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Review Article

Polyphenols with antiglycation activity and mechanisms of action: A review of recent findings

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ABSTRACT

Advanced glycation end products (AGEs) are substances composed of amino groups of proteins and reducing sugars. The initial and propagation phases of the glycation process are accompanied by the production of a large amount of free radicals, carbonyl species, and reactive dicarbonyl species, of which, methylglyoxal (MG) is the most reactive and can cause dicarbonyl stress, influencing normal physiological functions. In the advanced phase, the production of AGEs and the interaction between AGEs and their receptor, RAGE, are also considered to be among the causes of chronic diseases, oxidative stress, and inflammatory reaction. Till date, multiple physiological activities of polyphenols have been confirmed. Recently, there have been many studies discussing the ability of polyphenols to suppress the MG and AGEs formation, which was also confirmed in some *in vivo* studies. This review article collects recent literatures concerning the effects of polyphenols on the generation of MG and AGEs through different pathways and discusses the feasibility of the inhibition of glycative stress and dicarbonyl stress by polyphenols.

1. Introduction

The spontaneous post-translational modification of proteins or amino acids through reducing sugars is called the Maillard reaction or nonenzymatic glycation, and the products resulting after the exposure to reducing sugars are called as advanced glycation end products (AGEs) [1]. In the course of food processing, heating, and storage, the Maillard reaction can enhance food flavor and color; however, excessive AGEs in food have been confirmed to cause many chronic diseases in organisms, including diabetes mellitus (DM) [2] and kidney diseases [3], and are among the causes of the development and malignancy of tumors [4]. Therefore, there have already been many studies investigating various factors in the application of the Maillard reaction in food chemistry, physiology, and toxicology.

The production of dicarbonyl compounds during the Maillard reaction is an important step in the production of AGEs [5], among which methylglyoxal (MG) is one of the

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most highly reactive carbonyl species (RCS) in the human body [6]. In addition to investigating the effects of AGEs, recent studies have also addressed the effects of MG on many chronic diseases and aging-related diseases in clinical practice [7]. The MG concentration in the blood of DM patients is reported to be significantly higher than that in non-DM patients, reaching 400μM [8]. Additionally, endogenous MG is produced in the bodies of organisms. Under pathological conditions, an even higher concentration of MG will be accumulated in the body, which might be associated with the imbalance of the antiglycation system, known as the glyoxalase system [9]. Therefore, the accumulation of RCS, such as MG, in organisms and the associated metabolic imbalance will result in the development of many human diseases.

Recently, antiglycation has been considered as an effective strategy to slow down human aging and disease development. The inhibition of glycation can suppress inflammasome activation to reduce the development of inflammatory reactions [3,10]. The antioxidant and anti-inflammation abilities of polyphenol substances have been extensively studied, and their antiglycation functions have been screened in many *in vitro* experimental platforms. The results show that polyphenols can inhibit the biosynthesis of AGEs through their antioxidant properties, metal-chelating ability, protein interaction, MG trapping, and/or blocking the receptor for advanced glycation end products (RAGE) [11,12]. Polyphenols were classified into four large groups in this article, phenolic acids, stilbenes, lignans, and flavonoids, and different antiglycation functions of polyphenols found in recent years were examined to evaluate the antiglycation potential of polyphenols.

2. AGEs formation

The Maillard reaction is a nonenzymatic glycation function. It involves many steps, and the reaction usually requires several days or even several weeks to complete (Figure 1).

2.1. *Initial phase*

In the initial phase of the Maillard reaction, reducing sugars, such as glucose, fructose, or ribose, will act on the terminal amino groups of proteins, nucleic acids, or phospholipids to form unstable Schiff bases, which will further become more stable keto-amines, also called Amadori products, after rearrangement. The reactions in this phase are all reversible, and depending on the substrate concentrations and reaction time, these reactions have different effects. In addition, Schiff bases are prone to oxidation to produce free radicals, resulting in the formation of active carbonyl intermediate products [13].

