinases (ERK), p38 and c-Jun N-terminal Kinase (JNK) MAPKs families [107]. ERK signal transduction pathway is involved principally in cell growth, survival, and differentiation. JNK signaling participates in many physiological responses, such as cell growth, differentiation, and apoptosis, while p38 mediates important cellular processes, like cell differentiation, inflammation, cell death, and tumorigenesis [70]. Several studies reported the inhibitory effect of phenolic compounds on ERK, JNKs and p38, leading to a decrease in proinflammatory mediators, such as TNF-α [108]. Quercetin, a flavonoid mainly presents in *Houttuynia cordata*, *Cap-*

paris spinosa and *Allium cepa*, has a wide range of therapeutic effects, such as anti-inflammatory and antioxidant effects. It has been found that quercetin treatments (6.25, 12.5 and 25 μM) inhibit the MAPK signaling factors p38, ERK1/2 and JNK in both 3T3-L1 adipocytes and RAW 264.7 macrophages [59]. Moreover, a recent *insilico* study highlighted that quercetin might have therapeutic applications in T2DM by targeting the MAPK signaling pathway. Indeed, through molecular dynamic simulation studies some potential molecular mechanisms, relevant to T2DM treatment, in which quercetin can interfere were found. Among them, the MAPK signaling pathway appears to be the core target of quercetin [83]. Punicalagin, an ellagitannin found mainly in the peel of pomegranate (*Punica granatum*), has been reported to have beneficial effects on inflammation, it is indeed able to reduce the production of pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) through the suppression of p38, JNK and ERK phosphorylation levels in LPS-induced RAW 264.7 macrophages [60]. Curcumin, a polyphenol derived from the rhizomes of *Curcuma longa*, is known for its antioxidant and anti-inflammatory properties [109]. A growing body of literature highlights the anti-inflammatory effects of curcumin; in particular, its protective effect appears to be related to the inhibition of the p38/MAPK signal pathway [110]. A molecular docking study by Selim *et al.* [84] revealed a high affinity towards p38. Moreover, curcumin was found to effectively reduce BPA-induced insulin resistance in HepG2 cells through the inhibition of JNK and p38 pathways [85] and also Kahkhaie *et al.* [111] reported curcumin to inhibit inflammation through NF-κB signaling pathway. Interestingly, also p38 inhibitors reduced the activation of NF-κB; thus, curcumin can act as an anti-inflammatory not only through the inhibition of NF-κB upstream activators, like p38, but also via its direct interaction with NF-κB [111]. Rosmarinic acid is an ester of caffeic acid and 3,4-dihydroxyphenyllactic acid. It was isolated for the first time from *Rosmarinus officinalis*, however, it represents one of the main bioactive components of several other medicinal plants, such as *Salvia officinalis*, *Thymus vulgaris* and *Mentha piperita*. The anti-diabetic effect of rosmarinic acid was studied in a high-fat diet (HFD)-STZ-induced T2DM Wistar albino rat model. Results showed that oral administration of rosmarinic acid (100 mg/kg) increased insulin sensitivity index and reduced blood glucose, AGEs, IL-1β, p38, TNF-α, IL-6, p-JNK, and NF-κB levels [86]. Ellagic acid is a phenolic compound found in many fruits, such as raspberries (*Rubus idaeus*), strawberries (*Fragaria ananassa*), pomegranates (*Punica granatum*) and peaches (*Prunus persica*), and seeds such as pecans (*Carya illinoinensis*) and walnuts (*Juglans regia*). It has strong antioxidant and anticancer properties as well as anti-inflammatory effects. It has been observed that ellagic acid inhibited high glucose-induced ERK activation and decreased vascular ROS production human aortic endothelial cells (HAEC) [87]. More-

over, ellagic acid was found to be able to reduce the JNK activity and pro-inflammatory cytokines levels in LPS-induced bone marrow-derived dendritic cells [61]. Chrysin, a flavonoid widely present in propolis, honey and passion fruit (*Passiflora edulis*), was found to be able to down-regulate phosphorylated ERK, and AKT in high glucose-stimulated chorioretinal endothelial cells [88]. Vitexin, a phenolic compound found in many plants such as buck-wheat (*Fagopyrum esculentum*), hawthorn (Crataegus spp.) and mung bean (*Vigna radiata*), has several pharmacological effects [112]. In a study on INS-1 pancreatic β-cells the treatment with vitexin (50 µM) alleviates LPS-induced damage by decreasing the levels of pro-inflammatory cytokines and, also, suppresses the activation of p38 [89]. Rosa *et al*. [90], investigating the mechanisms involved in the anti-inflammatory effect of vitexin, evidenced that it was able to reduce the releases of TNF-α, NO, IL-1β, PGE2 and to increase IL-10 release in LPS-elicited RAW 264.7 macrophages. Furthermore, it was shown that vitexin treatments at 25, 50 and 100 µg/mL downregulated the expression of p-p38, p-ERK1/2 and p-JNK. The highest effects were reported with 25 µg/mL for p38 (39.2%) and JNK (75.1%) and at 50 µg/mL (81.2%) for ERK1/2, relative to the respective LPS group [90]. These findings highlight the ability of several phenolic compounds to downregulate MAPK pathways (Fig. 3 and Table 1), providing evidence for a protective role of these bioactive molecules against inflammation-related diseases.

