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Mechanistic Modulation of Food Bioactives and Metabolites on Reactive Carbonyl Species and Advanced Glycation End Products

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ABSTRACT: Reactive carbonyl species (RCS) and advanced glycation end products (AGEs) are strongly linked to numerous chronic diseases, including diabetes complications, nephropathy, hepatopathy, neurodegenerative diseases, cardiovascular diseases, and certain cancers. While extensive drug development efforts have targeted RCS and AGE inhibition, several candidates, even those reaching Phase III trials, were ultimately terminated due to safety concerns and economic reasons. In contrast, food-derived bioactive compounds and their metabolites are generally recognized as safe and well accepted by consumers, presenting promising alternatives for modulating RCS and AGEs and preventing related diseases. This review provides a comprehensive overview of such bioactives with potent RCS and/or AGE modulation capabilities, detailing their action mechanisms. Covered compounds include flavonoids (e.g., tea catechins, citrus flavanones like hesperetin and didymin, apple dihydrochalcones such as phloretin and phloridzin, and myricetin), non-flavonoids (e.g., oxyresveratrol, emodin, and physcion from *Polygonum multiflorum*; 6 shogaol and 6 gingerol from ginger; curcumin from turmeric), and macromolecules (e.g., the dipeptide carnosine and various polysaccharides). Mechanistically, these compounds act through primarily direct trapping of RCS and Amadori intermediates, inhibition of AGE formation (via carbonyl stress alleviation, glycoxidation suppression, crosslink cleavage), and upregulation of detoxifying enzymes such as glyoxalase I. Many food bioactives demonstrate better RCS/AGE inhibition capabilities than pharmaceutical positive controls such as aminoguanidine. However, their poor oral bioavailability remains a major hurdle and requires further research in economic improvement strategies. Exploring new bioactive compounds and metabolites is also a key area for future research.

Keywords: food bioactives, metabolites, anti-glycation, polyphenols, polysaccharides

1. Introduction

Maillard reaction (MR), a well-known and pivotal chemical reaction in the food flavor industry, refers to a cascade of reactions between carbonyl groups of reducing sugars, such as glucose, and *N*-terminal amine groups of amino acids, peptides, or proteins.^[1, 2] In the intermediate stage, reactive carbonyl species (RCS) are produced, including reactive α -dicarbonyl compounds (α -DCs).^[3] The α -DCs play a dominant role among RCS, and representative ones include glyoxal (GO), methylglyoxal (MGO), 2,3-butanedione/diacetyl (DA), hydroxypyruvaldehyde, glucosone (GS), 1/3-deoxyglucosone (1/3-DG), 3-deoxygalactosone (3-DGal), and

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malonaldehyde.^[4] RCS also includes acrolein (ACR) and 4-hydroxy-2-nonenal (HNE), among others. In the final stage of reactions, advanced glycation end products (AGEs) and melanoidins, contributing to the dark color, are produced. The α -DCs are the main precursors of AGEs, as are Schiff base and Amadori compounds.^[5] About 38 AGEs have been identified up to now.^[6] Representative AGEs can be divided into three groups: lysine-based, arginine-based, and lysine-arginine-based, including *N* ϵ -(carboxymethyl)lysine (CML), *N* ϵ -(carboxyethyl)lysine (CEL), pyrraline, glyoxal-derived lysine dimer (GOLD), methylglyoxal-derived lysine dimer (MOLD), 3-deoxyglucosone-derived lysine dimer (DOLD), glycolic acid lysine amide (GALA), glyoxal lysine amide (GOLA), pyrraline; *N*⁷-carboxymethyl arginine (CMA), glyoxal-derived hydroimidazolone-1/3 (G-H1/3), methylglyoxal-derived hydroimidazolone-1/3 (MG-H1/3), *N*⁷-carboxyethyl arginine (CEA), pyrimidine; imidazolium crosslink derived from glyoxal and lysine-arginine (GODIC), imidazolium crosslink derived from methylglyoxal and lysine-arginine (MODIC), and imidazolium crosslink derived from 3-deoxyglucosone and lysine-arginine (DODIC). Chemical structures of representative RCS and AGEs are illustrated in Figure 1.

