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AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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REVIEW

Emerging and multifaceted potential contributions of polyphenols in the management of type 2 diabetes mellitus

Ileana González, Cristian Lindner, Ivan Schneider, Erik Diaz, Miguel Angel Morales, Armando Rojas

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Abstract

Type 2 diabetes mellitus (T2DM) is recognized as a serious public health concern with a considerable impact on human life, long-term health expenditures, and substantial health losses. In this context, the use of dietary polyphenols to prevent and manage T2DM is widely documented. These dietary compounds exert their beneficial effects through several actions, including the protection of pancreatic islet β-cell, the antioxidant capacities of these molecules, their effects on insulin secretion and actions, the regulation of intestinal microbiota, and their contribution to ameliorate diabetic complications, particularly those of vascular origin. In the present review, we intend to highlight these multifaceted actions and the molecular mechanisms by which these plant-derived secondary metabolites exert their beneficial effects on type 2 diabetes patients.

Key Words: Polyphenols; Antioxidants; Oxidative stress; Type 2 diabetes mellitus; Health benefits

Core Tip: At present, a compelling body of evidence suggests that dietary polyphenols may represent an important alternative source to the management of type 2 diabetes mellitus due to their multifaceted actions on glucose homeostasis as well as in attenuating many diabetes complications raised because of the hyperglycemic condition. Additionally, new data derived from either clinical trials or meta-analyses have started to figure out the usefulness of these bioactive compounds thus providing solid clinical shreds of evidence.

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INTRODUCTION

Diabetes mellitus (DM) is a heterogeneous group of chronic metabolic disorders characterized by hyperglycemia resulting from defects of insulin action, insulin secretion, or both[1]. This metabolic disease is a global health issue, which has been increasing from time to time and it is now considered as one of the most important disorders worldwide. According to International Diabetes Federation, 10.5% of adults of the world population are currently living with diabetes and this alarming indicator is predicted to rise to 11.3 % (643 million people) by 2030 and to 12.2 % (783 million) by 2045 [2].

Noteworthy, a considerable proportion of the world's burden of diabetes is caused by type 2 DM (T2DM). In this regard, T2DM is recognized as a serious public health concern with a considerable impact on human life and health expenditures[3]. The onset and progression of T2DM are determined by a complex pathophysiological basis where oxidative stress is a crucial contributor not only involved in the disease development but also to diabetes complications, particularly those associated with both microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular complications (ischemic heart disease, peripheral vascular disease, and cerebrovascular disease[4].

Acute or chronic hyperglycemia upregulates reactive oxygen species (ROS) production in the mitochondrial electron transfer chain. This excessive production of superoxide mediates the downregulation of glyceraldehyde-3-phosphate dehydrogenase levels, which in turn activates the major pro-oxidative pathways involved in the pathogenesis of diabetes complications, such as the activation of protein kinase C, the polyol and hexosamine pathways, the formation of advanced glycation end products productions (AGEs), as well as the increased expression of the receptor for AGEs[5-7]. On the other hand, antioxidant mechanisms are diminished in diabetic patients, which may further augment oxidative stress[8-10].

During the last few years, compelling shreds of evidence have shed light on the usefulness of dietary antioxidants as an alternative option in the treatment of T2DM, considering both the adverse effects conferred by conventional pharmacological treatments as well as the enormous economic burden that lifelong treatments place on patients[11].

In this regard, dietary polyphenols have emerged as an option to manage T2DM[12]. These compounds are one of the most abundant secondary plant metabolites, which are grouped into four major families, flavonoids, ligands, stilbenes, and phenolic acids, and are widely found in fruits, vegetables, nuts, cereals, and in many beverages such as tea, coffee, and red wines. These bioactive phytochemicals can reach and act at several cellular compartment levels including cellular membranes by binding to the bilayer interface or by interacting with the hydrophobic fatty acid tails[13].

A growing body of experimental and clinical evidence supports the protective role of these compounds on several human diseases through their antioxidant activity and diverse molecular mechanisms[14-18] (Figure 1). This review aims to highlight the roles of this large and heterogeneous family of secondary metabolites of plants containing phenol rings, on pancreatic islet β-cell functioning and promotion of insulin production and signaling, protection against micro-and microvascular complications, protection against the progression of T2DM-associated obesity, management of dyslipidemia and gut microbiome dysbiosis. In addition, the capacity of polyphenols to reduce both the formation of advanced glycation products and their pathologic consequences is also addressed.