Modulation of P13K/AKT Pathway

PI3K/AKT signaling pathway plays a fundamental role in numerous cellular processes involving survival, proliferation, and metabolism. PI3K/AKT pathway is considered to be the main effector of the insulin action [113]. The activated PI3K catalyzes the conversion of phosphatidylinositol (4,5)-phosphate (PIP2) into phosphatidylinositol (3,4,5)-phosphate (PIP3). PIP3 stimulates the phosphoinositide-dependent protein kinase 1 (PDK1), which in turn stimulates the activation of AKT. AKT (or protein kinase B, PKB) is one of the main targets of PI3K and PDK1 [70]. Under physiological conditions insulin initiates PI3K/AKT signaling pathway, increasing glucose uptake and reducing gluconeogenesis in the liver and muscle, and increasing body lipid deposition in adipose tissue and insulin production in the pancreas. However, the PI3K/AKT pathway is suppressed when an excessive energy intake occurs, thus causing insulin resistance that could lead to the development of T2DM [114]. Therefore, this pathway is an interesting target for antidiabetic agents. Phenolic compounds can modulate several targets in PI3K signaling such as AKT and PDK-1 [115]. Epigallocatechin-3-gallate (EGCG) is one of the main active ingredients of green tea (*Camellia sinensis*). Several studies demonstrated its broad antioxidant activity, moreover, a growing body of evidence indicates that EGCG has anti-obesity properties and can improve glucose tolerance and increase glucose-stimulated insulin secretion [116]. As reported by Xu *et al*. [66], EGCG can enhance glucose uptake via PI3K/AKT signaling pathway in L6 skeletal muscle cells; in particular, cells treated with EGCG increased AKT phosphorylation (Ser473) in a dose-dependent way, with the highest response at 50 µM, thus highlighting its role as a promising antidiabetic agent. Baicalein is a flavonoid compound derived principally from the roots of *Scutellaria baicalensis* and *Scutellaria lateriflora*. The antidiabetic effect of baicalein derives mainly from its hypoglycemic, hypolipidemic, anti-oxidative, anti-inflammatory properties and from improving β-cell function. These effects may involve the regulation of several signaling pathways, among which PI3K/AKT signaling. Indeed, it is reported that baicalein treatment (from 10^{-8} to 10^{-5} mol/L) could increase glucose consumption, exerting significant anti-insulin resistance effects on HepG2 cells by the regulation of InsR/IRS-1/PI3K/AKT signaling pathway [91]. Moreover, baicalein was found to be active in alleviating diabetic complications in animal models. Ma *et al*. [117] highlighted the role of baicalein against the damage from oxidative stress and inflammation in diabetic cardiomyopathy rats, treated with 100 mg/kg and 200 mg/kg, as well as the role of PI3K/AKT signaling pathway in mediating these effects. Oleuropein is one of the main secoiridoids found in the leaves and fruits of olive trees (*Olea europaea*). A growing body of evidence demonstrates the role of oleuropein as a potential agent against metabolic syndrome [118]. In a recent work by Hadrich *et al*. [92] the role of oleuropein in improving insulin sensitivity in 3T3-L1 cells and high-fat diet-fed rats was shown. The *in vivo* model showed that oleuropein might exert its activity via PI3K/AKT signaling pathway. Ferulic acid, as previously mentioned, can protect the functionality of the diabetic rat cerebellum through NOS-mediated mechanisms. Additionally, another study suggested that ferulic acid improved diabetic cardiomyopathy in STZ-induced Wistar rats; it was able to ameliorate the translocation of glucose transporter type 4 (GLUT4) to the cardiac membrane through the activation of PI3K/AKT signaling cascade [93]. Among phenolic compounds, citrus flavonoids are valuable antidiabetic substances since they can modulate signaling pathways related to glucose uptake [119]. Nobiletin is a flavone found in citrus fruits peel, such as orange (*Citrus sinensis*) and tangerine (*Citrus reticulata*). It has shown important medicinal properties in the prevention of severe pathologies, such as T2DM and cancer. In addition, it was reported that nobiletin improved glucose uptake in a dose-dependent behaviour (5–50 µM) in murine 3T3-F442A differentiated adipocytes through the PI3K/AKT signaling pathway. In the same study the authors reported that tangeretin, another phenolic compound from peels of orange and tangerines, was able to increase glucose uptake in a dose-dependent manner (5–50 µM) in differentiated adipocytes by the PI3K/AKT pathway [94].

The concentrations utilized in the mentioned study appear to be consistent with the pharmacological doses that can be utilized *in vivo*; indeed, a pharmacokinetic study on nobiletin revealed that the oral administration of a dose of 50 mg/kg in Winstar rats gave a serum concentration of around 10 μg/mL [120], equal to approximately 25 μM of nobiletin [94], moreover, Lee *et al*. [121] highlighted that the oral administration of 200 mg/kg nobiletin reduced the body weight and glucose levels in *ob/ob* mice. These pharmacological effects underline the important anti-diabetic action of nobiletin. Furthermore, didymin is a bioactive compound found in lemon (*Citrus limon*), grapefruit, mandarin (*Citrus reticulata*) and bergamot (*Citrus bergamia*). Ali *et al*. [95] evaluated its antidiabetic potential in the insulin-resistant HepG2 cell line. Didymin significantly increased glucose uptake and, in addition, activated insulin receptor substrate (IRS)-1 and enhanced the phosphorylation of PI3K and AKT [95]. Hesperetin is a bitter molecule found mainly in bitter orange (*Citrus aurantium*) and lemon known for its anti-inflammatory and antioxidant properties. Hesperetin, activating the PI3K/AKT pathway in the liver, inhibited NF-κB activation and inflammatory cytokine secretion [96]. The ability of different phenolic compounds to modulate the P13K/AKT pathway (Fig. 3 and Table 1) supports the beneficial effects of these compounds on inflammation processes related to diabetes.