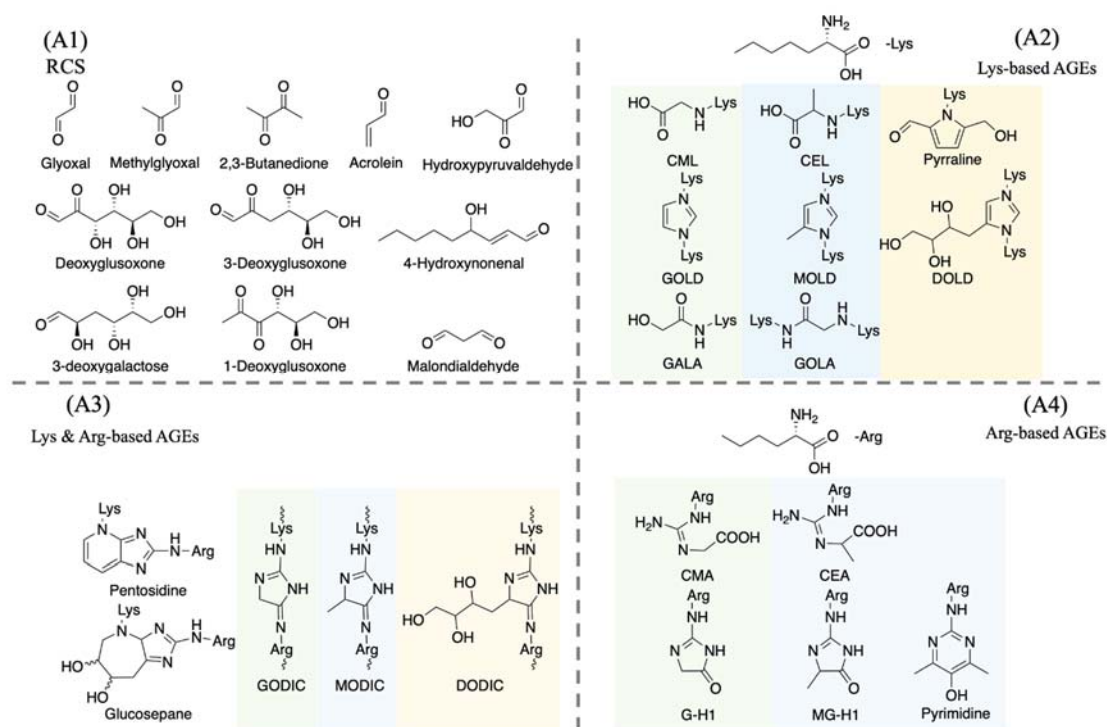


Figure 1. Chemical structures of RCS (A1) and AGEs (A2-A4) (green background-glyoxal derived; blue background-methylglyoxal derived; and yellow background-3-deoxyglucosone derived).

Growing health concerns are driving increased research into analyzing dietary RCS, particularly α -DCs, and AGEs.^[7] RCS are mainly found in high-temperature-treated foods with long storage periods, especially for sugary products such as honey, syrup, candies, jams, as well as bakery products, beverages, and condiments, as shown in Table 1.^[8,9] 3-DG was the predominant 1,2-dicarbonyl, and the overall dietary intakes of 3-DG and MGO were estimated to range from 20 to 160 and 5 to 20 mg/day, respectively.^[9] Dietary AGEs are mainly found in foods and beverages such as cereal, meat, dairy, coffee, cocoa, and tea products, as shown in Table 2.^[10] Although detection methods are at the cutting technology from ELISA to LC-MS(/MS),

analytical targets remain primarily limited to CML, CEL, pyrrolidine, limited mentioned MG-H1/3, GALA, CMA, GALA, MOLA, and others.

Table 1. RCS contents in dietary sources.

Product category	Dietary products	Detection methods (derivatization agent)	RCS contents (mg/kg or mg/L)	Ref.
Cereal products	Butter cookies (130-180 °C) 12 min	LC-MS/MS (OPD)	3-DG: 0-16; MGO: 0-10; GO: 0-1	[188]
	Butter cookies (8-16 min) 160 °C	LC-MS/MS (OPD)	3-DG: 0-28; MGO: 0-25; GO: 0-4	[188]
	Bread	HPLC-UV, HPLC-DAD-ESI-MS (OPD)	3-DG: 13-619; 3-DGal: 0-47; MGO: 0-28	[189]
	Cookies	HPLC-UV, HPLC-DAD-ESI-MS (OPD)	3-DG: 8.5-385; 3-DGal: 0-88; MGO: 1.8-68	[189]
Beverages	Soft drinks	UHPLC-DAD, UHPLC-MS/MS (OPD)	3-DG:0-87.26; 3-DGal: 0-7.68; MGO: 0-0.64; GS: 0-21.04; 1-DG: 0-2.76	[190]
	Juices	HPLC-MS (OPD)	3-DG: 16.20-129.64; MGO: 0-2.88; GO: 0-23.22; GS: 0-623.17	[191]
	Coffee	GC-NPD (OPD)	GO: 1.31-6.57; MGO: 25.5-159; DA: 1.50-12.9	[192]
	Beer	HPLC-UV, HPLC-DAD-ESI-MS (OPD)	3-DG: 19-136; 3-DGal: 4.8-33; MGO: 0-1.0	[189]
	Wine	HPLC-UV, HPLC-DAD-ESI-MS (OPD)	3-DG: 2.2-95; 3-DGal: 0-49; MGO: 0-4.5	[189]
Sugary products	Jams, jellies, sweeteners	HPLC-UV, HPLC-DAD-ESI-MS (OPD)	3-DG: 1.7-1061; 3-DGal: 0-124; MGO: 0-13	[189]
	Honey	UPLC-MS/MS (OPD)	3-DG: 221.6-687.3; MGO: 29.3-497.1; GO: 14.4-27.3	[193]
	Syrup	HPLC (OPD)	3-DG: 27.13-74.49; MGO: 1.12-3.85; GO: 0.18-0.50	[194]
	Candies	HPLC-UV, HPLC-DAD-ESI-MS (OPD)	3-DG: 141-1011; 3-DGal: 0-36; MGO: 0-1.1	[189]
Dairy products	Milk products	LC-MS/MS (OPD)	GS: 0-225.03; 3-DG: 0.19-102.79; 3-DGal: 0-18.42; GO: tr-0.58; MGO: 0.06-2.22; DA: 0.04-49.53	[195]
	Cheese	HPLC-MS (OPD)	MGO: 1.99; GO: 0.10; DA: 0.62	[196]
	Baby foods	HPLC-ESI-MS (OPD)	3-DG: 1.9-827.1; MGO: 0-17.3; GS: 0-7.6; 1-DG: 0-50.6	[197]
Condiments	Vinegars	HPLC-UV, HPLC-DAD-ESI-MS (OPD)	3-DG: 4.6-2622; 3-DGal: 1.1-162; MGO: 1.7-53	[189]
	Soy sauce	GC (OPD)	MGO: 1.73-3.27; GO: 0.88-2.84; DA: 0.53-0.86	[198]
Fruits	Dried fruit	UPLC-ESI-MS (OPD)	3-DG: 21.9-4117.0; MGO: 1.4-254.1; GO: 0.2-48.7; DA: 0.5-18.4; GS: 13.0-768.1; 1-DG: 0.6-47.8	[199]
	Cocoa	HPLC-ESI-MS (OPD)	3-DG: 1.2-17.3; MGO: 2.7-5.6; GO: 2.4-3.6; DA: 1.9-6.5; GS: 0-19.2	[200]
Nuts	Hazelnut	HPLC-ESI-MS (OPD)	3-DG: 0-6.7; MGO: 0-6.6; GO: 1.7-8.5; 1-DG: 0-0.22	[201]