LITERATURE SEARCH

The literature search was conducted using Medline/PubMed, Embase, Cochrane, and *RCA*, databases. Search terms included "type-2 diabetes mellitus", "prediabetes", "polyphenols", "natural antioxidants", "oxidative stress" and "abnormal glucose homeostasis". Articles published between January 2013 to March 2023 and additional publications were retrieved by snowballing. Exclusion criteria included T1DM (autoimmune β-cell destruction), gestational DM, pancreatogenic diabetes, drug-induced diabetes, and the monogenic diabetes syndromes.

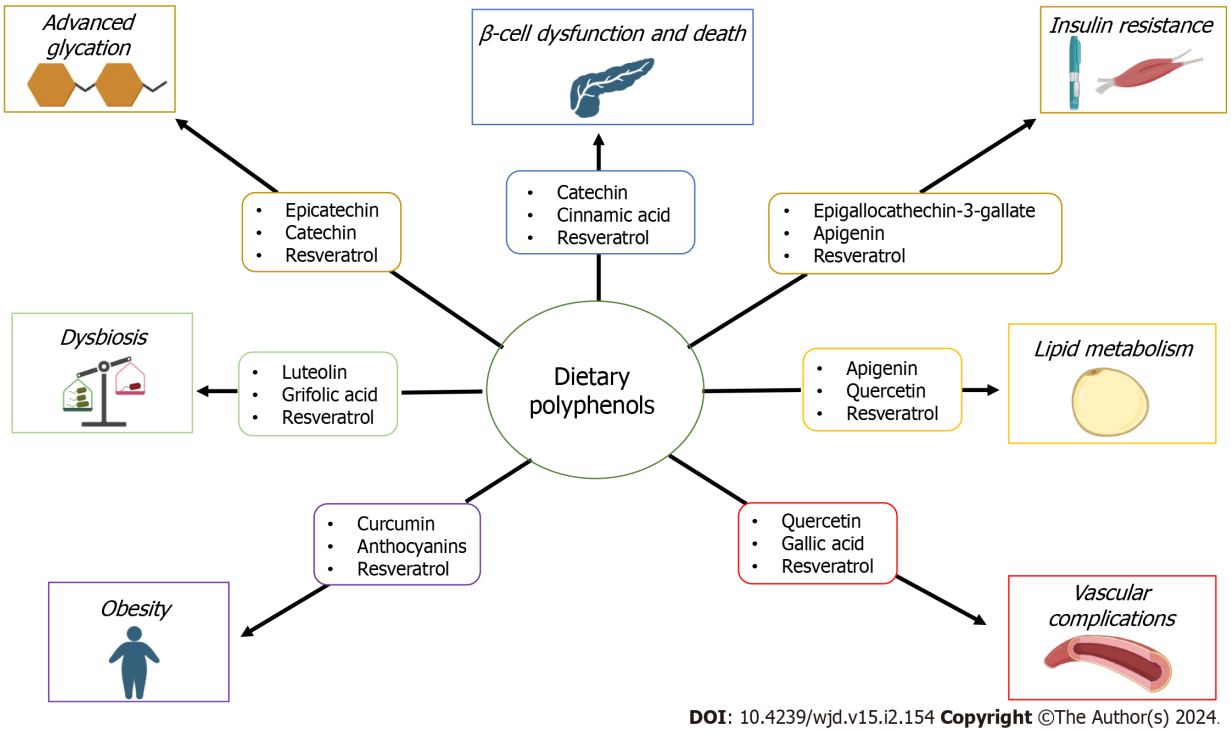

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Figure 1 Some polyphenols for which there is documented information about their beneficial properties in the management of the main alterations observed in type 2 diabetes mellitus.

B-CELL DYSFUNCTION AND DEATH

Currently, both clinical and experimental data support that during the development of T2DM, there is not only a progressive deterioration in β-cell functioning but also a marked reduction of the β-cell mass in the pancreatic islets of Langerhans[19-21]. Many factors such as the glucotoxicity associated with the hyperglycemic state, the oxidative and endoplasmic reticulum stresses, as well as the lipotoxicity due to chronic exposure to saturated free fatty acids, are crucial elements in decreased β-cell functioning and, eventually in β cell death through apoptosis[19,22,23].

Hyperglycemia is a crucial factor in the onset of oxidative stress in T2DM and it even correlates with the progression of disease[24]. Additionally, β-cells are very susceptible to oxidative damage, because of their low antioxidant capacity[25,26], and consequently, oxidative stress is a very important contributor to the impairment of β-cell functioning[23,27,28]. Furthermore, oxidative stress mediates the permeabilization of mitochondrial membranes, and consequently the release of cytochrome C and thus β-cell death by apoptosis[29].