Phenolic Compounds Activity on the Cytokine System

Cytokines are essential proteins that mediate networking communication for the immune system. Cytokines can be produced by lymphocytes or by monocytes, and they can have either pro-inflammatory (IL-1β, TNF-α, IL-2, IL-8, IL-6, IFN-γ) and anti-inflammatory effects (IL-10, TGFβ, IL-4). The balance between pro-inflammatory and anti-inflammatory cytokines is necessary in immune response homeostasis and inflammation [102]. Inflammatory cytokines play a pivotal role in diabetes; indeed, inflammation has emerged as a significant pathophysiological trait. IL-1β, which plays an important role in the regulation of inflammatory responses, in β-cells activates the JNK pathway, which mediates the downregulation of insulin gene transcription; moreover, this cytokine decreases the expression of the insulin receptor substrate (IRS-1), reduces insulin-stimulated glucose uptake and inhibits glucose transporter (GLUT)-4 translocation to the plasma membrane. TNF-α, a pro-inflammatory cytokine produced predominantly by macrophages and monocytes, plays several roles in metabolic disorders. Indeed, it promotes insulin resistance through the downregulation of key genes necessary for insulin action. IL-6 is a multifunctional cytokine expressed in several cell types. IL-6 is responsible for macrophage recruitment to adipose tissue in obesity. Moreover, it exerts long-term inhibitory effects on the gene transcription of IRS-1, PPAR and GLUT4. In humans elevated levels of IL-6 are typical of T2DM [122]. Thus, cytokines represent an interesting therapeutic target. Caffeic acid is a phenolic compound largely found in edible plants, such as potato (*Solanum tuberosum*) and apple (*Malus domestica*). The anti-inflammatory effects of caffeic acid in diabetic mice kidney was investigated, demonstrating upon treatment a reduction of renal levels of IL-6, TNF-α and IL-1β. In the same work, it was evidenced that also ellagic acid decreased the levels of the pro-inflammatory cytokines above mentioned [123]. Daidzin and daidzein are the major isoflavones found in soybean (*Glycine max*). Daidzin is the corresponding glucoside form of daidzein. According to Tan *et al*. [124] these molecules were able to reduce LPS-induced inflammation in RAW 264.7 cells, significantly suppressing IL-6 and slightly TNF-α expression. In addition, in the same work, it was highlighted that daidzin and daidzein are able to modulate MAPK and NF-κB signaling pathways [124]. Cyanidin-3-O-glucoside is an anthocyanin. Its potential effects on diabetic retinopathy were explored indicating that the expression of pro-inflammatory cytokines TNF-α, IL-6, and IL-1β was remarkably suppressed by cyanidin-3-O-glucoside in the STZ-mouse model [125]. In a different study, cyanidin-3-O-glucoside from black rice decreased the TNF-α and NF-κB mRNA levels, as well pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) levels in a rat model of diabetic nephropathy [126]. Sogo *et al*. [127] explored the anti-inflammatory activity of the anthocyanin delphinidin 3-sambubioside, isolated from *Hibiscus sabdariffa*, in LPS-stimulated RAW 264.7 cells. Their results showed that this compound reduced the levels of both inflammatory cytokines IL-6 and TNF-α and inflammatory mediators iNOS and NO. Furthermore, cellular signaling analysis showed that this compound downregulated NF-κB and MEK1/2-ERK1/2 signaling pathways [127]. Honokiol is a phenolic compound isolated from the bark and leaves of different *Magnolia* spp. It was able to improve hepatic inflammation, decreasing TNF-α and IL-6 expression, in type 2 diabetic mice [128]. Additional research demonstrated that honokiol treatment inhibited the high glucose-induced expression of inflammatory cytokines IL-1β, IL-18 and TNF-α in a dose-dependent way in human renal mesangial cells [129]. Various phenolic compounds, thus, proved to be helpful in preventing inflammatory diseases related to the overproduction of inflammatory cytokines.

Conclusions

DM is a complex metabolic disorder and at a global scale the number of people suffering from this syndrome is steadily rising, leading to alarming adverse health and socioeconomic repercussions. A complete understanding of the pathophysiological mechanisms is essential to develop novel approaches to tackle this disease. Oxidative stress,

along with chronic inflammation, participates in the development of metabolic diseases, including diabetes. Currently, the positive correlation between good health and the consumption of plant food is well known: the antioxidant and anti-inflammation abilities of phenolic substances have been broadly studied and their antiglycation effects have also been screened. Therefore, new therapeutic strategies involving the use of different natural products have been explored. Many phenolic compounds have been shown to alleviate inflammation and oxidative stress and this effect is due, to their ability to modulate molecular signaling pathways. Therefore, the combined targeting of multiple inflammation-associated cell signaling networks using phenolic compounds is emerging as a new approach in the prevention, treatment and management of inflammatory-related diseases, such as diabetes and its complications. In this review the inhibitory effects of several phenolic compounds from natural sources on oxidative stress, AA, NO and NOS, NF-κB, MAPK, AGEs and PI3K/AKT cell signaling pathways have been discussed. Notably, interactions or synergistic effects between phenolic compounds within natural extracts or nutraceutical formulations could have multiple effects on various intracellular targets, thus amplifying the pharmacological effect. In this context, the review presented here could be a useful tool to explore novel modular combinations of phenolic compounds that, aiming at multiple key targets, could result in more effective therapeutic approach in inflammatory-related diseases such as diabetes. The results described the promising therapeutic potential of phenolic compounds and open the way to future research perspectives concerning the development of pharmaceutical and nutraceutical formulations for the prevention and treatment of diabetes and related disorders. Indeed, phenolic compounds presented in this review could be used as prophylactic agents or as synergistic components in addition to conventional treatments for DM therapy. Further extensive investigations will be needed to test their combined effect and fully elucidate the molecular mechanisms, the real bioavailability and potential side effects of these compounds. Moreover, *in vivo* studies concerning the standardization of the dosage and the comparison between pure compounds and extracts would be needed in order to yield valuable insights into their therapeutic potential.

Author Contributions

EP took care of the conceptualization. LD, LDG and LSan provided the resources. EP and LSpa wrote and prepared the original draft. EP and LSpa curated the literature review and the preparation of the table and figures. EP, LSpa, LD, LDG and LSan wrote, edited and reviewed the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Tuomi T, Santoro N, Caprio S, Cai M, Weng J, Groop L. The many faces of diabetes: a disease with increasing heterogeneity. The Lancet (London, England). 2014; 383: 1084–1094.

[2] Baynes HW. Classification, Pathophysiology, Diagnosis and Management of Diabetes Mellitus. Journal of Diabetes & Metabolism. 2015; 6: 1–9.

[3] Katsarou A, Gudbjörnsdottir S, Rawshani A, Dabelea D, Bonifacio E, Anderson BJ, et al. Type 1 diabetes mellitus. Nature Reviews. Disease Primers. 2017; 3: 17016.

[4] Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. The Lancet (London, England). 2017; 389: 2239–2251.

[5] Eizirik DL, Pasquali L, Cnop M. Pancreatic β-cells in type 1 and type 2 diabetes mellitus: different pathways to failure. Nature Reviews. Endocrinology. 2020; 16: 349–362.

[6] Szablewski L. Glucose Homeostasis–Mechanism and Defects. In Rigobelo E (eds) In Diabetes—Damages and Treatments (pp. 227–256). InTech. 2011.

[7] Nair GG, Tzanakakis ES, Hebrok M. Emerging routes to the generation of functional β-cells for diabetes mellitus cell therapy. Nature Reviews. Endocrinology. 2020; 16: 506–518.