Table 2. AGE contents in dietary sources.^[10]

Product category	Dietary products	Influencing Factors	Detection methods	AGE contents (mg/kg or mg/L)	Ref.
Cereal products	Flour tortilla, corn tortilla	N/A	LC-MS	CML: 2.09–2.51; CEL: 2.1-8.1; CEA: 7-19;	[202]

				N ⁶ -lactoyl lysine:0.15-0.72; MG-H1: 13-27; MG-H3: 0.28-0.72	
	Bread	N/A	HPLC-FID	CML:4.5-10.4; GALA:0.23-0.59; CMA:1.1-1.6; N ⁶ -formyl lysine: 2.8-5.6; G-H3: 3.8-5.5; N ⁶ -acetyl lysine: 1.3-3.6; pyrroline: 28-78	[203]
	Cookies	N/A	LC-MS/MS	CML: 6.32–22.84	[204]
	Cookies, biscuits, breads, mooncakes, instant noodles	N/A	UPLC-QqQ-MS/MS	CML: 4.48–35.88; CEL: 1.99–14.49	[205]
	Cookies (8-16 min) 160 °C	Heating time	LC-MS/MS	free CML: 0–0.07; free CEL: 0.1-0.4; protein-bound CML: 0–0.02; protein-bound CEL: 0.1–0.45	[188]
	Cookies (0-21 min) 155 °C	Heating time	UPLC-MS	CML: 0–328.9	[206]
	Cookies (130-180 °C) 12 min	Heating temperature	LC-MS/MS	free CML: 0–0.1; free CEL: 0.05-0.8; protein-bound CML: 0–0.1; protein-bound CEL: 0.1–0.7	[188]
	Cookies (155-230 °C) 30 min	Heating temperature	UPLC-MS	CML: 0–329.3	[206]
Meat products	Raw pork	Heat treatment	LC-MS/MS	CML: 3.0; CEL:0.9; GALA: 0.9	[207]
	Roast pork	Heat treatment	LC-MS/MS	CML: 9.2; CEL:40; GALA: 5; MOLA: 6; GOLA: 1.2; MOLD: 0.5; GOLD: 0.25; MGLA: 0.2	[207]
	fried fish nuggets (180 °C, 4–6 min)	Heat treatment	GC-MS	CML: 29.26–59.17	[208]
	beef (60–300 °C; (grilled, fried, boiled, and baked)	Heat treatment	UPLC-MS	CML: 0.8–13.4	[209]
	beef steak, pork top loin, chicken breast, salmon, tilapia	Type of meat	HPLC-FLD	CML: 1.07–2.05	[210]
	sausage (0–5 g/100g salt; 0–15 mg/100g NaNO ₂)	Food additives	UPLC-MS/MS	CML: 2.37–6.52; CEL: 5.54–6.56	[211]
	pork (acetic acid, ethanol, and NaCl)	Food additives	UPLC-MS/MS	CML: 2.29–15.35; CEL: 2.75–39.33	[212]
Dairy products	pasteurized milk and sterilized milk	Sterilization process	LC-MS	free CML: 0.008–0.014; protein-bound CML: 2.58–5.56	[213]
	milk powder	Sterilization process	UPLC-MS/MS	CML: 21.07–128.34; protein-bound CEL: 13.78–56.62; protein-bound pyrroline: 2.85–81.48	[214]
	whole milk powder (0–18 months)	Storage conditions	LC-MS/MS	CML: 20–150; CEL: 5–55; pyrroline: 0.15–0.55	[215]
	infant formulas (65 °C, 48 days)	Storage conditions	UPLC-MS; HPLC-UV	CML: 280; CEL: 180; MG-H: 190; GO-H: 280; GOLD: 40; MOLD: 20; pyrroline: 60	[216]
Coffee, cocoa, and tea products	Coffee beans (230-245 °C, 10-18 min)	Heating temperature	LC-MS/MS	CML: 0.008-0.038	[217]
	Commercial coffee substitutes and instant coffees	N/A	LC-MS/MS	CML: 0.17-47	[218]
	Defatted cocoa (Alkali-treated)	Process method	UPLC-MS/MS	CML: 0.125	[200]
	Tea samples	Tea types	LC-MS/MS	CML: 11.0-1701; CEL: 4.6-133	[219]