Based on their antioxidant activities polyphenols are major regulators of oxidative stress and consequently the improvement of mitochondrial functions. At present, compelling pieces of evidence support that many metabolic disorders such as type 2 diabetes, are associated with impaired mitochondrial function such as diminished oxidative capacity and antioxidant defense, mainly due to the onset of an oxidative stress condition[30,31].

Oxidative stress condition is established by the imbalance between the production of ROS and antioxidant defense mechanisms, and where the detrimental ROS activities exceed the antioxidant capacities of the cell. Mitochondrial dysfunction is defined by several features including a diminished mitochondrial biogenesis, an altered membrane potential, a decrease in the mitochondrial number as well as by an altered activity of oxidative proteins due to the accumulation of ROS in cells and tissue[32,33].

Polyphenols can not only exert powerful antioxidant actions and thus protect against oxidative stress[34], they have additional capacities to modulate crucial pathways in mitochondrial functionality such as mitochondrial biogenesis, mitochondrial membrane potential, ATP synthesis, intra-mitochondrial oxidative status, and apoptosis cell death[35-38]. Cocoa catechins can also improve insulin secretion by increasing the expression of some genes involved in mitochondrial respiration[39].

Resveratrol is known for its remarkable activities in improving pancreatic β-cell function mainly by its effect on sirtuin 1 (SIRT1), a master regulator for β-cell function[40]. Cinnamic acid derivatives can improve the insulin-secreting capacity of β-cells, by raising the levels of intracellular calcium[41]. Noteworthy, compelling pieces of evidence support that the hyperglycemia-associated overexpression of human amylin, also known as islet amyloid polypeptide, can form aggregates to favor amylin fibril formation, and these fibrils evoke the activation of caspases cascade, and thus leading to β-cell death by apoptosis[42,43]. Several polyphenols such as rosmarinic acid, ferulic acid, epigallocatechin gallate, and resveratrol, among many others, can interfere with the formation of fibrillar structures and thus avoid β-cell death[44,45].

INSULIN RESISTANCE

Insulin receptor (IR) is a tyrosine kinase receptor, which is autophosphorylated upon insulin binding and it is expressed in all tissues. The major responders to IR engagement by insulin are the liver, skeletal muscle, and adipose tissue[46]. Upon insulin binding complex signaling is activated including several substrates such as insulin or insulin-like growth factor-1, IR, IR substrate (IRS)-1, and phosphatidylinositol-3 kinase (PI3K)/Akt or ERK kinases. The phosphorylation of IRS1 can recruit PI3K rendering Akt phosphorylated, which in turn can regulate crucial events such as the translocation of glucose transporter-4 (GLUT4) to the cell surface, promoting glycogen synthesis through inhibition of glycogen synthase kinase 3 activity, the induction of protein synthesis *via* activation of mammalian target of rapamycin and the inhibition of Forkhead transcription factors of the O class (FoxO) transcription factors[47,48].

The inactivation of Akt and activation of FoxO1, through the suppression of IRS1 and IRS2 in different organs following hyperinsulinemia, over-nutrition, and inflammation, represent crucial mechanisms for insulin resistance in humans[49,50]. Compelling shreds of evidence support that oxidative stress is an important contributor to insulin resistance in T2DM[51], and that the overproduction of mitochondrial H_2O_2[52,53], and the overactivation of NAPDPH oxidase, *via* angiotensin II/AT1 receptor can mediate skeletal muscle insulin resistance[54-56].

ROS are known to actively participate in several crucial physiological processes at the cellular level such as differentiation, cellular signaling, and phosphorylation/dephosphorylation events among many others[57]. The existence of various endogenous antioxidant systems is responsible for maintaining ROS at the low levels required to contribute to cellular homeostasis[58]. However, the hyperglycemia condition, which is a hallmark of T2DM, is crucial in the acquisition of a dysfunctional state of these antioxidant systems, thus favoring the onset of the oxidative stress condition [59,60]. Thus, this condition is a crucial element in the multifactorial etiology of insulin resistance. Oxidative stress impairs β-cell function, which markedly reduces not only insulin production but also its secretion into the circulation. Additionally, oxidative stress can reduce GLUT-4 gene expression and translocation to the membrane[61-63].

The c Jun-N-terminal kinases (JNKs) is major signal transducer driving the physio-logical response to several cellular stressors, including oxidative stress. Epigallocatechin gallate, the major green tea catechin can protect both the IR and IRS proteins from phosphorylation by JNKs, a crucial event in the onset of insulin resistance[63], as well as by reducing the expression of the negative regulator of IR protein tyrosine phosphatase 1B (PTP1B)[64].

