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Antiglycating effects of citrus flavonoids and associated mechanisms

Yunli Xiao[a,1], Junfeng Shen[a,1], Jianfeng Zhan[a], Limin Guo[b], Chi-Tang Ho[c], Shiming Li[a,c,*]

[a] College of Biology and Agricultural Resources, Huanggang Normal University, Huanggang 438000, China
[b] Institute of Agro-Products Storage and Processing, Xinjiang Academy of Agricultural Sciences, Urumqi 830091, China
[c] Department of Food Science, Rutgers University, New Brunswick 08901, USA

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ABSTRACT

Glycation of proteins and DNA forms advanced glycation end products (AGEs) causing cell and tissue dysfunction and subsequent various chronic diseases, in particular, metabolic and age-related diseases. Targeted AGE inhibition includes scavengers of reactive carbonyl species (RCS) such as methylglyoxal (MG), glyoxalase-1 enhancers, Nrf2/ARE pathway activators, AGE/RAGE formation inhibitors and other antiglycatng agents. Citrus flavonoids have demonstrated antioxidant and anti-inflammatory effects and are also found to be effective antiglycating agents. Herein, we reviewed the up to date progress of the antiglycation effects of citrus flavonoids and associated mechanisms. Major citrus flavonoids, hesperedin and its aglycone, hesperetin, inhibited glycation by scavenging MG forming mono- or di-flavonoid adducts with MG, enhanced the activity of glyoxase-1, activated Akt/Nrf2 signal pathway while inhibiting AGE/RAGE/NF-κB pathway, reduced the formation of N^{ε}-(carboxylmethyl)lysine (CML) and pentosidine, inhibited aldol reductase activity and decreased the levels of fructosamine. The antiglycating activity and mechanisms of other flavonoids was also summarized in this review. In conclusion, citrus flavonoids possess effective antiglycating activity via different mechanisms, yet there are many challenging questions remaining to be studied in the near future such as *in vivo* testing and human study of citrus flavonoids for efficacy, effectiveness and adverse effects of citrus flavonoids as a functional food in managing high levels of AGEs and controlling AGE-induced chronic diseases, diabetic complications in particular.

1. Introduction

Happening ubiquitously *in vivo* and *in vitro*, glycation is a non-enzymatic reaction between carbonyl groups on reducing sugars and reactive carbonyl species (RCS) and free amino groups on amino acid residues of proteins, DNA and lipids. Products formed from direct addition and subsequent rearrangements, cyclization and or dehydration are called advanced glycation end products (AGEs)[1-2]. RCS, including methylglyoxal (MG) and glyoxal (GO), could be generated *in vitro* from Mallard reaction and glucose auto-oxidation[3] and *in vivo* through various metabolic pathways including the glycolysis[4]. Due to the high electrophilic reactivity of RCS toward nucleophiles such as electron-rich amino groups on proteins, glycation happens rapidly once RCS are generated and AGEs formed. The carbonyl groups on reducing sugars are electron-deficient and readily attacked by amino residues on proteins to form AGEs. The most noticeable AGE is glycated hemoglobin (HbA_{1c}) found half century ago, a diagnostic biomarker for diabetes mellitus and diabetic complication[5].

There have been reported pathological mechanisms that the accumulation of AGEs may seriously cause many physiological dysfunctions, particularly in a prolonged period of time[6-7]. Exposure of dietary AGEs resulted in inflammation and associated diabetic angiopathy, whereas, restricted intake of dietary AGEs improved

[1] Authors contributed equally.
[*] Corresponding author at: College of Biology and Agricultural Resources, Huanggang Normal University, Huanggang 438000, China.
E-mail address: shiming@rutgers.edu (S.M. Li)
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insulin resistance in human type 2 diabetes[8-10]. Due to the glycation, amino acid residues and proteins will alter even loss functionality and lead to oxidative stress induced age-related cataract and neurodegenerative diseases[11], tissue injury[12], cell apoptosis[13-14] and others, resulting in many degenerative diseases[11-12,14-15], such as cardiovascular disease[16-18], cancer[19], diabetic complications[12,18,20-22], brain health problems[23-26] and ageing among others[26-28].

This review will start briefly with the mechanism of glycation and thus formed AGEs with proteins and DNA and then focus on the effective control of AGEs by citrus flavonoids via multiple mechanisms including trapping MG and other RCS, enhancing glyoxalase-1 activity, inhibiting AGE formation, scavenging formed AGEs, inhibiting the activity of AGE receptor (RAGE), and other associated pathways.

1.1 Glycation

Glycation happens when the amino acid residues of a protein react with a reducing sugar such as glucose and fructose. As depicted in Fig. 1, this non-enzymatic and spontaneous reaction occurs stepwise[29]. The initial reaction is between an amino acid and a sugar forming an imine or Schiff's base, which undergoes rearrangement to generate a stable Amadori product (Fig. 1). The resulting Amadori product generates different types of dicarbonyl compounds after cleavage at different bonds on the sugar moiety. Thus yielding dicarbonyl compounds, i.e. reactive carbonyl species including glyoxal, methylglyoxal, glucosone, 3-deoxyglucosone and others, are very reactive due to their electron deficient nature and readily attacked by electron-rich nucleophiles, such as side chain amino groups of amino acid residues on a protein. This is the glycation process that forms AGEs[29-30].