AGEs are generated by several pathways: the ionic pathway, oxidation pathway, and free radical pathway.^[3, 11] As shown in Figure 2, Schiff base and Amadori product are intermediates that would contribute to the RCS and subsequent AGE formation, starting with the classical glycoxidation/Hodge pathway along

with Namiki pathway (autoxidation of Schiff base) (1) and non-oxidative glucose degradation pathway (2), respectively. Reducing sugars undergo a direct autoxidation pathway, also called the Wolff pathway (3), to result in RCS formation. In addition, detailed endogenous pathways include glycolysis of glucose and intermediates, including dihydroxyacetone phosphate and glyceraldehyde-3-phosphate (4), fructose degradation (5), myoglobin-catalysed catabolism of ketone bodies (acetoacetate and aminoacetone) generated from fatty acid metabolism or threonine pathway (6), lipid peroxidation (7), and haemoglobin-mediated aminoacetone co-oxidation pathway (8).^[12]

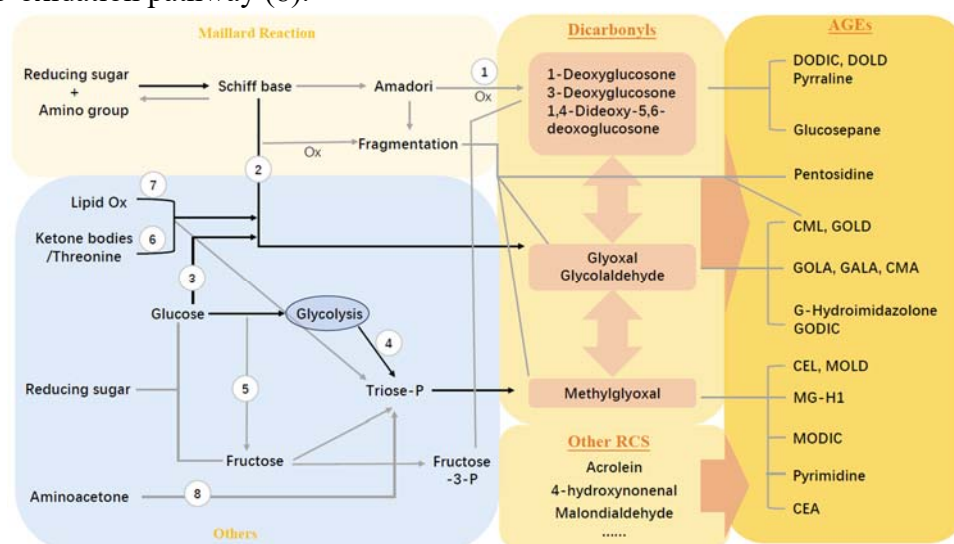


Figure 2. The major formation pathways of RCS and AGEs.

Free form of dietary α -dicarbonyls (α DCs) and AGEs are absorbed directly into the circulation system via passive diffusion. For α -DCs, baseline endogenous levels in healthy individuals are 50–300 nmol/L (plasma) and 1–4 nmol/L (cells) for GO, MGO, and 3DG.^[13] Within cells, nearly all MGO (99%) forms reversible complexes with biopolymers or small metabolites, playing a key role in mediating albumin glycation.^[14] As for AGEs, Low-molecular-weight peptide-bound AGEs require intestinal transporter proteins and gut microbial metabolism for uptake. In contrast, high-molecular-weight AGEs undergo direct fecal excretion.^[15] Research indicates that approximately 10% of ingested AGEs reach systemic circulation. Renal excretion clears only one-third of AGEs, and the accumulated remainder (two-thirds) drives disease development.^[16]

Dietary strategies and recommendations are provided to lower AGE accumulation related to MGO/AGE intake, including the Healthy Eating Pyramid of Spanish Society of Community Nutrition and the Healthy Eating Plate proposed by Harvard University for reducing dietary contribution to the body's AGE burden.^[7, 17] Recommendations emphasize eating a wide variety of fresh produce, non-added sugar beverages containing MR inhibitors, and cooking primarily using steaming or poaching. It is also beneficial to include supplements and innovative food products that are low in sugar and fat, yet rich in natural bioactive compounds capable of regulating carbohydrate metabolism and reducing the body's AGE buildup.^[7] Therefore, summarizing dietary bioactives that modulate RCS/AGE levels is critical and is an objective of this review.