2.2. *Propagation phase*

During the process of Amadori rearrangement, the oxidation function induced by the catalytic function of metal ions or oxygen will produce many carbonyl compounds, including MG, glyoxal, and 3-deoxyglucosone. This stage is the intermediate phase of the Maillard reaction.

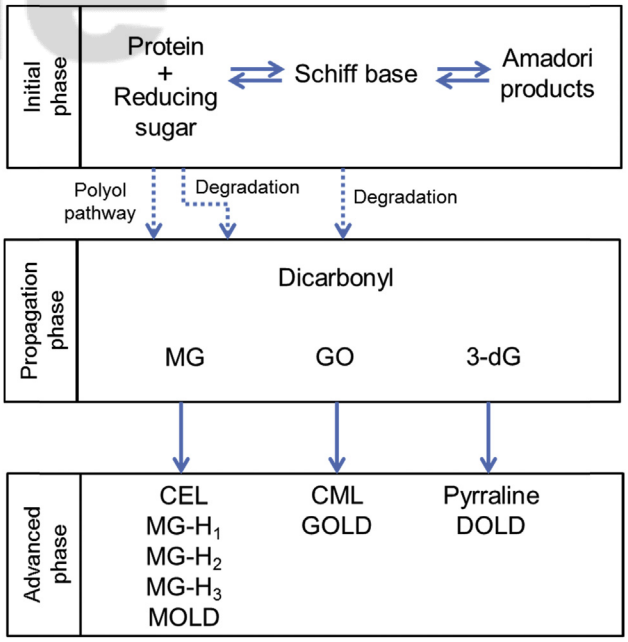

Figure 1 – Pathway for AGE formation. The N-terminal amino groups of protein and reducing sugar form dicarbonyls including methylglyoxal, glyoxal, and 3-deoxyglucosone through polyol pathway, glycolysis, or autoxidation of reducing sugar, leading to generation of pathological AGEs. AGE = advanced glycation end product; CEL = N$^{\varepsilon}$-carboxyethyllysine; CML = N$^{\varepsilon}$-carboxymethyllysine; 3-dG = 3-deoxyglucosone; DOLD = 3-deoxyglucosone lysine dimer; GO = glyoxal; GOLD = glyoxal-lysine dimer; MG = methylglyoxal; MG-H = MG-derived-hydroimidazalone; MOLD = methylglyoxal-lysine dimer.

2.3. *Advanced phase*

The advanced phase is the last phase of the Maillard reaction. In the advanced phase, dicarbonyl compounds form isomers with the arginine and lysine residues of proteins, called AGEs. They are characterized by thermal stability. The major AGEs are classified into 3 groups: (1) fluorescent crosslinking AGEs, such as crossline and pentosidine; (2) nonfluorescent crosslinking AGEs, such as imidazolium dilysine crosslinks; and (3) nonfluorescent non-crosslinking AGEs, such as N$^{\varepsilon}$-carboxyethyllysine (CEL) and N$^{\varepsilon}$-carboxymethyl-lysine (CML). Except for pyrraline and pentosidine, the production of AGEs is irreversible.

3. Carbonyl stress mediated by MG

The propagation phase of the glycation process produces RCS, which are considered as precursors for the formation of AGEs. MG is a highly reactive substance and is considered as one of the most reactive precursors of AGEs, which can be produced by endogenous enzymatic reactions or nonenzymatic reactions [14]. MG can produce many types of AGEs through the

modification of arginine or lysine residues of proteins, including N_{δ}-(5-methyl-4-imidazolon-2-yl)-L-ornithine, 2-amino-5-(2-amino-5-hydro-5-methyl-4-imidazolon-1-yl) pentanoic acid, 2-amino-5-(2-amino-4-hydro-4-methyl-5-imidazolon-1-yl) pentanoic acid, CEL, argpyrinidine, 4-methyl-imidazolium (methylglyoxal-lysine dimer, MOLD), and 2-ammonio-6-({2-[4-ammonio-5-oxido-5-oxopent-ly) amino]-4-methyl-4,5-dihydro-1H-imidazol-5-ylidene}amino) hexanoate (Figure 2). The above AGEs derived from MG are all found in the bodies of organisms and are considered to be associated with DM and related to large and small blood vessel diseases as well as aging-related diseases [15].