Fig. 2 illustrates several common examples of such AGE compounds formed from MG and arginine- or lysine-containing proteins, such as N^{δ}-(5-methyl-4-imidazolon-2-yl)-*L*-ornithine (MG-H1) from arginine and MG, 2-amino-5-(2-amino-5-hydro-5-methyl-4-imidazolon-1-yl)pentanoic acid (MG-H2) from arginine and MG, N^{ω}-(carboxylethyl)arginine (CEA) from arginine and MG, N^{ε}-(carboxylmethyl)lysine (CML) from lysine and GO, and N^{ε}-(carboxylethyl)lysine (CEL) from lysine and MG; 6-{1-[(5*S*)-5-ammonio-6-oxido-6-oxohexyl]-4-methyl-imidazolium-3-yl}-*L*-norleucine (MOLD) from lysine dimer and MG; 2-ammonio-6-({2–[4-ammonio-5-oxido-5-oxopentyl) amino]-4-methyl-4,5-dihydro-1H-imidazol-5-ylidene}amino)hexanoate (MODIC) from lysine, arginine and MG, and others, among which MG-H1 is a major methylglyoxalated protein derived AGEs[30-31]. For example, MG-H1 accounts for about 1%–2% of arginine-containing proteins in mammalian tissue, plasma, and extracellular matrix proteins[32]. MG-H1 is the most abundant AGEs in aged human lenses and levels could reach 6 nmol/mg proteins. Glycated human lens proteins (AGEs) could stimulate further glycation, oxidation, and protein aggregation, leading to cataract formation[30]. In elder people without diabetes, MG-H1 was the most abundant AGE in bone compared to non-MG derived AGEs[18]. Immunoglobulins contain about 75% lysine residue, which is susceptible to glycation forming AGEs, resulting in the loss of bind affinity with antigens and its immune functionality[20-21].

Upon the modification by MG, proteins will lose or alter their original biofunctionality because of the compositional and conformational structure change of proteins such as cross-link of extracellular and cellular proteins. Fig. 2 also demonstrated common AGEs from MG and DNA, such as MG reacting with 2-deoxyguanosine generating N^2-(1-carboxyethyl)-2′-deoxyguanosine (CEdG) and with 2′-deoxyadenosine forming N^6-(1-carboxyethyl)-2′-deoxyadenosine (CEdA)[33-34].

1.2 Inhibion of RCS and AGE by phytochemicals

Clearance of RCS and AGEs with phytochemicals has been broadly studied, particularly with polyphenolic compounds. Tea polyphenols could effectively trap MG in simulated physiological conditions to form mono- and di-MG adducts with catechins and theaflavins[31,35]. Both rutin and its aglycone quercetin expressed antiglycation effects by decreasing the levels of protein carbonyl groups and inhibited the formation of AGEs in a concentration dependent manner, but rutin has demonstrated more potent effects of antiglycation than quercetin[36]. Dietary myricetin and its mono- and di-methylated *in vivo* metabolites effectively trapped MG forming mono- and di-MG adducts, demonstrated the efficacy of myricetin in scavenging MG after myricetin-fruits/vegetables consumption[37].

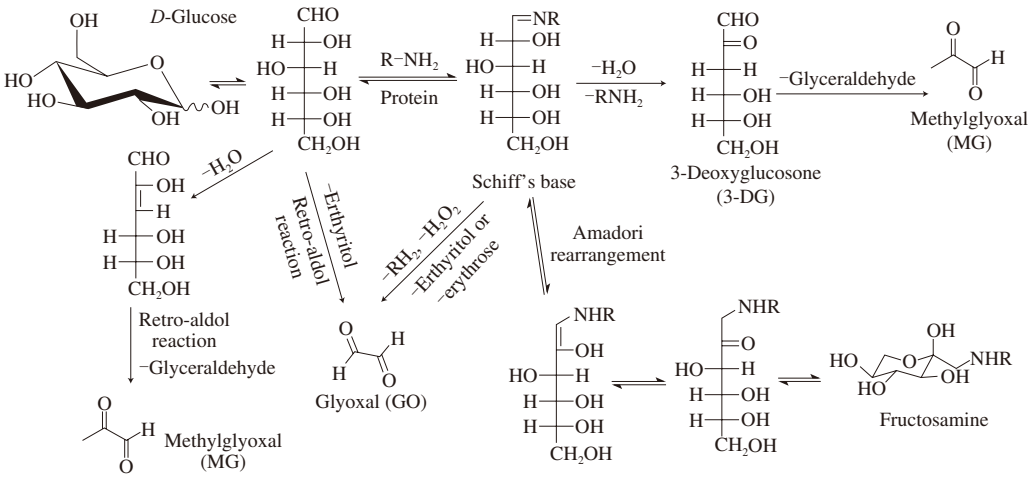


Fig. 1 Formation of RCS.