Resveratrol, which is one of the main polyphenolic compounds of red wines, peanuts, and apples, is a potent activator of SIRT1, which is a potent intracellular inhibitor of oxidative stress, and thus attenuates insulin resistance and improves insulin signaling in the skeletal muscle cells[65,66]. Additionally, some polyphenols can also stimulate glucose uptake in both skeletal muscle and adipocytes by translocating GLUT4 to the plasma membrane through an adenosine monophosphate (AMP)-activated protein kinase (AMPK)-dependent pathway[67].

PTP1B is an intracellular enzyme responsible for the deactivation of the IR, resulting in insulin resistance in various tissues[68,69]. Hence, PTP1B has become an important target for controlling insulin resistance and T2DM. In this regard, many polyphenols have inhibitory activity on PTP1B as demonstrated either by screening platforms for detecting the inhibition activity or by Quantitative Structure-Activity Relationship analysis[70,71].

OBESITY

Obesity is the major driving factor of T2DM and it is characterized by chronic low-grade inflammation with permanently increased oxidative stress[72,73]. The onset of a chronic condition of oxidative stress in obesity is supported by different mechanisms implicated in the homeostasis of adipose tissue, which contributes to the development of pathological systemic consequences[74].

On one hand, those associated with increased ROS production such as the adipocytes-associated endoplasmic reticulum stress, a sustained increase of NOX activities, as well as the high level of post-prandial-associated ROS generation, and on the other, the altered antioxidant defenses observed in obese patients[75-78]. In addition to the antioxidant properties of polyphenols, they exert several beneficial effects on obesity far beyond their antioxidant capacity[79], such as the attenuation of obesity-linked inflammation[80-82], the beneficial regulation of several key obesity path-ways such as the modulation of food intake[81], the inhibition of pancreatic lipase[82,83], decreasing lipogenesis by inhibiting both fatty acid synthase activity and the activation of the AMP-AMPK[84,85], and by increasing thermogenesis and mitochondrial biogenesis[86].

Finally, some polyphenols have been reported to mediate the suppression of the conversion of preadipocytes into adipocytes, which can store an excessive lipid load. This polyphenols-mediated suppression of adipocyte differentiation occurs by the regulation of crucial factors such as the CCAAT/enhancer binding protein α, the nuclear receptor peroxisome proliferator-activated receptor γ 1 and 2, (PPARγ1, PPARγ2), and GLUT-4 in mature adipocytes[84,86-88].

DYSBIOSIS

Human gut microbiota is considered a complex microbial ecosystem composed of different microorganisms, including bacteria, archaea, viruses, fungi, and protists, which are involved in the regulation of many physiological processes and numerous diseases[89].

Firmicutes and Bacteroidetes are the main phyla that compose the adult gut flora, regulating the homeostatic production of microbiota-induced metabolites such as butyrate, which have anti-inflammatory and antioxidative properties, and the production of lipopolysaccharide (LPS), which can promote systemic inflammation and insulin resistance through induction of metabolic endotoxemia[90,91].

Growing data raised from both clinical and experimental evidence shows that T2DM patients have an altered gut microbiota, where the Bacterioidetes/Firmicutes ratio of the intestinal flora of diabetic patients significantly differs from non-T2DM adults[92,93]. A crucial consequence of the quantitative change in gut microbiota composition in T2DM patients is the impairment of the expression of gut-microbiota-related metabolites, which have crucial consequences in the metabolic regulation of glucose homeostasis, and insulin sensitivity[93].

Short-chain fatty acids (SCFAs) are considered one of the main microbial metabolites, that have crucial effects on the expression of glucagon-like peptide-1 (GLP-1) and GLP-2 *via* stimulating G-protein-coupled receptors, thus contributing to improving glucose homeostasis and amplification of insulin sensitivity[94].

Under this dysbiosis condition that affects T2DM patients, structural changes in the intestinal epithelium barrier allow LPS translocation into the bloodstream, resulting in increased plasmatic levels of LPS, which in consequence, activates Toll-like receptor-4 leading to the production of pro-inflammatory mediators, and sustaining low-grade systemic inflammation[95].

This condition known as metabolic endotoxemia induces a significant decrease in bacterial populations which are crucial producers of beneficial gut-derived metabolites such as SCFA, thus supporting the impairment of glucose metabolism and insulin resistance[96,97]. In addition, different studies have demonstrated that specific gut microbiota dysbiosis in mice models of T2DM, induces GLP-1 resistance and consequently, the impairment of GLP1-induced insulin secretion, which is crucial in the acquisition of the insulin resistance condition in diabetic individuals[98].

At present, polyphenols have emerged as novel compounds that could interact with microbiota and exert strong regulatory effects on intestinal bacteria, with subsequent regulation of gut microbiota and its derivate metabolites[99]. These interactions between polyphenols and gut microbiota can positively affect crucial metabolic markers of T2DM, improving systemic inflammation and insulin sensitivity[100,101].