4. Exogenous MG

Many foods, drinks, and substances in nature, including water, rain, and clouds, contain MG [16]. Sugars in food and drinks, the presence of microorganisms during processing and the cooking process, and overly long storage time are all major causes of MG production. During the manufacturing and processing of foods and drinks, the level of MG production after the heating of monosaccharides, such as glucose, is significantly higher than that after the heating of disaccharides, such as sucrose. The composition of carbohydrates in food and drinks also influences the production of MG [17,18]. In addition, during the fermentation of drinks, MG is naturally synthesized and released by microorganisms. During the fermentation of red wine, strains such as *Saccharomyces cerevisiae* produce MG through the malolactic fermentation process [19]. Many natural plants also have high concentrations of MG; additionally, in the presence of stress factors, such as a harsh environment, the MG concentration increases significantly [20].

Once MG is produced in food, its uptake into the body may cause negative effects. The results of one study showed that after the application of 50 mg MG/kg body weight/day in the drinking water of mice for 5 months, a large amount of collagens accumulated in the kidney. The fluorescent staining of kidney sections showed that the accumulation of collagen in mice fed with MG water was approximately twice the amount in healthy mice [21]. With the progressive application of 50–75 mg MG/kg body weight/day in the drinking water of rats for 7 weeks, the serum creatinine and total cholesterol concentrations increased in rats, and the tubular epithelial cells in the kidney exhibited ballooning, necrosis, or tubular basal membrane detachment. The immunostaining results also showed glomerular tufts and the accumulation of transforming growth factor-β in tubular epithelial cells and interstitial endothelial cells. These pathological phenomena were considered to be similar to diabetic nephropathy [22].

5. Endogenous MG

Endogenous MG in organisms can be produced through enzymatic pathways, such as triosephosphate isomerase catalysis, or nonenzymatic pathways, such as the Maillard