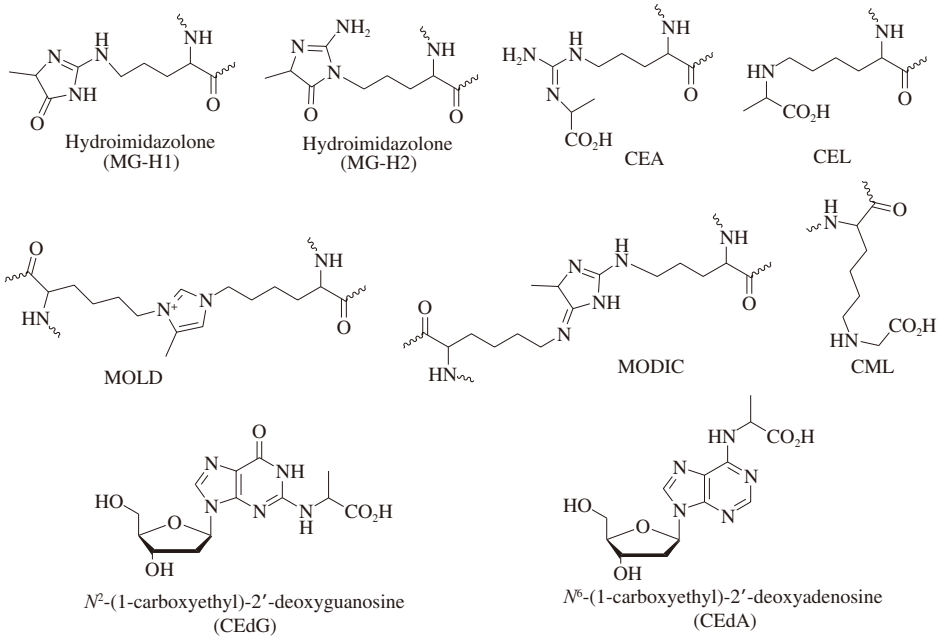


Fig. 2 Structures of common AGEs from MG and protein and DNA.

In diabetic patients, high blood sugar and its *in vivo* derived RCS such as MG, GO and 3-deoxyglucosone trigger glycation reaction, which continues even the levels of glucose are reduced[38]. Baicalein from *Scutellaria baicalensis* has efficiently inhibited the glycation of human serum alubimin (HSA), marked by the reduced levels of AGE after addition of baicalein to a pre-incubated MG-containing HSA[39]. Pholorotannis in brown algae *Fucus vesiculous* also inhibited the glycation of bovine serum albumin (BSA) by 50% in 2 h[40]. The effective RCS trapping and inhibition of AGE formation have been demonstrated by other phytochemicals such as stilbene compounds to prevent diabetes complication[41-42].

1.3 Citrus flavonoids

Citrus fruits in general are the most-grown fruits globally, contributing to various health-promoting and valuable phytochemicals. Belonging to the family of Rutaceae, the major species and main industrialized citrus crops include oranges, mandarins, grapefruits and lemons among others[43-44]. Citrus processing for juice and concentrated products makes up one third or more of total citrus consumption, thus massive amounts of citrus peels are left wasted. Actually, intensive research from the past two decades has demonstrated that there are many food bioactives in citrus peels, such as essential oils, flavonoids and other polyphenolic compounds, organic acids, polysaccharides, dietary fiber and other valuable phytochemicals[43]. Citrus fruits as a whole are a rich source of flavonoids, majorly flavanones (Table 1) and a certain amount of polymethoxyflavones can also be found in citrus peels (Fig. 3)[45]. It is demonstrated that citrus flavonoids have antioxidant[44,46-49], anti-obesity[50-51], inhibition of chronic inflammation[46,52-53], anti-cancer[54-56], protective effects against brain-injury[57-58], Alzhemer's[53,59-61] and Parkinson's diseases[61], anti-diabetic effects[62-64], regulation of gut microbiota[44,51,65] and anti-ageing activity[66-67]. In addition, citrus flavonoids have been found recently to have effective anti-glycation properties[63,68]. This review will be focused on the inhibitory effects of citrus flavonoids, particularly, hesperedin and PMFs on glycation.

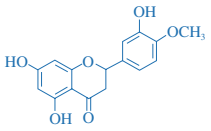
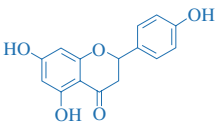
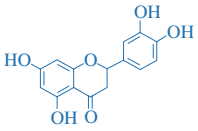
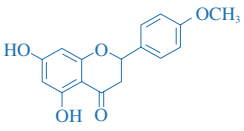
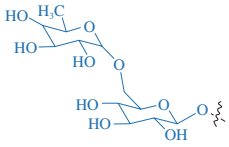
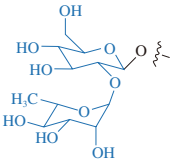
2. Anti-glycation of citrus flavonoids

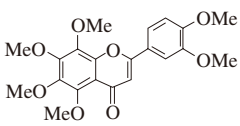
In searching for effective agents to inhibit glycation and disease prevention, much research has been dedicated to natural products, such as tea and other polyphenols[35,69]. In this review, we concentrated on the anti-glycation activity and associated mechanisms of citrus flavonoids.