Growing evidence reveals that distinct types of polyphenolic compounds, such as genistein, curcumin, and grifolic acid can increase GLP-1 secretion from L-cells *via* different mechanisms[102-105]. Besides their effect to directly stimulate GLP-1 secretion, some polyphenols, particularly luteolin, apigenin, and resveratrol may also naturally suppress DPP-IV activity, which potentially increases the half-life of GLP-1, thus stimulating glucose-dependent insulin secretion and regulating glycemia[106,107].

Different studies demonstrate that different doses of oral intake of polyphenols including catechins, and (-)-epigallocatechin-3-gallate, can also favor the increase of different microbial populations of SCFA-producing agents in fecal samples of human patients, thus improving the insulin sensitivity and glucose homeostasis of individuals[108,109].

In addition, other phenolic compounds including chlorogenic and ferulic acid can also act as antidiabetic agents, through significant upregulating of the expression of GLUT4 and PPAR-γ, thus favoring the uptake of 2-deoxyglucose in time- and dose-dependent manner, and improving the pathogenesis of T2DM progression[110-112]. Branched-chain amino acids (BCAAs) include leucine, isoleucine, and valine, which cannot be synthesized *de novo* by mammalians and consequently, they are acquired either from the diet or gut microbiota. Elevated plasma circulating levels of BCAAs and their ketoacids are associated with insulin resistance in obesity and T2DM[113-117].

Conversely, experimental results have demonstrated that lowering BCAA and branched-chain alpha-keto acid levels is associated with improved insulin sensitivity and reduced fat accumulation in mouse models[118]. Emerging studies have suggested that polyphenol administration may accelerate the catabolism of BCAA, inducing a lowering of circulating BCAA levels, thus improving glucose homeostasis and insulin sensitivity[119].

Additionally, some evidence also supports that intestinal catabolites of polyphenolic compounds by the action of the gut microbiota could act as a strong antiglycative agent[120,121]. In this sense, dietary polyphenolic intake may have a significant positive impact on the generation of glycation products and diabetes-related complications[122,123]. Taken together, those findings suggest that a polyphenols-enriched diet can strongly modulate the dysbiotic changes induced by hyperglycemia, improving the regulation of metabolites that mediate glucose homeostasis and insulin sensitivity in T2DM patients.

VASCULAR COMPLICATIONS

Vascular complications in T2DM are those long-term complications that affect the blood vessel network, and are responsible for most of the morbidity, and required hospitalization in these patients[124]. The vascular complications of diabetes are classified as either microvascular (retinopathy, nephropathy, and neuropathy) or macrovascular, which includes coronary artery, peripheral, and cerebral vascular diseases[125].

At present, a large body of compelling evidence supports that oxidative stress has a key role in the pathogenesis of vascular complications in diabetes[126-128]. As a major regulator of vascular homeostasis, the vascular endothelial cells play crucial roles by controlling vascular tone through a balance between vasodilation and vasoconstriction, fibrinolysis, platelet adhesion and aggregation, leukocyte activation, adhesion, and transmigration, smooth muscle cell proliferation, and modulating the growth of blood vessels[129,130].

The onset of an imbalanced vasodilation and vasoconstriction, elevated ROS, and proinflammatory factors, as well as a reduced nitric oxide (NO) bioavailability, are crucial elements in the onset of the systemic disorder known as endothelial dysfunction[131]. NO is produced in the endothelium by the endothelial NO synthase (eNOS), a Ca^{2+}-calmodulin-

dependent enzyme that can convert the L-arginine to NO plus citrulline. By activation of soluble guanylyl cyclase and modulation of cation channels, NO promotes vascular smooth muscle cells relaxation and thus regulates vascular tone. Additionally, NO is a crucial mediator in controlling platelet activation and aggregation[132].

When ROS bioavailability overtakes the antioxidant defenses due to the onset of oxidative stress, superoxide (O^{2-}) rapidly inactivates NO and forms peroxynitrite ($ONOO^-$). It is known that peroxynitrite inactivates prostacyclin synthase thus favoring the deterioration of vascular health due to the vasodilatory, growth-inhibiting, antithrombotic, and antiadhesive effects of prostacyclin. Additionally, peroxynitrite increases the release of prostaglandin H2 and thromboxane A2, which are potent vasoconstrictors, prothrombotic, growth- and adhesion-promoting agents[133-135]. A growing body of data supports the beneficial roles of polyphenols in protecting against endothelial dysfunction induced by oxidative stimuli[136-138].