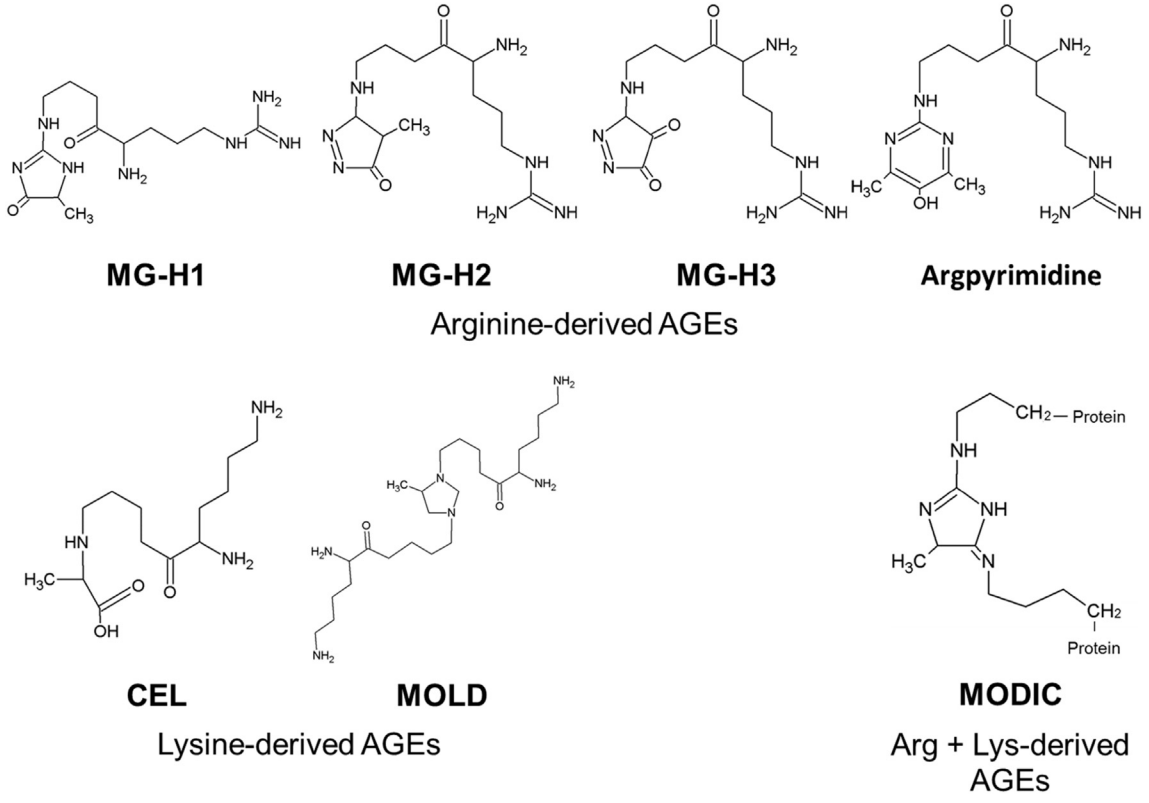

Figure 2 – Chemical structures of MG-derived AGEs. AGE = advanced glycation end product; CEL = N $^{\varepsilon}$-carboxyethyllysine; MG = methylglyoxal; MG-H = MG-derived-hydroimidazalone; MODIC = imidazolium cross-link derived from methylglyoxal and lysine-arginine; MOLD = methylglyoxal-lysine dimer.

reaction. The most important pathway for endogenous MG formation is the conversion from triose phosphate through glycolysis [23,24]. The chronic accumulation of MG and MG-glycated proteins in the kidney also induces capillary and renal tubule damage, thus causing impaired kidney function [25]. The MG concentration in the blood of DM patients reached as high as 400μM [8]. In rats with acute kidney injury, the expression level of glyoxalase I (GLO I) decreased, causing a significant increase in the concentration of MG [9]. The application of drugs to reduce the concentrations of MG and MG-derived AGEs in clinical experiments had positive influences on diabetic neuropathy [26]. Therefore, diseases cause MG accumulation, which in turn aggravates the diseases in a vicious cycle, resulting in more serious consequences.

6. Pathways that inhibit AGE formation

There are many steps in AGE synthesis. Therefore, antiglycation functions may occur at any step. Several possible mechanisms that can delay or reduce AGE synthesis are listed below [27,28]. (1) Reduction of free radical production during the glycation process: the early stage of the Maillard reaction is accompanied by the production of a large amount of free radicals. In addition, Schiff bases are prone to oxidation to produce free radicals and reactive carbonyl groups. Therefore, at the early stage of glycation, capturing free radicals to reduce oxidative stress and decreasing the production of reactive carbonyl and dicarbonyl groups can inhibit the glycation function. (2) Reduction of the production of Schiff base and Amadori products: blocking the carbonyl or dicarbonyl groups of reducing sugars can inhibit AGE production. (3) Detoxification of the reactive dicarbonyl metabolite MG: GLO I is a part of the glyoxalase system present in the cytosol of cells. It catalyzes the isomerization of hemithioacetal to cause the spontaneous conversion of α-oxoaldehyde RCOCHO and glutathione (GSH) into S-2-hydroxyacylglutathione derivatives, RCH(OH)CO-SG, thus reducing the production of a-oxoaldehyde and glycation-related substances in the body [29] (Figure 3). Therefore, it is considered to be an antiglycation enzyme. (4) Inhibition of the generation of Amadori products in the advanced phase. (5) Blocking the crosslinking of AGEs can also inhibit AGE production. (6) AGE production is associated with the presence of transition metal ions. Therefore, the chelation of metal ions may inhibit AGE production. (7) Blocking the function of RAGE and reducing the subsequent development of oxidative stress and inflammation.

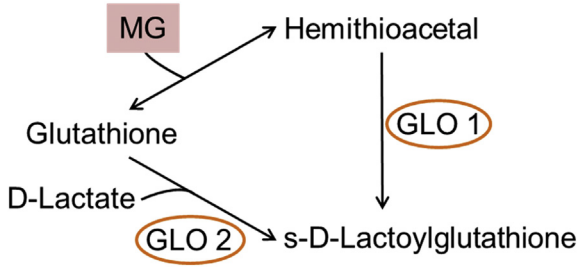

Figure 3 – Glyoxalase system. The detoxification system of MG in all cells. GLO 1 plays a first step in catalyzing MG to s-D-Lactoylglutathione. It is a key enzyme in glyoxalase system for regulating the MG formation.
MG = methylglyoxal; GLO = glyoxalase.