[8] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010; 33: S62–S69.

[9] Harding JL, Pavkov ME, Magliano DJ, Shaw JE, Gregg EW. Global trends in diabetes complications: a review of current evidence. Diabetologia. 2019; 62: 3–16.

[10] Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Research and Clinical Practice. 2019; 157: 107843.

[11] Aziz KMA. Management of type-1 and type-2 diabetes by insulin injections in diabetology clinics - a scientific research review. Recent Patents on Endocrine, Metabolic & Immune Drug Discovery. 2012; 6: 148–170.

[12] Kong M, Xie K, Lv M, Li J, Yao J, Yan K, et al. Anti-inflammatory phytochemicals for the treatment of diabetes

and its complications: Lessons learned and future promise. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2021; 133: 110975.

[13] Sun C, Zhao C, Guven EC, Paoli P, Simal-Gandara J, Ramkumar KM, et al. Dietary Polyphenols as Antidiabetic Agents: Advances and Opportunities. Food Frontiers. 2020; 1: 18–44.

[14] Wang Y, Alkhalidy H, Liu D. The Emerging Role of Polyphenols in the Management of Type 2 Diabetes. Molecules (Basel, Switzerland). 2021; 26: 703.

[15] Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. Oxidative Medicine and Cellular Longevity. 2009; 2: 270–278.

[16] Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chemico-Biological Interactions. 2006; 160: 1–40.

[17] Pacher P, Beckman JS, Liaudet L. Nitric oxide and peroxynitrite in health and disease. Physiological Reviews. 2007; 87: 315–424.

[18] Dandona P, Chaudhuri A, Ghanim H, Mohanty P. Anti-inflammatory effects of insulin and the pro-inflammatory effects of glucose. Seminars in Thoracic and Cardiovascular Surgery. 2006; 18: 293–301.

[19] Zhang H, Tsao R. Dietary polyphenols, oxidative stress and antioxidant and anti-inflammatory effects. Current Opinion in Food Science. 2016; 8: 33–42.

[20] Evans JL, Maddux BA, Goldfine ID. The molecular basis for oxidative stress-induced insulin resistance. Antioxidants & Redox Signaling. 2005; 7: 1040–1052.

[21] Guo Q, Li F, Duan Y, Wen C, Wang W, Zhang L, et al. Oxidative stress, nutritional antioxidants and beyond. Science China. Life Sciences. 2020; 63: 866–874.

[22] Papuc C, Goran GV, Predescu CN, Tudoreanu L, Ștefan G. Plant polyphenols mechanisms of action on insulin resistance and against the loss of pancreatic beta cells. Critical Reviews in Food Science and Nutrition. 2022; 62: 325–352.

[23] Martín MA, Ramos S, Cordero-Herrero I, Bravo L, Goya L. Cocoa phenolic extract protects pancreatic beta cells against oxidative stress. Nutrients. 2013; 5: 2955–2968.

[24] Bahar E, Akter KM, Lee GH, Lee HY, Rashid HO, Choi MK, et al. β-Cell protection and antidiabetic activities of Crassocephalum crepidioides (Asteraceae) Benth. S. Moore extract against alloxan-induced oxidative stress via regulation of apoptosis and reactive oxygen species (ROS). BMC Complementary and Alternative Medicine. 2017; 17: 179.

[25] Yin P, Zhao S, Chen S, Liu J, Shi L, Wang X, et al. Hypoglycemic and hypolipidemic effects of polyphenols from burs of Castanea mollissima Blume. Molecules (Basel, Switzerland). 2011; 16: 9764–9774.

[26] Yan SF, Ramasamy R, Schmidt AM. Mechanisms of disease: advanced glycation end-products and their receptor in inflammation and diabetes complications. Nature Clinical Practice. Endocrinology & Metabolism. 2008; 4: 285–293.

[27] Gaens KHJ, Stehouwer CDA, Schalkwijk CG. Advanced glycation endproducts and its receptor for advanced glycation endproducts in obesity. Current Opinion in Lipidology. 2013; 24: 4–11.

[28] Luevano-Contreras C, Chapman-Novakofski K. Dietary advanced glycation end products and aging. Nutrients. 2010; 2: 1247–1265.

[29] Hemmler D, Roullier-Gall C, Marshall JW, Rychlik M, Taylor AJ, Schmitt-Kopplin P. Evolution of Complex Maillard Chemical Reactions, Resolved in Time. Scientific Reports. 2017; 7: 3227.

[30] Perrone A, Giovino A, Benny J, Martinelli F. Advanced Glycation End Products (AGEs): Biochemistry, Signaling, Analytical Methods, and Epigenetic Effects. Oxidative Medicine and Cellular Longevity. 2020; 2020: 3818196.

[31] Sebeková K, Somoza V. Dietary advanced glycation endproducts (AGEs) and their health effects–PRO. Molecular Nutrition & Food Research. 2007; 51: 1079–1084.

[32] Vistoli G, De Maddis D, Cipak A, Zarkovic N, Carini M, Aldini G. Advanced glycoxidation and lipoxidation end products (AGEs and ALEs): an overview of their mechanisms of formation. Free Radical Research. 2013; 47: 3–27.

[33] Hu H, Jiang H, Ren H, Hu X, Wang X, Han C. AGEs and chronic subclinical inflammation in diabetes: disorders of immune system. Diabetes/metabolism Research and Reviews. 2015; 31: 127–137.

[34] Negrean M, Stirban A, Stratmann B, Gawlowski T, Horstmann T, Götting C, et al. Effects of low- and high-advanced glycation endproduct meals on macro- and microvascular endothelial function and oxidative stress in patients with type 2 diabetes mellitus. The American Journal of Clinical Nutrition. 2007; 85: 1236–1243.

[35] Yamagishi SI, Fukami K, Matsui T. Crosstalk between advanced glycation end products (AGEs)-receptor RAGE axis and dipeptidyl peptidase-4-incretin system in diabetic vascular complications. Cardiovascular Diabetology. 2015; 14: 2.

[36] Ott C, Jacobs K, Haucke E, Navarrete Santos A, Grune T, Simm A. Role of advanced glycation end products in cellular signaling. Redox Biology. 2014; 2: 411–429.