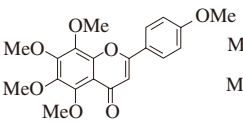
2.1 Citrus flavonoids scavenging RCS

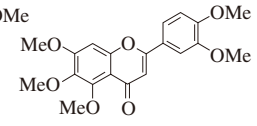
In citrus flesh and peels, hesperedin is one of the richest flavonoids[65-66]. It has been demonstrated that hesperedin has antioxidant[70], inhibitory effects on inflammation[47,70], and protective effects against CVD, among others[71]. For instance, a recent human study with hesperedin enriched orange juice consumption reduced insulin resistance and the expression of proinflammatory genes after a 12-week treatment[72]. Hesperedin regulated mineralized tissue formation through the mechanism of osteoblast cell differentiation and matrix organization, a potential adjunct therapy in bone regeneration[73]. Moreover, hesperedin has strong anti-glycation effects and hence can ameliorate multiple AGE-related chronic diseases. The anti-glycation effects of hesperedin is the most studied among citrus flavonoids. Numerous research results have associated RCS-induced AGEs with improvement in diabetes complication. Commercial anti-diabetes drugs can control blood sugar but usually cannot prevent diabetes-related complications. As it was discussed in the introduction, reducing the formation of AGEs by scavenging its precursor–RCS, MG in particular and removing formed AGEs in a bio-system are two of the strategies to prevent diabetes complications. Hesperedin possesses strong antioxidant effects, and thus can effectively scavenge reactive oxygen species (ROS). Owing to its nucleophilic structural nature, it can react and remove RCS rapidly to

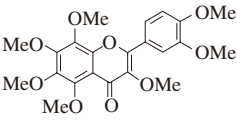
Table 1
Common polyhydroxylated flavonoids in citrus genus.

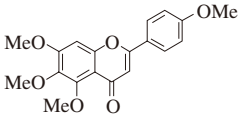
Aglycones	 Hesperetin	 Naringenin	 Eriodictyol	 Isosakuranetin
Sugar moiety	Glycosylated flavanones and citrus fruits			
 7-*O*-Rutinose glycosides	Hesperedin Sweet orange Tangerine Mandarin Tangor	Narirutin Sweet orange Tangerine Mandarin Tangor	Eriocitrin Orange Tangerine Mandarin	Didymin Sweet orange Blood orange Mandarin
 7-*O*-Neohesperedinose	Neohesperedin Sour orange Tangelo Grapefruit	Naringin Sour orange Tangelo Grapefruit	Neoeriocitrin Sour orange	Poncirin Trifoliate orange

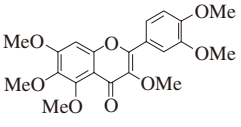

Nobiletin

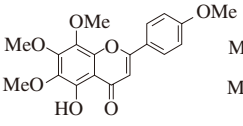

Tangeretin

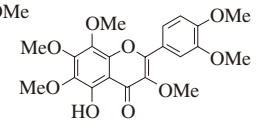

Sinensetin

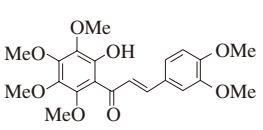

3,5,6,7,8,3′,4′-Heptamethoxylflavone


5,6,7,4′-Tetramethoxyflavone


3,5,6,7,3′,4′-Hexamethoxylflavone


5-Hydroxy-6,7,8,4′-tetramethoxyflavone


5-Hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone


2′-Hydroxy-3,4,3′,4′,5′,6′-hexamethoxyflavone

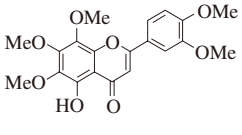

5-Hydroxy-6,7,8,3′,4′-pentamethoxyflavanone

Fig. 3 Chemical structure of major polymethoxylated flavonoids from citrus genus.

prevent RCS, e.g. MG, from glycating proteins and DNA. Hence it plays an important role as an anti-glycation agent.