In summary, reducing the production of free radicals and carbonyl groups in the glycation process or increasing GLO I activity to decrease MG accumulation can both reduce the production of Amadori products and thus decrease AGEs formation. Many antioxidant substances have a free radical-capturing function to reduce the damage caused by free radicals in the glycation process. The chelation of metal ions can prevent the autoxidation of reducing sugars and Amadori products to reduce AGE production (Figure 4). There are also many polyphenols in natural products that have antioxidant properties and may influence AGE production through different mechanisms (Table 1).

7. Polyphenol substances in natural products have antiglycative properties

Polyphenols are a large group of chemical substances in plants. Their main sources include vegetables, fruits, beans, red wine, tea, and coffee. The most common polyphenol substances include phenolic acids, stilbenes, lignans, and flavonoids. Many studies have confirmed that different polyphenol substances have antiglycation functions *in vivo* and *in vitro*. Reducing the production of carbonyl compounds can achieve cardiovascular protection [30] or delay the development of DM and its complications through the antiglycation function [31]. They can also prevent MG production during food storage and processing [11].

7.1. *Phenolic acids*

Phenolic acids, especially hydroxybenzoic acid (HBA) and hydroxycinnamic acid (HCA), are the polyphenols with the highest concentrations in food from plants. Their concentrations are higher than flavonoid concentrations [32]. In an *in vitro* experiment that simulated the early stage of glycation, the HBA and HCA groups of phenolic acids exhibited inhibition of the early stage of glycation. Gallic acid, vanillic acid, chlorogenic acid, and ferulic acid can all significantly inhibit glucose-mediated protein modification. In addition, a protein crosslinking experiment showed that chlorogenic acid, sinapic acid, ferulic acid, vanillic acid, and syringic acid could inhibit AGE production and the subsequent crosslinking of proteins. The structural features and the antiglycation ability of phenolic acids remain inconclusive but might be associated with the antioxidant function [33]. The basic structure of phenolic acid has many hydroxyl groups; therefore, it may have excellent antiglycative and MG trapping functions When a benzene ring has one to two –OH groups, its MG trapping ability is not good; however, with three or more –OH groups, its MG trapping ability may be better. However, different positions of the carboxylic group may produce different effects. The compound 2,4,6-trihydroxybenzoic acid is considered to have a good MG trapping structure [34].

Phenolic acids found in food can act as AGE inhibitors during cooking in hot oil [12]. Ferulic acid is present in many