[37] Shen CY, Wu CH, Lu CH, Kuo YM, Li KJ, Hsieh SC, et al. Advanced Glycation End Products of Bovine Serum Albumin Suppressed Th1/Th2 Cytokine but Enhanced Monocyte IL-6 Gene Expression via MAPK-ERK and MyD88 Transduced NF-κB p50 Signaling Pathways. Molecules (Basel, Switzerland). 2019; 24: 2461.

[38] van der Lugt T, Weseler AR, Gebbink WA, Vrolijk MF, Opperhuizen A, Bast A. Dietary Advanced Glycation Endproducts Induce an Inflammatory Response in Human Macrophages in Vitro. Nutrients. 2018; 10: 1868.

[39] Byun K, Yoo Y, Son M, Lee J, Jeong GB, Park YM, et al. Advanced glycation end-products produced systemically and by macrophages: A common contributor to inflammation and degenerative diseases. Pharmacology & Therapeutics. 2017; 177: 44–55.

[40] Thomas MC, Woodward M, Neal B, Li Q, Pickering R, Marre M, et al. Relationship between levels of advanced glycation end products and their soluble receptor and adverse outcomes in adults with type 2 diabetes. Diabetes Care. 2015; 38: 1891–1897.

[41] Loomis SJ, Chen Y, Sacks DB, Christenson ES, Christenson RH, Rebholz CM, et al. Cross-sectional Analysis of AGE-CML, sRAGE, and esRAGE with Diabetes and Cardiometabolic Risk Factors in a Community-Based Cohort. Clinical Chemistry. 2017; 63: 980–989.

[42] Perera HKI, Handuwalage CS. Analysis of glycation induced protein cross-linking inhibitory effects of some antidiabetic plants and spices. BMC Complementary and Alternative Medicine. 2015; 15: 175.

[43] Song Q, Liu J, Dong L, Wang X, Zhang X. Novel advances in inhibiting advanced glycation end product formation using natural compounds. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2021; 140: 111750.

[44] Bhattacherjee A, Datta A. Mechanism of antiglycating properties of syringic and chlorogenic acids in in vitro glycation system. Food Research International. 2015; 77: 540–548.

[45] Arena K, Trovato E, Cacciola F, Spagnuolo L, Pannucci E, Guarnaccia P, et al. Phytochemical Characterization of Rhus coriaria L. Extracts by Headspace Solid-Phase Micro Extraction Gas Chromatography, Comprehensive Two-Dimensional Liquid Chromatography, and Antioxidant Activity Evaluation.

Molecules (Basel, Switzerland). 2022; 27: 1727.

[46] Wu CH, Yeh CT, Shih PH, Yen GC. Dietary phenolic acids attenuate multiple stages of protein glycation and high-glucose-stimulated proinflammatory IL-1beta activation by interfering with chromatin remodeling and transcription in monocytes. Molecular Nutrition & Food Research. 2010; 54: S127–S140.

[47] Buttari B, Profumo E, Facchiano F, Ozturk EI, Segoni L, Saso L, et al. Resveratrol prevents dendritic cell maturation in response to advanced glycation end products. Oxidative Medicine and Cellular Longevity. 2013; 2013: 574029.

[48] Kanlaya R, Thongboonkerd V. Molecular Mechanisms of Epigallocatechin-3-Gallate for Prevention of Chronic Kidney Disease and Renal Fibrosis: Preclinical Evidence. Current Developments in Nutrition. 2019; 3: nzz101.

[49] Alizadeh M, Kheirouri S. Curcumin against advanced glycation end products (AGEs) and AGEs-induced detrimental agents. Critical Reviews in Food Science and Nutrition. 2019; 59: 1169–1177.

[50] Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002; 420: 860–867.

[51] Hotamisligil GS, Erbay E. Nutrient sensing and inflammation in metabolic diseases. Nature Reviews. Immunology. 2008; 8: 923–934.

[52] Tsalamandris S, Antonopoulos AS, Oikonomou E, Papamikroulis GA, Vogiatzi G, Papaioannou S, et al. The Role of Inflammation in Diabetes: Current Concepts and Future Perspectives. European Cardiology. 2019; 14: 50–59.

[53] Lehuen A, Diana J, Zaccone P, Cooke A. Immune cell crosstalk in type 1 diabetes. Nature Reviews. Immunology. 2010; 10: 501–513.

[54] La Noce M, Nicoletti GF, Papaccio G, Del Vecchio V, Papaccio F. Insulitis in Human Type 1 Diabetic Pancreas: From Stem Cell Grafting to Islet Organoids for a Successful Cell-Based Therapy. Cells. 2022; 11: 3941.

[55] Fu Z, Gilbert ER, Liu D. Regulation of insulin synthesis and secretion and pancreatic Beta-cell dysfunction in diabetes. Current Diabetes Reviews. 2013; 9: 25–53.

[56] Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nature Reviews. Immunology. 2011; 11: 98–107.

[57] Gao D, Jiao J, Wang Z, Huang X, Ni X, Fang S, et al. The roles of cell-cell and organ-organ crosstalk in the type 2 diabetes mellitus associated inflammatory microenvironment. Cytokine & Growth Factor Reviews. 2022; 66: 15–25.

[58] Gothai S, Ganesan P, Park SY, Fakurazi S, Choi DK, Arulselvan P. Natural Phyto-Bioactive Compounds for the Treatment of Type 2 Diabetes: Inflammation as a Target. Nutrients. 2016; 8: 461.

[59] Seo MJ, Lee YJ, Hwang JH, Kim KJ, Lee BY. The inhibitory effects of quercetin on obesity and obesity-induced inflammation by regulation of MAPK signaling. The Journal of Nutritional Biochemistry. 2015; 26: 1308–1316.

[60] Du L, Li J, Zhang X, Wang L, Zhang W. Pomegranate peel polyphenols inhibits inflammation in LPS-induced RAW264.7 macrophages via the suppression of TLR4/NF-κB pathway activation. Journal of Functional Foods. 2018; 43: 62–69.

[61] Noh KT, Cha GS, Kim HC, Lee JH, Ahn SC, Kim DK, et al. Ellagic acid modulates LPS-induced maturation of dendritic cells through the regulation of JNK activity. Journal of Medicinal Food. 2014; 17: 996–1002.