Removing RCS is the first step in reducing AGE. Anti-glycation activity of plant extracts and their major bioactives have been evaluated. Notable examples include tea and tea polyphenols[29,74], mung bean[75], apple[76], soybean isoflavones[77] and myricetin from fruits and vegetables[37]. It has been revealed so far that the majority of phytochemicals that demonstrated the most effective anti-glycation property are polyphenols, more specifically flavonoids. Alkaloids bearing primary or secondary amino groups may have stronger affinity toward combining with RCS but should be explored with caution, due to their potential toxicity in general. The RCS scavenging property of hesperedin has been evaluated recently. Additionally, the adduct structures of hesperedin and hesperetin with MG were characterized as mono- and di-MG addition[78-79]. Hesperedin and hesperetin (0.2 mmol/L) were incubated under mimicked physiological conditions using phosphate buffer saline (PBS; pH 7.4) and at 37 °C, 0.6 mmol/L MG. After a certain amount of time, e.g. 1 h, the trapping reaction was terminated and new compounds of adducts were identified by liquid chromatography. There were 6 new adduct peaks formed from the incubation of MG and hesperedin, and they were identified as primarily mono-6-MG-hesperedin. The stereo center at 2-position and loss of rutinosyl group yielded more than expected peaks in liquid chromatography[68]. Structures of MG adducts with hesperedin and hesperetin are depicted in Fig. 4[78-79]. Hesperetin is an aglycone of hesperedin. The release of the 7-*O*-rutinosyl sugar group also enhances the nucleophilic attack at 6- and 8-position of hesperetin and subsequent formation of a stable hemiacetal 5-member ring structure between MG and hesperetin at 6- and 5-positions; or 8- and 7-postions, which mostly rendered two mono-MG-hesperetin adducts. Similar to other adducts identified between MG and polyphenolic compounds such as tea catechins, MG-hesperedin/hesperetin adducts are in the most stable form, but were only identified from liquid chromatography and mass spectroscopy. Further characterization is warranted to discover definitive structures. Fig. 4 also illustrates the deduced structures of adducts between MG and another citrus flavonoid–diosmetin, from which we can see that the nucleophilic reaction occurred at 6- or 8-postion for mono MG addition or at both 6- and 8-postion for di-MG addition[78]. It should be reminded that all the adduct structures in Fig. 4 have regioisomers, thus NMR confirmation is required to illustrate the yielded structures of MG adducts with citrus flavonoids with much confidence.

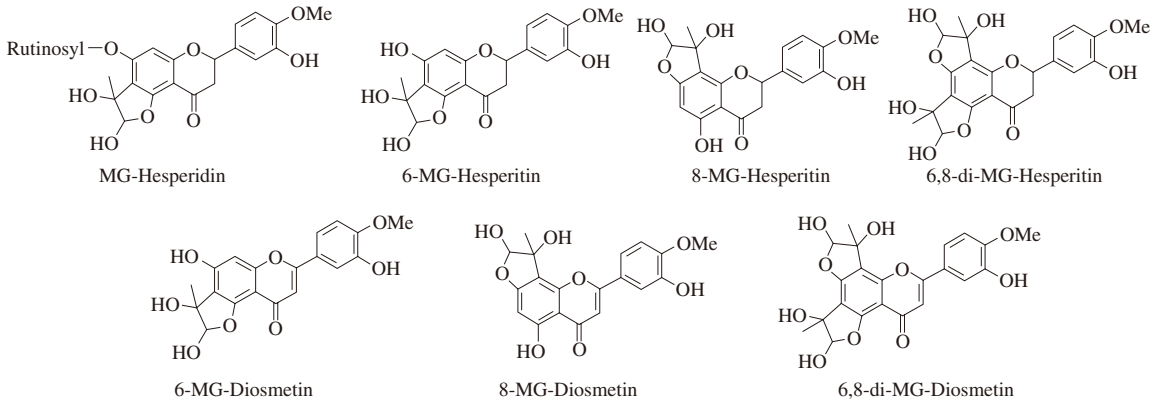


Fig. 4 Adducts of MG and hesperedin and hesperetin[78-79].

2.2 Citrus flavonoids enhancing Glo-1 activity, activating Nrf2/ARE pathway and inhibiting AGE/RAE/NF-κB pathway

1,2-Dicarbonyl (or α-dicarbonyl) aldehydes are the most reactive class of RCS, such as methylglyoxal and glyoxal generated *in vitro* from the Maillard reaction, glucose auto-oxidation (Fig. 1) or endogenously from the glycolytic pathway by nonenzymatic degradation of triosephosphates, glyceraldehyde-3-phosphate (GA3P) and dihydroxyacetonephosphate (DHAP) in anaerobic glycolysis, gluconeogenesis, glyceroneogenesis and photosynthesis[80]. As mentioned in previous sections, α-dicarbonyl aldehydes are highly reactive and readily react with electron rich amino groups on proteins and DNA, leading to glycation and consequent pathological process of chronic diseases such as diabetic complication. Glyoxalase 1 (Glo-1) and glyoxalase 2 (Glo-2) in the body play pivotal roles in the clearance and detoxication of α-dicarbonyl aldehydes, among which Glo-1 is the rate-limiting enzyme. In the presence of glutathione (GSH) as a cofactor, Glo-1 rapidly removes methylglyoxal under normal physiological conditions. In pathological conditions such as hyperglycemia, enhancing the activity of Glo-1 by a drug or nutrient is another strategy to remove MG and GO[80]. Indeed, Glo-1 over expression has been reported to improve the pathological features of diabetic complications[81-82]. Glo-1 is controlled by transcription factor-nuclear factor erythroid-2-related factor 2 (Nrf2)/anti-oxidant response through regulatory antioxidant response element (ARE) pathway. Elevated MG levels in hyperglycemia conditions induce oxidative stress, which consequently cause down-regulation of Glo-1 leading to increased levels of AGE[83]. Existing in the cell membrane, the receptor for advanced glycation end products (RAGE) was discovered as a signal transduction receptor for AGEs such as CEL. AGEs bind to RAGE and consequently trigger the nuclear factor κB (NF-κB) signaling pathway, inducing inflammatory response and causing oxidative stress and a cascade of biological consequences, such as cell damage[84].