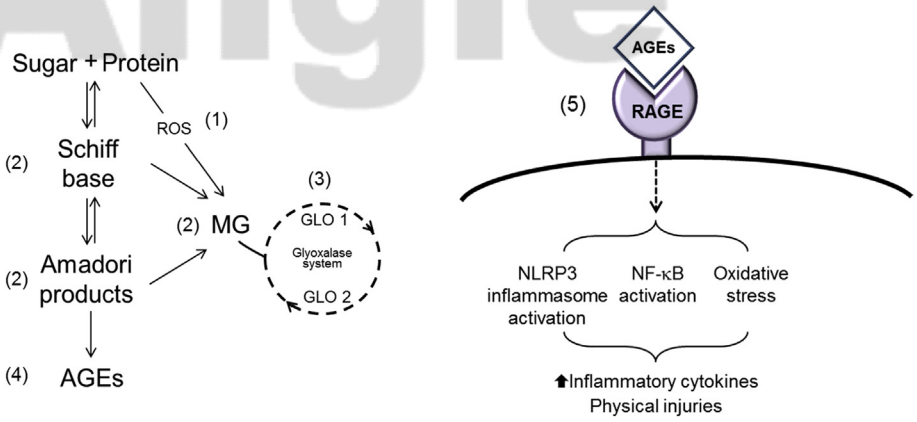

Figure 4 – Antiglycation mechanisms of polyphenols. Several strategies are designed of AGE inhibitor. (1) Inhibition of ROS formation during glycation. (2) Inhibition of Schiff base, Amadori products, and subsequent dicarbonyl groups formation. (3) Detoxification of AGE precursor- MG by glyoxalase system. (4) Inhibition of harmful AGEs formation. (5) Blocking of AGE–RAGE interaction inhibits oxidative stress and ROS generation, inflammatory stimuli, and physical injury through different pathways. AGE = advanced glycation end product; GLO = glyoxalase; MG = methylglyoxal; RAGE = receptor of AGEs; ROS = reactive oxygen species.

Table 1 – Antiglycative effects of polyphenols.

Antiglycation mechanism	Type of polyphenol	Function	Reference
(1) Inhibition of ROS	Phenolic acids	Antioxidative properties	[33]
	Lignan - sesamin	Inhibition of NADPH oxidase mediated ROS	[47]
	Stilbenes - resveratrol	Antioxidative properties	[54,56]
	Flavonoids	Antioxidative properties	[42]
(2) Inhibition of MG formation	Phenolic acids	Trapping MG	[34]
	Stilbenes - Stilbene glucoside	Trapping MG	[62]
	Flavonoids - hesperidin	Trapping MG	[63]
	Flavonoids - quercetin	Trapping MG	[64]
	Flavonoids - EGCG	Trapping MG	[65]
	Flavonoids - procyanidins	Trapping MG	[69]
(3) Detoxification of MG	Stilbenes - resveratrol + Flavonoids - hesperidin	Activation of GLO 1	[30]
(4) Inhibition of harmful AGE formation	Phenolic acids	Inhibition of AGE (e.g., CEL and CML) formation	[37,41]
	Stilbenes - resveratrol	Inhibition of AGE formation	[61]
	Flavonoids - flavones	Inhibition of AGE formation	[35]
	Flavonoids - hesperidin	Inhibition of AGEs formation	[63]
(5) Block RAGE	Stilbenes - resveratrol	Ameliorate DM complications	[58,60]

AGE = advanced glycation end product; CEL = N $^{\varepsilon}$-carboxyethyllysine; CML = N $^{\varepsilon}$-carboxymethyl-lysine; DM = diabetes mellitus; GLO = glyoxalase; MG = methylglyoxal; RAGE = receptor of advanced glycation end product; ROS = reactive oxygen species.

natural foods, such as rice, wheat, oats, vegetables, and fruits [35]. Ferulic acid in food model systems can reduce CML and CEL concentrations [36]. An *in vitro* protein–fructose model system also confirmed that ferulic acid could reduce the production of early Maillard reaction products [37]. In the past, gallic acid has been considered to have antioxidant and anti-inflammation functions. Recently, the antiglycation function of gallic acid has also been confirmed in *in vivo* and *in vitro* experiments; in addition to inhibiting AGE-induced inflammatory reactions [38], it could also attenuate the cardiac remodeling caused by AGEs [39]. In an MG-bovine serum albumin (BSA) system, chlorogenic acid was able to inhibit AGE production [40]. The antiglycation function of ellagic acid was achieved through the inhibition of CML production but not through antioxidant potential, metal chelation, or post-Amadori inhibition [41]. The results in glucose-, fructose-, and ribose-BSA systems showed that caffeic acid, ellagic acid, ferulic acid, and gallic acid in the three platforms reduced AGEs; however, the activity of ellagic acid and gallic acid in the glucose-BSA platform was not very significant [42]. In a diabetic nephropathy mouse model, the addition of ellagic acid and caffeic acid to the diet could reduce both AGE accumulation and inflammatory hormone concentrations in the kidney [43]. However, other studies found that caffeic acid could promote glycation [33] and could stimulate macrophages to produce pro-inflammatory hormones and reactive oxygen species (ROS) [44]. Therefore, the antiglycation effects of phenolic acids might produce inconsistent results in different experimental models, and the antiglycation mechanisms might also be different.