[62] Islam S, Hassan F, Mu MM, Ito H, Koide N, Mori I, et al. Piceatannol prevents lipopolysaccharide (LPS)-induced nitric oxide (NO) production and nuclear factor (NF)-kappaB activation by inhibiting IkappaB kinase (IKK). Microbiology and Immunology. 2004; 48: 729–736.

[63] O'Neill EJ, Hartogh DJD, Azizi K, Tsiani E. Anticancer Properties of Carnosol: A Summary of in Vitro and In Vivo Evidence.

Antioxidants (Basel, Switzerland). 2020; 9: 961.

[64] Bachewal P, Gundu C, Yerra VG, Kalvala AK, Areti A, Kumar A. Morin exerts neuroprotection via attenuation of ROS induced oxidative damage and neuroinflammation in experimental diabetic neuropathy. BioFactors (Oxford, England). 2018; 44: 109–122.

[65] Han JM, Jin YY, Kim HY, Park KH, Lee WS, Jeong TS. Lavandulyl flavonoids from Sophora flavescens suppress lipopolysaccharide-induced activation of nuclear factor-kappaB and mitogen-activated protein kinases in RAW264.7 cells. Biological & Pharmaceutical Bulletin. 2010; 33: 1019–1023.

[66] Xu L, Li W, Chen Z, Guo Q, Wang C, Santhanam RK, et al. Inhibitory effect of epigallocatechin-3-O-gallate on α-glucosidase and its hypoglycemic effect via targeting PI3K/AKT signaling pathway in L6 skeletal muscle cells. International Journal of Biological Macromolecules. 2019; 125: 605–611.

[67] Beauchamp GK, Keast RSJ, Morel D, Lin J, Pika J, Han Q, et al. Ibuprofen-like activity in extra-virgin olive oil. Nature. 2005; 437: 45–46.

[68] Choi EY, Bae SH, Ha MH, Choe SH, Hyeon JY, Choi JI, et al. Genistein suppresses Prevotella intermedia lipopolysaccharide-induced inflammatory response in macrophages and attenuates alveolar bone loss in ligature-induced periodontitis. Archives of Oral Biology. 2016; 62: 70–79.

[69] Farzaei MH, Singh AK, Kumar R, Croley CR, Pandey AK, Coy-Barrera E, et al. Targeting Inflammation by Flavonoids: Novel Therapeutic Strategy for Metabolic Disorders. International Journal of Molecular Sciences. 2019; 20: 4957.

[70] Jantan I, Haque MA, Arshad L, Harikrishnan H, Septama AW, Mohamed-Hussein ZA. Dietary polyphenols suppress chronic inflammation by modulation of multiple inflammation-associated cell signaling pathways. The Journal of Nutritional Biochemistry. 2021; 93: 108634.

[71] Kongpichitchoke T, Hsu JL, Huang TC. Number of Hydroxyl Groups on the B-Ring of Flavonoids Affects Their Antioxidant Activity and Interaction with Phorbol Ester Binding Site of PKCδ C1B Domain: In Vitro and in Silico Studies. Journal of Agricultural and Food Chemistry. 2015; 63: 4580–4586.

[72] Bai Y, Zhou J, Zhu H, Tao Y, Wang L, Yang L, et al. Isoliquiritigenin inhibits microglia-mediated neuroinflammation in models of Parkinson's disease via JNK/AKT/NFκB signaling pathway. Phytotherapy Research: PTR. 2023; 37: 848–859.

[73] Kim JY, Park SJ, Yun KJ, Cho YW, Park HJ, Lee KT. Isoliquiritigenin isolated from the roots of Glycyrrhiza uralensis inhibits LPS-induced iNOS and COX-2 expression via the attenuation of NF-kappaB in RAW 264.7 macrophages. European Journal of Pharmacology. 2008; 584: 175–184.

[74] Lee D, Cuendet M, Vigo JS, Graham JG, Cabieses F, Fong HH, et al. A novel cyclooxygenase-inhibitory stilbenolignan from the seeds of Aiphanes aculeata. Organic Letters. 2001; 3: 2169–2171.

[75] Rehman K, Khan II, Akash MSH, Jabeen K, Haider K. Naringenin downregulates inflammation-mediated nitric oxide overproduction and potentiates endogenous antioxidant status during hyperglycemia. Journal of Food Biochemistry. 2020; 44: e13422.

[76] Kim JH, Kim MY, Kim JH, Cho JY. Fisetin Suppresses Macrophage-Mediated Inflammatory Responses by Blockade of Src and Syk. Biomolecules & Therapeutics. 2015; 23: 414–420.

[77] Sheu F, Lai HH, Yen GC. Suppression effect of soy isoflavones on nitric oxide production in RAW 264.7 macrophages. Journal of Agricultural and Food Chemistry. 2001; 49: 1767–1772.

[78] Eo H, Lee HJ, Lim Y. Ameliorative effect of dietary genistein on diabetes induced hyper-inflammation and oxidative stress during early stage of wound healing in alloxan induced diabetic mice. Biochemical and Biophysical Research Communications.

2016; 478: 1021–1027.

[79] Celik S, Erdogan S. Caffeic acid phenethyl ester (CAPE) protects brain against oxidative stress and inflammation induced by diabetes in rats. Molecular and Cellular Biochemistry. 2008; 312: 39–46.

[80] Elhessy HM, Eltahry H, Erfan OS, Mahdi MR, Hazem NM, El-Shahat MA. Evaluation of the modulation of nitric oxide synthase expression in the cerebellum of diabetic albino rats and the possible protective effect of ferulic acid. Acta Histochemica. 2020; 122: 151633.

[81] Lee JH, Song MY, Song EK, Kim EK, Moon WS, Han MK, et al. Overexpression of SIRT1 protects pancreatic beta-cells against cytokine toxicity by suppressing the nuclear factor-kappaB signaling pathway. Diabetes. 2009; 58: 344–351.

[82] Serreli G, Melis MP, Corona G, Deiana M. Modulation of LPS-induced nitric oxide production in intestinal cells by hydroxytyrosol and tyrosol metabolites: Insight into the mechanism of action. Food and Chemical Toxicology: an International Journal Published for the British Industrial Biological Research Association. 2019; 125: 520–527.