Of note, some polyphenols, as reported for resveratrol and its derivatives show dual protecting activities, either by the expression of Nox4, a ROS-generating enzyme highly expressed in the endothelium, and by enhancing the expression of two crucial members of the antioxidant defense of the vascular wall, such as glutathione peroxidase 1 and superoxide dismutase 1[139]. Moreover, polyphenols seem to have peroxynitrite-scavenging activity[140]. Furthermore, different reports have demonstrated that some polyphenols such as resveratrol and others derived from strawberry and grape skin and seeds, can promote the phosphorylation of eNOS at Ser1177 by PI3K/Akt pathway, which is essential for NO production[141-143]. In addition, resveratrol is reported to increase both endothelial eNOS mRNA and protein levels[144-146]. This effect seems to be associated with the effects of resveratrol on SIRT1 and FOXO factors[147].

POLYPHENOLS AND ADVANCED GLYCATION

Advanced glycation is one of the major pathways involved in the onset and progression of T2DM complications, particularly those associated with the cardiovascular system[148]. Since the pioneering works of the Vlassara group[149,150], a huge and compelling body of evidence has demonstrated the paramount importance of AGEs in diabetes complications, due to the hyperglycemic condition[151,152].

The formation of AGEs involves the reaction of reducing sugars, such as glucose, with the terminal amino groups of proteins, nucleic acids, or phospholipids to initially form unstable Schiff bases, which evolve towards the formation of more stable compounds called Amadori products, which by a series of complex reaction yield the AGEs. Degradation of both Schiff bases and Amadori products rise to highly reactive short-chain carbonyl compounds, called α-dicarbonyls [153].

These highly reactive compounds can also be formed by hexose autoxidation, as well as by-products of either the glycolytic or polyol pathways and from lipid oxidation. Dicarbolyls can then react non-enzymatically with lysine or arginine residues to produce AGEs[154,155].

The AGEs exert their deleterious effects, either directly by cross-linking of proteins, thus disrupting protein functioning and turn-over[156,157], or indirectly by binding to a signaling receptor for AGE-modified proteins, known as the receptor of advanced glycation end-products (RAGE)[158,159]. Noteworthy, oxidative stress is an important contributor to the formation of endogenous eAGEs, by leading to the increased formation of endogenous reactive aldehydes such as glyoxal, methylglyoxal (MG), and thus favoring the formation of AGEs[160]. Additionally, when AGEs activate RAGE, NADPH oxidase is activated and thus increases ROS levels[161].

At present, compelling evidence derived from experimental and clinical data studies supports the role of different polyphenols as very active inhibitors of the deleterious effects of AGEs, through several mechanisms[162,163]. By their antioxidant activities, polyphenols are potent antiglycation compounds and antiglycation activity strongly correlates with the free radical scavenging activity and antiglycation activity[120], as reported catechins, proanthocyanidins, anthocyanin, stilbenoids, and flavonols[164,165]. Additionally, polyphenols have other properties, which are essential to reduce the formation of AGEs, such as the chelation of transition metal, as reported for chlorogenic and caffeic acids[166,167].

The capacity of trapping dicarbonyl compounds is another crucial activity reported for some polyphenols considering that dicarbonyls are one of the main precursors of AGEs[154], epigallocatechin-3-gallate, resveratrol, catechin, and epicatechin as well as different procyanidins can efficiently trap both glyoxal and MG[162,168,169]. Dicarbonyls are detoxified by the glyoxalase system a highly specific enzyme responsible for the detoxification of dicarbonyl species[170]. Some polyphenols can even stimulate this detoxifying system[171]. Finally, several reports have demonstrated that polyphenols can actively reduce the undesired consequences of the activation of RAGE, either by interfering with receptor signaling as well as by reducing its expression[172-174].

LIPID METABOLISM

T2DM has been widely associated with an increased risk for atherosclerotic cardiovascular disease, which is closely related to raised plasmatic low-density lipoprotein (LDL) levels with important oxidative changes[175], which support diabetic hyperlipidemia and accelerated atherosclerosis, increasing the risk of macrovascular complication and cardiovascular morbidity. Noteworthy, LDL is a highly sensitive molecule to hyperglycemia-induced hyperglycemia damage and modification, making it highly pathogenic and atherogenic[176,177]. Under hyperglycemic conditions, transition metals in the presence of oxygen catalyze the autoxidation of glucose or lipid peroxidation[178]. In addition, excess ROS formation in T2DM patients fuels vascular inflammation and mediates oxidized LDL (ox-LDL) formation,