Since its discovery in 1912, MR research initially prioritized flavor formation and nutritional impacts.^[18] A pivotal turning point occurred in 1969 with the identification of glycated hemoglobin in diabetic patients, redirecting focus toward MR's physiological consequences.^[19] Subsequent studies established strong associations between RCS/AGEs and diverse pathologies, including diabetes mellitus and associated complications, cancers, cardiovascular diseases, chronic kidney diseases, joint diseases, osteoporosis, neurodegenerative diseases, skin disorders, liver diseases, eye diseases, lung diseases, obesity, intestinal diseases, and reproductive disorders.^[3, 20] The AGE accumulation leads to covalent cross-linking to collagen or elastin in the extracellular matrix, slowing down protein flexibility and thus thickening the basement membrane, compromising blood vessels' integrity, and increasing hemorrhagic pathologies across various organs or membranes, and skin.^[21] Receptors of AGEs are called RAGEs. A key mechanism involves the AGE-RAGE axis, which triggers reactive oxygen species (ROS) generation, creating a pathological loop that drives inflammation and deleterious effects such as tissue damage and lesions.^[22] RAGE is located on the cell membrane, while soluble receptor for AGE (sRAGE) is distributed in circulation.^[23] sRAGE originates from two resources: esRAGE forms when metalloproteinases trim RAGE's extracellular domain, shedding its transmembrane and cytoplasmic segments, while cRAGE is directly released from cells during alternative pre-mRNA splicing during protein synthesis.^[24] sRAGE, especially esRAGE, is considered the decoy form of RAGE. By competitively binding circulating AGEs without triggering harmful AGE-RAGE signalling, it effectively shields tissues from AGE-mediated damage.^[25] A few cohort studies, along with animal studies, suggested that higher plasma AGEs (CML, CEL, MG-H1) significantly contribute to the development of diabetes, disease severity, and associated complications affecting a wide range of organs and tissues.^[26, 27] AGE-restricted diet (less exposure to heat and thus less CML/MGO/total AGEs) reduced the incidence of T1DM and reduced the risk of T2DM and associated complications.^[28, 29] The accumulation of serum and tissue AGEs activates the AGE-RAGE axis and increases the risk of abnormal cell transformation, proliferation, and migration, and eventually leads to endothelial dysfunction and impaired vascular contraction and dilation related to cardiovascular diseases.^[30-32] Moreover, excessive production and accumulation of AGEs are featured in chronic kidney diseases (CKD) and promote related morbidity and mortality.^[33] For instance, MG-H1 is a risk marker for CKD in both non-diabetic and diabetic patients, and likewise, low serum MG-H1 indicates a lower risk, while MGO has a close clinical association with CKD.^[34-36] Neurodegenerative diseases (NDDs) include Alzheimer's disease (AD), Parkinson's disease, amyotrophic lateral sclerosis, and prion diseases. Abundant studies have illustrated a correlation between increased RCS/AGEs accumulation (notably CML, CEL, MGO, and pyrroles) and emerging brain dysfunction in NDDs.^[37] The association is observed through poorer cognitive function and a greater incidence of mild cognitive impairment, positioning AGEs as a potential biomarker for predicting NDDs' onset and progression.^[38] Specifically, AGE promoted aggregation of amyloid- β (A β) into insoluble fibrils, leading to the formation of amyloid plaque (a hallmark of AD pathology). AGEs also activated GSK-3, leading to excessive phosphorylation of the Tau protein (p-Tau) in response to ROS disruption, which further affected mitochondrial complex I activity and

synergistically promoted A β -mediated mitochondrial dysfunction and ROS production.^[39, 40] Besides, AGEs are also involved in the disruption of the blood-brain barrier, enhanced neuroinflammation by dysregulation of the AGR-RAGE axis, and elevated apoptosis of various brain cells.^[41, 42]

Therefore, modulation of RCS and AGEs in diet and body is critical for human health and well-being. Extensive research focuses on lowering RCS/AGE levels with effective compounds in three major categories: 1) RCS scavenging agents, 2) metal-ion chelators, and 3) AGE crosslink breakers.^[43] Other mechanisms include Amadori intermediate trapping/oxidation blocking and free radical scavenging.^[3, 44]

RCS scavenging agents function by directly trapping these compounds, preventing their participation in disease pathways. Meanwhile, AGE inhibition agents mainly include reactive RCS trapping agents for carbonyl stress alleviation, metal-ion chelators for glycoxidation suppression, and AGE crosslink breakers for crosslink cleavage.^[3]

Polyphenols play a big role in trapping RCS and suppressing AGE formation.^[3] In addition, pyridoxamine (a form of vitamin B6), carnosine, and quercetins, representatives of metal-ion chelators, also exhibit RCS trapping capability.^[45, 46] For instance, carnosine effectively neutralizes highly toxic lipid-derived RCS like ACR (from tobacco, wood smoke, and high-heat cooking oils) and HNE, a key lipid peroxidation product causing cell death, whose carbonyl groups bind with carnosine's amino groups at the linear carbon chain end and the carbocyclic ring. Notably, adducts formed by carnosine were undetectable in plasma and appeared exclusively in urine in a clinical study of overweight/obese individuals (n=29), resulting in renal excretion.^[47]

For metal-ion chelators, the mechanism involves binding catalytic Cu²⁺/Fe²⁺ ions to suppress AGE formation and associated oxidative damage.^[45] Examples include the pyridoxamine, carnosine, and quercetin, as mentioned above.^[45] Pyridoxamine demonstrates multimodal antiglycation activity against diabetic complications, functioning as: 1) an Amadori intermediate oxidation blocker, 2) an RCS trapping agent, 3) a metal-ion chelator, and 4) an ROS scavenger.^[48]

The mechanism of AGE crosslink breakers involves cleaving the crosslinks between accumulated AGEs and tissue proteins, since these crosslinks cause protein aggregation, tissue stiffness, and corresponding diseases and syndromes.^[2] Despite promising efficacy in synthetic compounds like aminoguanidine (Phase III trial failure due to anemia/kidney damage) and alegebrum, PTB derivatives (C-16, C-36), and TRC compounds (TRC4149, TRC4186), adverse effects terminated development.^[46, 49, 50] Consequently, natural food compounds represent safer, health-conscious alternatives and form the primary focus of this article. However, the AGE-protein crosslink-breaking potential remains understudied. Further investigations are worthwhile to explore natural AGE crosslink breakers.