[83] Zu G, Sun K, Li L, Zu X, Han T, Huang H. Mechanism of quercetin therapeutic targets for Alzheimer disease and type 2 diabetes mellitus. Scientific Reports. 2021; 11: 22959.

[84] Selim NM, Elgazar AA, Abdel-Hamid NM, El-Magd MRA, Yasri A, Hefnawy HME, et al. Chrysophanol, Physcion, Hesperidin and Curcumin Modulate the Gene Expression of Pro-Inflammatory Mediators Induced by LPS in HepG2: In Silico and Molecular Studies. Antioxidants (Basel, Switzerland). 2019; 8: 371.

[85] Geng S, Wang S, Zhu W, Xie C, Li X, Wu J, et al. Curcumin attenuates BPA-induced insulin resistance in HepG2 cells through suppression of JNK/p38 pathways. Toxicology Letters. 2017; 272: 75–83.

[86] Govindaraj J, Sorimuthu Pillai S. Rosmarinic acid modulates the antioxidant status and protects pancreatic tissues from glucolipotoxicity mediated oxidative stress in high-fat diet: streptozotocin-induced diabetic rats. Molecular and Cellular Biochemistry. 2015; 404: 143–159.

[87] Rozentsvit A, Vinokur K, Samuel S, Li Y, Gerdes AM, Carrillo-Sepulveda MA. Ellagic Acid Reduces High Glucose-Induced Vascular Oxidative Stress Through ERK1/2/NOX4 Signaling Pathway. Cellular Physiology and Biochemistry: International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology. 2017; 44: 1174–1187.

[88] Liao ZY, Liang IC, Li HJ, Wu CC, Lo HM, Chang DC, et al. Chrysin Inhibits High Glucose-Induced Migration on Chorioretinal Endothelial Cells via VEGF and VEGFR Down-Regulation. International Journal of Molecular Sciences. 2020; 21: 5541.

[89] Wang F, Yin J, Ma Y, Jiang H, Li Y. Vitexin alleviates lipopolysaccharide induced islet cell injury by inhibiting HMGB1 release. Molecular Medicine Reports. 2017; 15: 1079–1086.

[90] Rosa SIG, Rios-Santos F, Balogun SO, de Oliveira Martins DT. Vitexin reduces neutrophil migration to inflammatory focus by down-regulating pro-inflammatory mediators via inhibition of p38, ERK1/2 and JNK pathway. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology. 2016; 23: 9–17.

[91] Yang Z, Huang W, Zhang J, Xie M, Wang X. Baicalein improves glucose metabolism in insulin resistant HepG2 cells. European Journal of Pharmacology. 2019; 854: 187–193.

[92] Hadrich F, Mahmoudi A, Chamkha M, Isoda H, Sayadi S. Olive Leaves Extract and Oleuropein Improve Insulin Sensitivity in 3T3-L1 Cells and in High-Fat Diet-Treated Rats via PI3K/AkT Signaling Pathway. Oxidative Medicine and Cellular Longevity.

[93] Chowdhury S, Ghosh S, Rashid K, Sil PC. Deciphering the role of ferulic acid against streptozotocin-induced cellular stress in the cardiac tissue of diabetic rats. Food and Chemical Toxicology: an International Journal Published for the British Industrial Biological Research Association. 2016; 97: 187–198.

[94] Onda K, Horike N, Suzuki TI, Hirano T. Polymethoxyflavonoids tangeretin and nobiletin increase glucose uptake in murine adipocytes. Phytotherapy Research: PTR. 2013; 27: 312–316.

[95] Ali MY, Zaib S, Rahman MM, Jannat S, Iqbal J, Park SK, et al. Didymin, a dietary citrus flavonoid exhibits anti-diabetic complications and promotes glucose uptake through the activation of PI3K/Akt signaling pathway in insulin-resistant HepG2 cells. Chemico-biological Interactions. 2019; 305: 180–194.

[96] Li J, Wang T, Liu P, Yang F, Wang X, Zheng W, et al. Hesperetin ameliorates hepatic oxidative stress and inflammation via the PI3K/AKT-Nrf2-ARE pathway in oleic acid-induced HepG2 cells and a rat model of high-fat diet-induced NAFLD. Food & Function. 2021; 12: 3898–3918.

[97] Wang B, Wu L, Chen J, Dong L, Chen C, Wen Z, et al. Metabolism pathways of arachidonic acids: mechanisms and potential therapeutic targets. Signal Transduction and Targeted Therapy. 2021; 6: 94.

[98] Santangelo C, Varì R, Scazzocchio B, Di Benedetto R, Filesi C, Masella R. Polyphenols, intracellular signalling and inflammation. Annali Dell'Istituto Superiore Di Sanita. 2007; 43: 394–405.

[99] Zhou QYJ, Liao X, Kuang HM, Li JY, Zhang SH. LC-MS Metabolite Profiling and the Hypoglycemic Activity of Morus alba L. Extracts. Molecules (Basel, Switzerland). 2022; 27: 5360.

[100] Arafah A, Rehman MU, Mir TM, Wali AF, Ali R, Qamar W, et al. Multi-Therapeutic Potential of Naringenin (4',5,7-Trihydroxyflavonone): Experimental Evidence and Mechanisms. Plants (Basel, Switzerland). 2020; 9: 1784.

[101] Huang DD, Shi G, Jiang Y, Yao C, Zhu C. A review on the potential of Resveratrol in prevention and therapy of diabetes and diabetic complications. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2020; 125: 109767.

[102] Yahfoufi N, Alsadi N, Jambi M, Matar C. The Immunomodulatory and Anti-Inflammatory Role of Polyphenols. Nutrients. 2018; 10: 1618.

[103] Gasparrini M, Giampieri F, Alvarez Suarez J, Mazzoni L, Y Forbes Hernandez T, Quiles JL, et al. AMPK as a New Attractive Therapeutic Target for Disease Prevention: The Role of Dietary Compounds AMPK and Disease Prevention. Current Drug Targets. 2016; 17: 865–889.

[104] Ramadori G, Gautron L, Fujikawa T, Vianna CR, Elmquist JK, Coppari R. Central administration of resveratrol improves diet-induced diabetes. Endocrinology. 2009; 150: 5326–5333.

[105] Banik K, Ranaware AM, Harsha C, Nitesh T, Girisa S, Deshpande V, et al. Piceatannol: A natural stilbene for the prevention and treatment of cancer. Pharmacological Research. 2020; 153: 104635.