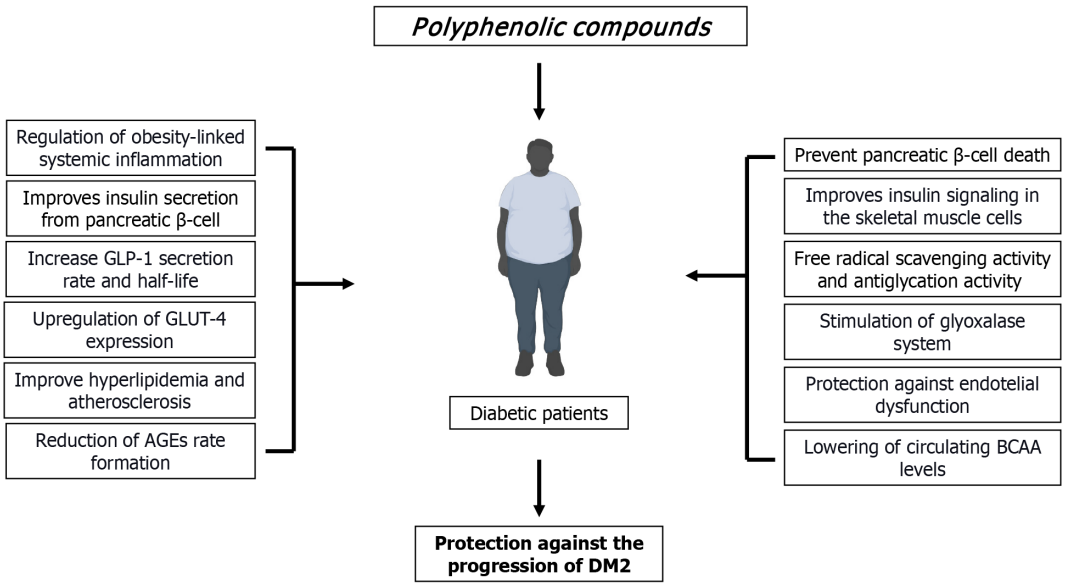

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Figure 2 Polyphenols have multifaceted actions to support their use in the management of type 2 diabetes mellitus. Due to their positive actions on multiple physiopathological mechanisms which are crucial not only in the onset of type 2 diabetes mellitus (T2DM) by protecting and supporting many functions of β-cells and insulin signaling, but also in those associated with common T2DM complications by improving dyslipidemia profiles, reducing systemic inflammation, dampening the deleterious consequences of the high rate formation of advanced glycation end products production, reducing oxidative stress, as well as by supporting vascular functionality. AGE: Advanced glycation end products production; GLP-1: Glucagon-like peptide-1; GLUT-4: Glucose transporter 4; BCAA: Branched-chain amino acid; DM: Diabetes mellitus.

which is considered a hallmark feature of atherosclerotic development due to the crucial induction of atherosclerotic plaque progression and destabilization in T2DM patients[179-181].

Besides the different pathways that conflux in activate NADPH oxidase and subsequent ROS production in T2DM patients, the increased expression of ox-LDL also stimulates NADPH oxidase, thus contributing to increment ROS formation and oxidative stress in T2DM patients[182]. In addition, hyperglycemia-mediated mitochondrial ROS production can also promote the nuclear factor kappa-beta-mediated entry of monocytes in atherosclerotic lesions, fueling the inflammation and progression of unstable plaques, and increasing the risk of macrovascular complication in T2DM patients[183], thus, sustaining a vicious cycle that perpetuating ROS production and ox-LDL formation, contributes to the progression of atherosclerosis unstable plaques on DM patients.

In recent years, polyphenols have been postulated to lower lipids through different mechanisms that imply beneficial effects on cardiovascular diseases of T2DM patients[184]. Based on their antioxidant effects, different studies have shown that many polyphenols including resveratrol, apigenin, and some synthetic polyphenol-like molecules can inhibit NAPDH oxidase activity, thus decreasing vascular oxidation and atherogenesis in nondiabetic apolipoprotein (apo) E–deficient mice[185], as well as improve hyperlipidemia and atherosclerosis in diabetic individuals[186].

Resveratrol based on its antioxidant activities can influence lipid metabolism and is considered an important protective compound against LDL oxidation and atherosclerosis progression[187]. In this sense, the free radical scavenging activity of resveratrol has been investigated, revealing that this polyphenol compound can interact with free radicals to form relatively stable free radicals and non-radicals, resulting in inhibition of lipid peroxidation by Fenton reaction products [188,189], which may decrease the progression of accelerated atherosclerosis through inhibition of oxidation in T2DM patients[190,191].