7.2. Lignans

Flaxseed and sesame are two substances in food with some of the highest lignan contents. However, studies concerning the antiglycation function of lignans remain quite limited. Sesamin is one type of lignan that is abundant in sesame oil and seeds. In the past, it was considered to have antioxidant and antihypertension functions and the ability to lower blood lipids [45,46]. In recent years, sesamin has been shown to inhibit the production of NADPH oxidase-mediated oxidative stress to slow down AGE-induced β-cell dysfunction and apoptosis [47]. Therefore, it might exert a protective function against β-cell injury induced by diabetes. Because flaxseed contains abundant lignins and alpha-linolenic acid, they are used extensively in the development of health food to lower blood lipids [48] and reduce inflammation. In particular, they can significantly reduce the function of C-reactive protein in the obese population [49]. The flaxseed-derived lignan phenolic secoisolariciresinol diglucoside is considered to have a strong antioxidant effect and can protect nonmalignant lung cells from radiation damage [50]. In addition, it can enhance the ability of antioxidant defenses to reduce asbestos-induced ROS generation and markers of oxidative stress in murine peritoneal macrophages [51]. Secoisolariciresinol diglucoside has many –OH groups and strong antioxidant properties; however, there has been no research on its antiglycation function, which warrants further validation.

7.3. Stilbenes

Resveratrol (3,5,4′-trans-trihydroxystilbene) is a phenolic compound in the stilbene family. It is mainly present in grape seeds and skin but occurs in over 70 types of plants [52]. Resveratrol is present in two forms, trans- and cis-form resveratrol. In 1992, Siemann and Creasy proposed that red wine was rich in resveratrol and that long-term appropriate red wine drinking might be associated with the lower prevalence of cardiovascular diseases in France and various Mediterranean countries, which was confirmed by many epidemiological studies and called the “French paradox” [53]. Many studies have already confirmed the antiglycation ability of resveratrol. In oocytes, resveratrol was found to inhibit the oxidative damage caused by MG by correcting the abnormality of the cellular ROS metabolism [54] and delayed MG-induced insulin resistance in hepatocytes through increasing the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) [55]. In addition, resveratrol can protect cells from MG-induced mitochondrial dysfunction and oxidative stress [56]. In a mouse model supplied with MG water, the regulatory effect of resveratrol on blood glucose and insulin did not show significant differences from pioglitazone; however, the expression of pancreatic insulin and Nrf2 in the pancreas both significantly increased. These results showed that resveratrol exerted an excellent attenuation effect on diabetic complications [57]. Resveratrol exerts a protective function against MG-induced injury and can reduce liver injury caused by type 2 DM by reducing the expression of RAGE in the liver [58]. In addition, it can inhibit the proliferation of smooth muscle cells and the expression of RAGE, which might help to reduce DM-induced vasculopathy [59]. Furthermore, it exhibits positive influences on diabetic nephropathy through inhibiting the function of RAGE in the kidney [60]. Therefore, resveratrol can delay long-term diabetic complications, which might be associated with the inhibition of AGE production [61] and of RAGE expression. In addition, stilbene glucoside extracted from *Polygonum multiflorum* Thunb was also confirmed to exhibit a reactive dicarbonyl species-MG trapping function in an *in vitro* study [62].

7.4. Flavonoids

Flavonoids are the largest group of polyphenols and are mainly present in tea, vegetables, and fruits. Because the structure of flavonoids includes three benzene rings and one –OH group, they have antioxidant properties. Therefore, the antiglycation features of flavonoids might be associated with their antioxidant function. Studies have shown that flavonoids are the group of polyphenols with the highest potential for the inhibition of glycoxidation; in addition, the inhibitory effects of polyphenols on glycation have been thought to be mainly due to their antioxidant rather than metal-chelating properties [42]. Wu and Yen [35] investigated the effects of 10 types of flavonoids on AGEs production in the early, propagation, and advanced phases of glycation, including flavanols [catechin, epicatechin (EC), epicatechin gallate (ECG), epigallocatechin-3-gallate (EGCG)], flavones (luteolin), flavonols (kaempferol, quercetin, rutin), and flavonols (naringenin). The results showed that luteolin, quercetin, and rutin significantly reduce the hemoglobin Amadori product, HbAlc, production in the early phase of glycation, with more significant effects than the AGE inhibitor aminoguanidine. In the propagation phase, luteolin and rutin showed better inhibitory effects on MG-mediated protein modification. In the advanced phase of glycation, luteolin had the highest ability to inhibit AGE production. Therefore, the authors considered flavones to be the type of flavonoids with the highest antiglycation potential.