Despite existing research, there is a notable lack of comprehensive reviews that systematically address RCS/AGE modulating compounds, particularly those providing clear and logical explanations of the underlying mechanisms. Therefore, this review aims to: 1) critically evaluate reported modulators (dietary/pharmaceutical), 2) elucidate their mechanisms of action, and 3) synthesize insights for practical

health applications. This review ultimately aims to stimulate the discovery of novel modulators and elucidate their underlying mechanistic pathways.

2. Modulation of RCS and AGEs by Food Bioactives and their Metabolites

Among bioactive compounds, several are well-tested for their outstanding RCS/AGE modulation activity, such as various polyphenols. Therefore, tea and tea polyphenols, flavonoids in citrus and apple, myricetin, and other polyphenols in fofi, ginger, and turmeric are mentioned as representatives in the following with corresponding mechanisms. In addition, macronutrients such as polysaccharides, peptides, and amino acids also present remarkable RCS/AGE modulation properties but are relatively lack of attention.

Besides, several medicines/pharmaceuticals with established activity are also mentioned, serving as comparative benchmarks for identifying novel dietary modulators and metabolites. The chemical structures of all the mentioned bioactives are shown in Figure 2A. Table 3 provides a list of food bioactives that have been shown to directly trap various RCS/ARP, forming mono- or di-RCS adducts with binding sites. The structural confirmation of these adducts was achieved through NMR analysis. The four RCS most frequently investigated in trapping studies are GO, MGO, ACR, and HNE.

The details of human intervention and cohort studies, chemical models, *in vitro*, and *in vivo* studies of the bioactives are listed in Tables 4-7, respectively.

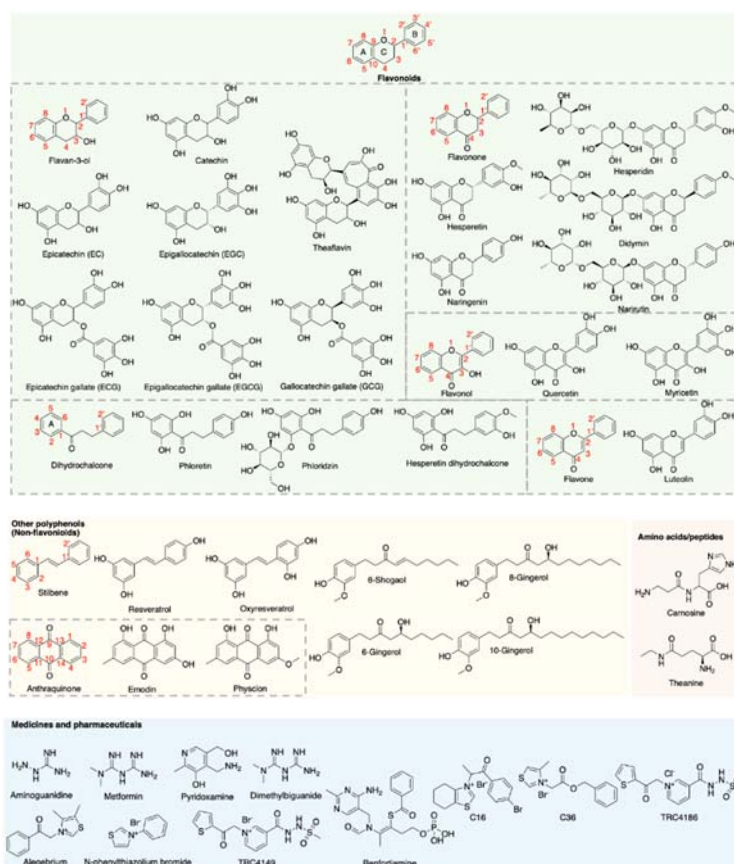


Figure 3. Chemical structures of food bioactive compounds (flavonoids, non-flavonoids, and proteins) and pharmaceuticals.

Table 3. Binding positions between food bioactives and RCS/ARPs to form adducts.