Hesperedin was found to have activated the Akt/Nrf2 signal pathway and inhibited the RAGE/NF-κB pathway[85]. In a 90-day APP/PS mouse study with a dose of 40 mg/kg, hesperedin effectively reduced levels of ROS, lipid peroxidation, protein glycation and 8-OHdG, while increasingthe activity of HO-1, superoxide dismutase (SOD), catalase, and glutathione peroxidase, overall significantly suppressing oxidative stress, leading to protective effects of neuroinflammation and against Alzheimer disease (AD)[85]. Hesperetin, the aglycone of hesperedin, occurs naturally in citrus fruits in a much smaller content than hesperedin, but can be increased dramatically as a metabolite of hesperedin after ingestion of citrus fruits or citrus juice that contains relatively larger amount of hesperedin. It has been reported that hesperetin combined with resveratrol improved metabolic and vascular health in overweight and obese human subjects as a Glo-1 inducer[86]. More importantly, this co-formulation of hesperetin and resveratrol significantly increased the expression and activity of Glo-1 by 27%, decreased the level of plasma MG by 237%, reduced the total protein glycation by 214%, decreased fasting glucose by 25% and increased oral glucose sensitivity index by 42 mL/(min·m^2)[86], indicating the great efficaciousness of hesperetin and resveratrol in scavenging MG and reducing AGE formation.

As above-mentioned, α-dicarbonyl aldehydes and their detoxifying enzyme Glo-1 play a vital role in the pathogenesis of diabetic complications, including nephropathy, neuropathy and depression, among others. A recent study revealed that hesperedin effectively ameliorated behaviors of depression and anxiety of diabetic rats, attributing to the enhancement of Glo-1 in scavenging MG and GO, etc. α-Dicarbonyl aldehydes and the activation of the Nrf2/ARE pathway[87]. In this controlled study, treatment containing hesperedin to diabetic rats induced by streptozotocin at a dose of 50 or 150 mg/kg led to many behavior changes toward normality, such as decreased immobility time in a forced swimming test and increased entry percentage and time spent in open arms in a maze test. More importantly, hesperedin enhanced Glo-1 activity, inhibited the AGEs/RAGE axis and oxidative stress in the brain, and significantly increased the Nrf2 levels and upregulated g-glutamylcysteine synthetase, demonstrating the antidepressant and anxiolytic effects of hesperedin in diabetic rats[87]. The renoprotective effects of hesperetin in diabetic nephropathic rats induced by streptozotocin have been evaluated and found that hesperetin at a dose of 50 or 150 mg/kg effectively ameliorated the renal morphological changes and improved renal functions and structural changes of the diabetic rats[62]. This study demonstrated that hesperetin treatment up-regulated the expression of Glo-1 and enhanced Glo-1 activity, reversed the declined kevels of Nrf2, and significantly increased levels of Nrf2 at both dosages. High dosage of hesperetin significantly facilitated the phosphorylation of Nrf2, thus remarkably raising the levels of p-Nrf2 in nucleus[62]. Furthermore, hesperetin significantly up-regulated the expression levels of γ-glutamylcysteine synthetase (γ-GCS), a downstream gene regulated by the Nrf2/ARE pathway,

confirming the Nrf2/ARE pathway activation by hesperetin. This study also found that hesperetin decreased AGE content and RAGE expression in the renal cortex of diabetic rats and inhibited IL-1β and TNF-α inflammatory cytokines significantly, further confirming the inhibitory effects of AGEs/RAGE related inflammation axis[62].

2.3 Citrus flavonoids inhibiting glycation and AGE formation

In addition to direct scavenging of RCS and enhancing Glo-1 activity, activating Nrf2/ARE pathway and inhibiting AGE/RAGE/NF-κB pathway by citrus flavonoids, there are a number of reports that have demonstrated the anti-glycation effects of citrus flavonoids or citrus extracts by inhibiting the formation of AGEs and or degrading the formed AGEs back to proteins.

When lysine residue is glycated by GO, the product is CML (Fig. 2). It has been reported that hesperedin reduced the content of CML compared to the model group[88] in a study that investigated the inhibitory effects of AGEs by hesperedin in a rheumatoid arthritis (RA) model. There were large amounts of free radicals produced in the RA model. These free radicals, ROS in particular, acted as active glycating agents after intra-structure rearrangements or other alterations[88], from which AGEs formed were increased dramatically after the injection of collagen type II suspension to Wistar rats. In the 21-day oral feeding study, hesperedin significantly inhibited bone loss, reduced the levels of CML and pentosidine (an AGE) concentrations significantly by hesperedin, by 20% (CML) and 26% (pentosidine) in plasma; and 21% and 16% in IgG, respectively. Therefore, the RA alleviation of hesperedin was achieved by scavenging ROS, inhibiting inflammation and also reducing the levels of AGEs[88]. A mouse study using human lens epithelial cell lines and mouse lens organ cultures found that AGEs in lens proteins increased with age. However, hesperetin at 50 or 100 μmol/L prevented the formation of AGEs and CML and also the modification of lens proteins in a dose-response manner[68]. In addition, hesperetin treatment also prevented lens hardening and decreased chaperone activity of lens proteins. Taken together, it has suggested that hesperetin and its derivatives could be agents for the prevention of presbyopia and cataracts[68].