The RNase A-MG assay system and the BSA-glucose assay were used to screen for the antiglycation function of hesperidin and its derivatives in the early and advanced phases of glycation. The results showed that hesperidin and its derivatives exhibited strong antiglycation functions and could be considered to have potential for the treatment of DM and aging-related diseases [63]. In addition, quercetin was considered to be able to inhibit AGE production through trapping MG and glyoxal [64]. Genistein, the major soy isoflavone, and its metabolites can trap MG in mice by promoting the formation of MG adducts which were identified in urine using liquid chromatography/electrospray ionization tandem mass spectrometry [65]. Zhu et al [66] found that 6-shogaol and 6-gingerol, the major active components in ginger, can also inhibit the MG-derived AGEs formation and consequently give rise to mono-MG adducts *in vitro*. The most abundant and bioactive flavonoid in tea, EGCG, was considered to have MG trapping ability and a possible carbonyl stress inhibitory function [67]. EGCG or rutin in low-density lipoprotein particles could protect lipoproteins from glycotoxin-mediated negative impacts [68]. *In vitro* experiments confirmed that cinnamon bark procyanidin B2 had an MG trapping function, while grape seed procyanidin B2, a dimeric procyanidin and

more biologically active, could significantly inhibit the vascular smooth muscle cell proliferation induced by AGE [69]. In addition, the combination of grape seed procyanidin B2 and resveratrol could protect against AGEs-induced endothelial cell apoptosis [70]. Oligomeric procyanidins extracted from lotus seedpods were found to scavenge MG, suggesting that carbonyl scavenging might be a major antiglycation mechanism [71]. They were all considered to have the potential to delay vascular complications in DM.

Flavonoids can affect AGE production in different phases of glycation; in addition, recent studies have shown that hesperidin, resveratrol, and their combination could increase GLO I mRNA and protein expression by 10–30% in the human hepatocyte-like HepG2 cell line *in vitro* and in primary culture of human aortic endothelial cells and BJ fibroblasts. Furthermore, the application of hesperidin and resveratrol together significantly increased the antioxidant enzyme GSH, and the increased GSH concentration might be helpful for the activation of GLO I. Therefore, the combination of hesperidin and resveratrol was further used for human studies. The results showed that after 8 weeks of supplementation with both 120 mg hesperidin and 90 mg resveratrol, GLO I activity increased by 22% in peripheral blood mononuclear cells of healthy overweight and obese subjects, while the plasma MG concentration decreased by 37%, which was considered to help the overweight and obese subjects to increase their metabolic and vascular health [30]. Therefore, supplementation with multiple types of polyphenols in combination might promote health through the influence of different factors on AGE production.

8. Conclusion

Recently, many studies have proposed many possibilities for antiglycation by polyphenols based on different properties of polyphenol substances, including their structures, antioxidant abilities, and metabolism in the body. In addition, many polyphenols extracted from natural products have also been confirmed to reduce glycative stress through various pathways [34,35,72]. However, there remains no consistent conclusion regarding the antiglycation abilities of different polyphenol substances. In addition, many studies have found that the use of two or more polyphenol substances exhibits better antiglycation functions than the use of a single substance. However, whether the experimental results for polyphenol substances in *in vitro* platforms truly reflect the situation *in vivo* still requires further study. In addition, polyphenols also tend to have low biological utilization rates. Therefore, future studies should clarify the effects of polyphenols on the production of MG and AGEs *in vivo* and investigate the application of polyphenols in relevant diseases resulting from the accumulation of MG and AGEs, thus allowing the development of health and functional foods for slowing down glycation-related diseases.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

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