Food Bioactives (FB)	Compound class	RCS	ARPs	-FB-Adducts	Binding positions of the FB	Ref
EGCG	Flavonoid-flavan-3-ol	GO, MGO		mono-GO, mono-MGO	C6 or C8 positions on the A-ring	[220]
EGCG	Flavonoid-flavan-3-ol	DHAA		mono-DHAA	C6 or C8 positions on the A-ring, forming ring structures with C5 and C7 hydroxyl group, respectively	[56]
EGCG	Flavonoid-flavan-3-ol	ACR, MGO		mono-ACR, mono-MGO	C6 or C8 positions on the A-ring	[55]
EGCG, GCG	Flavonoid-flavan-3-ol	DP, 3-DP, 1-DP	Alanine-xylose-ARP	mono/di-DP	C6 or C8 positions on the A-ring (LC-MS/MS)	[44]
EGCG	Flavonoid-flavan-3-ol		Alanine-xylose-ARP	mono-ARP	C6 position on the A-ring	[221]
EGC, ECG, EC	Flavonoid-flavan-3-ol	DHAA			C6 or C8 positions on the A-ring, forming ring structures with C5 and C7 hydroxyl group, respectively	[222]
EGC	Flavonoid-flavan-3-ol	ACR			C6 or C8 positions on the A-ring	[55]
EC	Flavonoid-flavan-3-ol	GO, MGO			C6 or C8 positions on the A-ring	[55]
Hesperetin	Flavonoid-flavonone	ACR		mono-ACR	C6 or C8 positions on the A-ring, forming ring structures with C5 and C7 hydroxyl group, respectively	[73]
Hesperetin dihydrochalcone	Flavonoid-dihydrochalcone	HNE		mono-HNE	C5 or C5-C6-hydroxyl group or C5-C4-hydroxyl group	[74]
Quercetin	Flavonoid-flavonol	GO, MGO		mono-GO, di-MGO	C6 and/or C8 positions on the A-ring	[79]
Phloretin	Flavonoid-dihydrochalcone	GO, MGO			C3 and C5 positions on the A ring	[223, 224]
Phloretin	Flavonoid-dihydrochalcone	ACR, HNE		mono/di-ACR, mono-HNE	C3 and C5 on the A ring, forming ring structures with C4 and C6 hydroxyl groups, respectively (ACR); C5 position on the A ring, forming a ring structure with C4 hydroxyl group (HNE)	[225]
Phloridzin	Flavonoid-dihydrochalcone	GO, MGO		mono/di-GO, mono/di-MGO,	C3 and/or C5 positions on the A ring	[223]
Myricetin	Flavonoid-flavonol	GO, MGO		mono-ACR, mono-MGO	C-8 in the A-ring and C-2' in the B-ring (ACR); C6 or C8 positions on the A-ring (MGO)	[93]
Myricetin	Flavonoid-flavonol	ACR		di-ACR	One ACR binds at the A-ring C6 or C8 position and further forms a ring with the hydroxyl group at the A-ring C7 position, and the second ACR binds at the B-ring C2' position	[93, 94]
Myricetin	Flavonoid-flavonol	MGO		di-MGO	C6 and C8 positions on the A ring	[93, 94]
Oxyresveratrol	Non-flavonoid-stilbene	MGO, ACR		mono-MGO, mono-ACR	C4 and C6 positions (ACR: forming ring structures with C3 and C5 hydroxyl group, respectively)	[103, 104]

Resveratrol	Non-flavonoid-stilbene	ACR		mono-ACR	C6 position, forming a ring structure with the C5-hydroxyl group	[73]
THSG		MGO			C4 and C6 positions on the A ring	[102]
6-Gingerol, 6-shogaol	Non-flavonoid-stilbene	MGO		mono-MGO	The α -carbon of the carbonyl group in the side chain (also the beta-carbon of the benzene ring)	[119]
Theanine	Amino acid	ACR, CRO, GO, MGO		mono/di-ACR, mono/di-CRO, mono-GO, mono-MGO	C2-amino group (di-ACR/CRO: forming ring structures by combining two RCS molecules)	[55, 92]
Carnosine	Peptide	ACR, HNE		mono-ACR, mono-HNE	The terminal amino group and imidazole ring nitrogen attack the electrophilic carbonyl groups of ACR and HNE	[47]
Carnosine	Peptide	HNE		Mono-HNE	The imidazole ring nitrogen attacks the electrophilic carbonyl groups of HNE	[130]
Glutathione	Peptide	HNE		Momo-HNE	The sulfhydryl group	[130]
Ergothioneine	Peptide-derivative	ACR		Momo-ACR	The sulfhydryl group	[131]

Table 4. Human intervention and cohort studies of food bioactives and/or metabolites on RCS/AGE modulation.

Compound	Panel size, age, sex, and other basic information	Medicine duration	Results	Ref.
Tea	7,931 participants aged 30-79 years from the CMEC Study and 5,998 participants aged 37-73 years from the UKB	Participants filled out surveys of tea consumption volume and frequency, and aging-related parameters and biomarkers	Tea consumption was consistently associated with attenuated BA acceleration in both cohorts Transitioning from non-drinking to tea-drinking was associated with $\downarrow$ BA acceleration (CMEC: $\beta = -0.319$, 95% CI: -0.620 to -0.017 years; UKB: $\beta = -0.267$, 95% CI: -0.831 to 0.297 years) compared to consistent nondrinking	[63]
Quercetin and epicatechin	Aged 40-80 years, healthy, non-smoking, and hypertensive (BP 125-150 mmHg) adults, $n = 35$	160 mg/day quercetin or 100 mg/day epicatechin, 4 weeks of ingestion	$\downarrow$ Plasma MGO	[80]
Quercetin	37 healthy, nonsmoking adults with a systolic BP of 125-160 mm Hg	(-)-epicatechin (100 mg/d), quercetin 3-glucoside (160 mg/d), or placebo capsules for periods of 4 wk separated by 4-wk washout periods	Treatment effect of quercetin on MGO was -40.2 nmol/L (95% CI: -73.6 , -6.8 nmol/L; $P = 0.019$), a decrease of 11% from baseline values; No significant change on GO, 3-DA, and AGEs	[80]
Quercetin	13 healthy males. Acute high-intensity interval exercise (HIIE) to induce oxidative stress	Acute and 21 days (1000 mg/day quercetin)	activated the SIRT6–Nrf2 axis during exercise-induced oxidative stress, sustaining DNA repair capacity and modulating systemic inflammatory markers.	[226]
6-Gingerol, 8-gingerol, 10-gingerol, and 6-shogaol	27 healthy volunteers (≥ 18 years)	Three participants were assigned to each dose level, starting from the lowest dose of 100 mg and increasing	Quickly absorbed and detected in the serum as glucuronide and sulphate conjugates. Most are detected as glucuronide metabolites	[227]