It has been known that oxidative stress and glycation are closely associated with diabetes complications. Also, serum fructosamine, a circulating glycated protein, is formed from the glycation of mostly albumin, and the levels of fructosamine can provide an estimate of the average blood glucose levels in the preceding 2–3 weeks. It has been shown that fructosamine correlates more consistently with continuous glucose monitoring than hemoglobin A1c (HbA1c), first identified AGE from diabetes patients more than 5 decades ago[5,89]. An *in vitro* study using human serum albumin has found that hesperedin at 50 μmol/L decreased the content of fructosamine by 40% and inhibited AGE formation by 71%[90], indicating the effective antioxidant and anti-glycation effect of hesperedin. Another *in vitro* study with ROS-induced oxidative stress in L6 myotubes, both hesperedin and hesperetin effectively reduced oxidative stress by scavenging intracellular ROS and up-regulating antioxidant defense system such as SOD and GPH. At 10 μmol/L, hesperedin and hesperetin inhibited protein glycation by 65.6% and 35.6%, respectively; significantly reduced the formation of AGEs, demonstrating that hesperedin and hesperetin, as functional food ingredients, could effectively suppress diabetic pathophysiology mediated by oxidative stress[63]. The complex of hesperetin-Cu (II) also demonstrated strong anti-glycation effects. In a BSA-fructose system, simplified mimicking diabetic complications model, the hesperetin-Cu (II) complex inhibited AGE formation by more than 88%, more effective than hesperetin (51%) and aminoguanidine (22%). The complex also reduced the levels of BSA carbonylation and oxidation, inhibited BSA crosslinking by 66%, scavenged 79% hydroxyl radical, and removed 85% MG after co-incubation, indicating that the hesperetin-Cu (II) complex could have a close interaction with BSA, strong MG scavenging capability, and effective removal of free radicals[91]. Also in the BSA-fructose model, pomelo extract, containing neohesperedin, hesperedin, naringin and naringenin in amounts of 25.4, 12.0, 11.0 and 9.2 mg/g measured by high-performance liquid chromatography, respectively, significantly decreased the fructosamine content and inhibited the formation of AGE and CML in a concentration-dependent manner[92]. Poncirin, another flavanone from citrus fruits, has been investigated for its anti-diabetic activity and associated mechanisms, including inhibitory effect against protein tyrosine phosphatase 1B, α-glucosidase, human recombinant aldose reductase, rat lens aldose reductase and AGE formation with respective IC_{50} values of 7.76, 21.31, 3.56, 11.91 and 3.23 μmol/L[92]. In a C2C12 cell study, pocirin significantly increased glucose uptake, decreased PTP1B expression, and consequently, increased the level of GLUT-4 expression by activating IRS-1/PI3K/Akt/GSK-3 signaling pathway. More importantly, during 4 weeks of study, poncirin effectively inhibited the formation of fluorescent AGE, CML, fructosamine and β-cross amyloid in a BSA glycation model induced by glucose-fructose[93].

Polymethoxyflavones (PMFs) from citrus peels have attracted great attention due to their multiple biological activities such as antioxidant[45,47,49,94], inhibition of inflammation[47,52,94-95], anti-cancer[54-56] and prevention of Alzheimer's disease[96-97] among others. However, the anti-glycation activity of PMFs was rarely explored. Ubiquitously existing in the peels of citrus genus, 5-demethylnobiletin significantly inhibited protein glycation (IC_{50} 64.2 μmol/L), more effectively than aminoguanidine (IC_{50} 484.3 μmol/L), through preventing the formation of fructosamine adducts and also dicarbonyl generation[98]. This is the first time that a PMF was identified as an effective AGE inhibitor. Further investigations on the AGE formation by PMFs and associated mechanisms elucidation are warranted.

2.4 Citrus flavonoids alleviated AGE induced stress

Formed AGEs cause pathological changes in the body and result in various diseases[6,12]. As aforementioned, citrus flavonoids have been reported to scavenge RCS directly and to elevate Glo-1's activity to quickly clear MG, GO and other α-dicarbonyl compounds, effectively reducing the formation of AGEs. However, AGEs already formed and existing in the body are slowly metabolized. In the meantime, pathophysiological conditions induced by AGEs need to be addressed to avoid potential tissue damage and chronic disease conditions.