More recently, it was demonstrated that resveratrol can upregulate eNOS expression by increasing cAMP levels, and decreasing ox-LDL-induced oxidative stress in human endothelial cells, leading to a significant improvement of endothelial dysfunction and atherosclerosis in mice[192]. Similar results have been demonstrated for quercetin, an important flavonoid, which has demonstrated protective effects in diabetic individuals through significantly reversed dyslipidemia and hepatic steatosis in diabetic mice, including lowered liver cholesterol and triglycerides contents[193, 194]. Taken together, these findings suggest that dietary polyphenols may be crucial in the regulation of dysregulated lipid metabolism through the modulation of antioxidative mechanisms in T2DM patients.

CONCLUSION

A compelling body of evidence suggests that dietary polyphenols may represent an important alternative to the management of T2DM due to their multifaceted actions on glucose homeostasis as well as by attenuating many diabetes complications raised because of the hyperglycemic condition (Figure 2). Most of the pieces of evidence derived from animals and *in vitro* studies support these issues. However, new emerging data derived from either clinical trials or meta-

Table 1 Clinical trials and meta-analysis studies in the last five years supporting the roles of dietary polyphenols in the management of type 2 diabetes mellitus

Type of study	Beneficial effects	Ref.
Randomized clinical trial	Increased antioxidant capacity and antioxidant gap in T2DM patients	García-Martínez *et al*[195], 2023
Double-masked, cross-over, dietary intervention trial	Improvement of endothelial function in both healthy individuals and T2DM patients	Bapir *et al*[196], 2022
Meta-analysis	Improving HbA1c, and insulin levels in T2DM	García-Martínez *et al*[197], 2021
Randomized, clinical trial	Lowering fasting blood glucose levels in T2DM	Sirvent *et al*[198], 2022
Systemic review and meta-analysis	Reduction of systolic and diastolic blood pressure and fasting blood glucose levels in T2DM patients	Gu *et al*[199], 2022
Systematic review and meta-analysis	Reduction of fasting blood glucose and HbA1c levels	Delpino *et al*[200], 2021
Randomized clinical trial	Improvement of glycemic control by reducing insulin resistance	Mahjabeen *et al*[201], 2022
Randomized clinical trial	Lowering effects on inflammatory status and oxidative stress biomarkers in diabetic patients	Grabež *et al*[202], 2022
Randomized clinical trial	Improvement of glycaemia markers	Gómez-Martínez *et al*[203], 2021
Systematic review and meta-analysis	Improvement of glycemic control and cardiometabolic parameters in patients with T2DM	Abdelhaleem *et al*[68], 2022
Meta-analysis	Reduction of insulin resistance, HbA1c levels and fasting blood glucose	Delpino and Figueiredo [204], 2022
Meta-analysis	Improvement of glucose control and lowering blood pressure	Nyambuya *et al*[205], 2020
Randomized clinical trial	Improvement of postprandial dyslipidemia and inflammation following a high-fat dietary challenge in adults with T2D	Davis *et al*[206], 2020
Meta-analysis	Significant reduction in CRP level in patients with T2D	Hosseini *et al*[194], 2021
Meta-analysis	Combined effects with anti-diabetic medication to lowering serum glucose levels in individuals with T2D	Raimundo *et al*[207], 2020
Randomized clinical trial	Improvement of glycemic control and lipid profile	Hoseini *et al*[208], 2019
Meta-analysis	Lowering fasting blood glucose, HbA1c, and HOMA-IR	Huang *et al*[209], 2019
Randomized clinical trial	Improvement of lipid profile and lowering serum biomarkers of inflammation	Adibian *et al*[210], 2019
Randomized clinical trial	Lowering postprandial hyperglycemia and serum biomarkers of inflammation	Schell *et al*[211], 2019
Randomized clinical trial	Lowering fasting blood glucose and improvement of lipid profile	Mollace *et al*[212], 2019
Systematic review and meta-analysis	Lowering the risk of T2D	Rienks *et al*[213], 2018
Randomized clinical trial	Reduction of plasma protein carbonyl content and increasing plasma total antioxidant capacity	Seyyedebrahimi *et al*[214], 2018

T2D: Type 2 diabetes; HbA1c: Glycosylated hemoglobin; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; CRP: C-reactive protein; T2DM: Type 2 diabetes mellitus.

analyses have started to figure out the usefulness of these bioactive compounds, and thus providing solid clinical shreds of evidence (Table 1). However, much more research is needed on some topics that may be crucial to explain the current controversial results in some clinical studies. In this regard, a full understanding of the metabolisms and bioavailability, the assessment of dietary intake by measuring urine or blood polyphenol metabolites, duration of exposure, delivery systems that guarantee high stability, as well as more efforts to understand the structure-activity relationship of polyphenols, are crucial elements to be considered in the design and execution of more double-blinded clinical trials.

FOOTNOTES

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