[106] Yu S, Liu X, Yu D, Changyong E, Yang J. Morin Protects LPS-Induced Mastitis via Inhibiting NLRP3 Inflammasome and NF-κB Signaling Pathways. Inflammation. 2020; 43: 1293–1303.

[107] Lawrence MC, Jivan A, Shao C, Duan L, Goad D, Zaganjor E, et al. The roles of MAPKs in disease. Cell Research. 2008; 18: 436–442.

[108] Khan H, Sureda A, Belwal T, Çetinkaya S, Süntar İ, Tejada S, et al. Polyphenols in the treatment of autoimmune diseases. Autoimmunity Reviews. 2019; 18: 647–657.

[109] Shehzad A, Rehman G, Lee YS. Curcumin in inflammatory diseases. BioFactors (Oxford, England). 2013; 39: 69–77.

[110] Li G, Duan L, Yang F, Yang L, Deng Y, Yu Y, et al. Curcumin

suppress inflammatory response in traumatic brain injury via p38/MAPK signaling pathway. Phytotherapy Research: PTR. 2022; 36: 1326–1337.

[111] Kahkhaie KR, Mirhosseini A, Aliabadi A, Mohammadi A, Mousavi MJ, Haftcheshmeh SM, et al. Curcumin: a modulator of inflammatory signaling pathways in the immune system. Inflammopharmacology. 2019; 27: 885–900.

[112] Babaei F, Moafizad A, Darvishvand Z, Mirzababaei M, Hosseinzadeh H, Nassiri-Asl M. Review of the effects of vitexin in oxidative stress-related diseases. Food Science & Nutrition. 2020; 8: 2569–2580.

[113] Schultze SM, Hemmings BA, Niessen M, Tschopp O. PI3K/AKT, MAPK and AMPK signalling: protein kinases in glucose homeostasis. Expert Reviews in Molecular Medicine. 2012; 14: e1.

[114] Huang X, Liu G, Guo J, Su Z. The PI3K/AKT pathway in obesity and type 2 diabetes. International Journal of Biological Sciences. 2018; 14: 1483–1496.

[115] Mirza-Aghazadeh-Attari M, Ekrami EM, Aghdas SAM, Mihanfar A, Hallaj S, Yousefi B, et al. Targeting PI3K/Akt/mTOR signaling pathway by polyphenols: Implication for cancer therapy. Life Sciences. 2020; 255: 117481.

[116] Legeay S, Rodier M, Fillon L, Faure S, Clere N. Epigallocatechin Gallate: A Review of Its Beneficial Properties to Prevent Metabolic Syndrome. Nutrients. 2015; 7: 5443–5468.

[117] Ma L, Li XP, Ji HS, Liu YF, Li EZ. Baicalein Protects Rats with Diabetic Cardiomyopathy Against Oxidative Stress and Inflammation Injury via Phosphatidylinositol 3-Kinase (PI3K)/AKT Pathway. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research. 2018; 24: 5368–5375.

[118] Ahamad J, Toufeeq I, Khan MA, Ameen MSM, Anwer ET, Uthirapathy S, et al. Oleuropein: A natural antioxidant molecule in the treatment of metabolic syndrome. Phytotherapy Research: PTR. 2019; 33: 3112–3128.

[119] Gandhi GR, Vasconcelos ABS, Wu DT, Li HB, Antony PJ, Li H, et al. Citrus Flavonoids as Promising Phytochemicals Targeting Diabetes and Related Complications: A Systematic Review of In Vitro and In Vivo Studies. Nutrients. 2020; 12: 2907.

[120] Manthey JA, Cesar TB, Jackson E, Mertens-Talcott S. Pharmacokinetic study of nobiletin and tangeretin in rat serum by high-performance liquid chromatography-electrospray ionization-mass spectrometry. Journal of Agricultural and Food Chemistry. 2011; 59: 145–151.

[121] Lee YS, Cha BY, Saito K, Yamakawa H, Choi SS, Yamaguchi K, et al. Nobiletin improves hyperglycemia and insulin resistance in obese diabetic ob/ob mice. Biochemical Pharmacology. 2010; 79: 1674–1683.

[122] Shi J, Fan J, Su Q, Yang Z. Cytokines and Abnormal Glucose and Lipid Metabolism. Frontiers in Endocrinology. 2019; 10: 703.

[123] Chao CY, Mong MC, Chan KC, Yin MC. Anti-glycative and anti-inflammatory effects of caffeic acid and ellagic acid in kidney of diabetic mice. Molecular Nutrition & Food Research. 2010; 54: 388–395.

[124] Tan Y, Zhang X, Cheang WS. Isoflavones daidzin and daidzein inhibit lipopolysaccharide-induced inflammation in RAW264.7 macrophages. Chinese Medicine. 2022; 17: 95.

[125] Zhao F, Gao X, Ge X, Cui J, Liu X. Cyanidin-3-o-glucoside (C3G) inhibits vascular leakage regulated by microglial activation in early diabetic retinopathy and neovascularization in advanced diabetic retinopathy. Bioengineered. 2021; 12: 9266–9278.

[126] Qi SS, He J, Dong LC, Yuan LP, Le Wu J, Zu YX, et al. Cyanidin-3-glucoside from black rice prevents renal dysfunction and renal fibrosis in streptozotocin-diabetic rats. Journal of Functional Foods. 2020; 72: 104062.

[127] Sogo T, Terahara N, Hisanaga A, Kumamoto T, Yamashiro T, Wu S, et al. Anti-inflammatory activity and molecular mechanism of delphinidin 3-sambubioside, a Hibiscus anthocyanin. BioFactors (Oxford, England). 2015; 41: 58–65.

[128] Kim YJ, Jung UJ. Honokiol Improves Insulin Resistance, Hepatic Steatosis, and Inflammation in Type 2 Diabetic db/db Mice. International Journal of Molecular Sciences. 2019; 20: 2303.

[129] Wu JP, Zhang W, Wu F, Zhao Y, Cheng LF, Xie JJ, et al. Honokiol: an effective inhibitor of high-glucose-induced upregulation of inflammatory cytokine production in human renal mesangial cells. Inflammation Research. 2010; 59: 1073–1079.