It has been observed that treatment of human SH-SY5Y neuroblastoma cells with AGEs in BSA triggered ROS overproduction and elevated levels of SOD, GPX and catalase, but hesperetin treatment effectively reduced the overproduction of ROS and decreased the levels of SOD, GPX and catalase, down-regulated the

expression of amyloid precursor protein and decreased β-amyloid (Aβ) production[99]. Furthermore, the application of hesperedin at 40 μmol/L significantly mitigated the expression of endoplasmic reticulum stress proteins induced by AGEs at a range of 50–250 μg/mL in BSA, hence, hesperedin played a crucial role in attenuating glycation-induced Aβ neurotoxicity and preventing Alzheimer's disease[99]. Another citrus flavonoid, diosmetin, also demonstrated the alleviating effect against AGE-induced AD-like pathology. At a concentration of 10 μmol/L, diosmetin treatment of human SH-SY5Y cells stimulated with 200 μg/mL of AGEs effectively inhibited the overproduction of ROS and down-regulated the expression of antioxidant enzymes such as SOD, GPX and catalase. Diosmetin also reversed amyloid precursor protein upregulation and increased production of amyloid-β, which was triggered by AGEs[100]. Diosmetin pre-treatment of SH-SY5Y cells prevented endoplasmic reticulum (ER) stress response to AGEs[100], thereby protecting neuroblastoma cells from ER injury induced by AGEs.

3. Other methods of alleviating AGEs and RAGE expression

As mentioned in previous sections, citrus flavonoids inhibited AGE formation and accumulation and could potentially prevent pathophysiological diseases via the scavenging of MG, GO, 3-GD and other RCS, prevention of oxidative stress, inhibition of fructosamine formation and aldose reductase activities, elevation of Glo-1 activity, inhibition of AGE formation and removal of formed AGEs among others. Other methods to control AGEs also include inhibition of RAGE formation[101-102], degradation of AGEs/RAGE by ubiquitin-proteasome system[103-105], autophagy[106-108] and physical exercise[109] combined with diet intervention[110]. Recent reviews briefly summarized the mechanisms targeting the inhibition and scavenging of AGEs[111-112]. However, due to the nature of multiplicity of the glycating process, an anti-glycation agent often plays multi-functional roles at different stages of glycation in preventing the damage caused by AGEs.

For instance, citrus flavonoids naringin and its aglycone naringenin have demonstrated their anti-glycating property in an incubated mixture of HSA, ribose and GO[113]. Both naringin and naringenin effectively inhibited the glycation of HSA by GO, marked by the significant decrease of the absorbance intensity of AGEs formed between HSA and GO at all three wavelength (335, 350 and 370 nm) tested by comparing to that of a reaction system with no flavonoids added[113]. In addition to expected anti-glycating mechanisms of these two citrus flavonoids such as antioxidation and direct trapping of GO, hydrogen bonding between flavonoids and HSA, and interactions between arginine and lysine residues and GO also prevented GO glycating HSA. It has been found that naringenin had stronger antiglycating than naringin for it binds to HSA sub-domains IIA and IIIA, whereas naringin only binds to HSA subdomain IIA. It is of great importance to investigate the inhibitory effects of HSA glycation by agents like citrus flavonoids because HSA is almost the most prevalent protein in the plasma and extremely susceptible to glycation. Furthermore, the two citrus flavonoids dramatically decreased the presence of fibrillar aggregates generated from HSA modification by GO and ribose[113].

In the polyol pathway, aldose reductase is enhanced in the hyperglycemic conditions, which results in overproduction of sorbitol and fructose that in turn converts to fructosamine and other AGEs, subsequently causing diabetic complications[114]. Therefore, inhibition of aldol reductase is one of the important strategies to control diabetes complications. In a recent enzyme binding assay with aldol reductase, naringenin has demonstrated inhibitory effects of aldose reductase with an IC_{50} of 2.6 μmol/L. At a concentration of 10 μmol/L, naringenin reduced the content of fructosamine by more than 31% and inhibited the production of fluorescent AGEs by 93%[115], indicating that naringenin can inhibit aldose reductase efficiently. From the aforementioned, we can see that naringenin has effective anti-glycation effects through multiple pathways[113,115]. Therefore, the mechanism of anti-glycation activity of citrus flavonoids such as hesperedin, naringin and their aglycones, has been found to be multidimensional.

4. Concluding remarks

Mounting evidence has attested that excessive AGEs are linked to numerous age-related diseases, particularly diabetes complication, cardiovascular and Alzheimer's diseases, while people with hyperglycemia produce more AGEs but have a slower clearance rate, resulting in the accumulation of AGEs in their bodies. Current strategies reducing AGEs include trapping RCS, enhancing Glo-1 activity, inhibiting glycation, reducing aldose reductase activity, degrading formed AGEs/RAGE, and activating the Nrf2/ARE pathway and inhibiting the AGE/RAGE/NF-κB pathway, autophagy, and exercise, among others. It has been demonstrated that citrus flavonoids such as hesperedin, hesperetin, naringin, naringenin, diosmetin, neohesperedin and polymethoxyflavones were involved in one or multiple pathways aforementioned in reducing AGEs and related detrimental effects. However, many challenges remain to be solved in addressing the antiglycation effects and associated mechanisms of citrus flavonoids, particularly in the efficacy and long term effectiveness in human consumption as functional foods.

Conflict of interest

Chi-Tang Ho is a senior editor, and Shiming Li is a scientific editor for *Food Science and Human Wellness* and were not involved in the editorial review or the decision to publish this article. None of the authors have any conflict of interest.

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