		to 250 mg, 500 mg, 1.0 g, 1.5 g, and 2.0 g		
Curcumin	Patients with NAFLD-induced fibrosis (n =55)	80 mg/day nano-curcumin for 16 weeks	Nano-curcumin improved liver enzymes but showed no significant effect on fibrosis or steatosis compared to placebo	[126]
Carnosine	29 overweight to obese non-vegetarian sedentary individuals, 8 females and 21 males, aged 42.62 ± 7.37 years; BMI 31.80 ± 4.12 kg/m ²	2g/day for 12 weeks	Carnosine <i>in vivo</i> trapped acrolein, and two carnosine-acrolein adducts were found in the urine samples of all subjects	[47]
Carnosine	Human volunteers (n=5 for MRI spectroscopy evaluation, n=4 for a long-term dosing study)	5, 10, and 15 g oral carnosine for 1 h and 4 weeks	Tolerate up to 10 g with peak plasma concentration in 1h. 15 g administration caused adverse effects	[182]
DailyColors™ polyphenol supplement	150 UK adults aged 50+ with a BMI ≥ 25 at risk of cognitive decline.	750, 2000 mg/day equivalent to 300, 750 mg polyphenol for 60 days	The high-dose group showed significant improvements in reaction time and physical fitness. Proteomic analysis revealed reduced serum proteins in immune and pre- β 1-HDL pathways, suggesting anti-inflammatory effects.	[228]
Rosemary extract supplement	104 females aged 40-65 years, with moderate-to-severe skin dullness and roughness.	16 capsules/day for 12 weeks	Significant reductions in skin AGEs and HNE-protein adducts with visible improvements in skin quality	[229]
Cocoa extract supplement	598 older US adults (women ≥ 65 , men ≥ 60)	500 mg cocoa flavanols/day, including 80 mg (-)-epicatechin for 2 years	significantly decreased high-sensitivity C-reactive protein (hsCRP) levels, indicating a modulation of the chronic inflammaging process.	[230]

Abbreviations: ACR, acrolein; BA, biological aging; BP, blood pressure; CMEC, China Multi-Ethnic Cohort; MGO, methylglyoxal; UKB, UK Biobank.

Table 5. Chemical models of food bioactives and/or metabolites on RCS/AGE modulation.

Compound	Chemical model	Results	RCS/AGE detection	Ref.
EC, EGC, ECG, EGCG, matcha	ACR	formed mono, di, tri-ACR conjugates of each catechin; ↓ AGE formation significantly during cake baking	HPLC-MS/MS	[231]
Catechin, EC	MGO/GO	↓ MGO/GO by >90%/40% ↓ CML level by ~50%	HPLC, LC-MS/MS	[16]
ECG, EGC, EGCG	Lysine+GO+MGO	↓ GO, MGO, CML, CEL levels significantly	LC-MS/MS	[232]
EC, EGCG	Glucose-lysine, coconut milk	↓ CML significantly	LC-MS	[233]
Genistein, daidzein, luteolin, quercetin, pyrogallol	MGO	Pyrogallol ↓ 90% MGO in 24 h; genistein 90% and daidzein 54.5% in 4h, genistein 90% and daidzein 54.5% in 4h, quercetin and luteolin 90% in 8 h, epicatechin 85% in 24h, quercetin and epicatechin 50% in 11.25 min	HPLC-UV-vis, LC/MS	[79]

Myricetin, galangin, kaempferol, quercetin	ACR	At simulated physiological conditions, myricetin ↓ 98.24% ACR in 24 h, quercetin 48.70%, kaempferol 23.52%, galangin 12.09%; at 100 °C, 94.44%, 66.93%, 44.26%, and 41.33% within 1 h	HPLC-UV	[93]
Myricetin	MGO	↓ MGO significantly by 50% in 30 min and 90% in 8h	GC	[94]
2,3,5,4'-tetrahydroxystilbene 2-O-β-d-glucoside	MGO	↓ > 60% of MGO in 24h	UPLC	[102]
Oxyresveratrol, piceatannol, resveratrol	ACR and MGO	↓ ACR by 82.56%, 80.00%, and 52.38% in 4h ↓ MGO by 92.80%, 94.06%, and 90.95% in 4h	HPLC-DAD	[103]
Emodin	MGO	↓ MGO with IC ₅₀ of 0.41 mM	Fluorogenic probe	[105]
Curcumin	ACR	↓ ACR significantly >90% in 2h with IC ₅₀ of 0.24-44 mM	HPLC-DAD	[120]
Curcumin & Quercetin	ACR	↓ ACR significantly with synergism	HPLC-DAD	[120]
Curcumin & other nine diarthleptanoids	MGO	↓ MGO effectively and inhibit AGE formation	HPLC, LC-MS	[121]
<i>Diaphragma Juglandis</i> Fructus polysaccharide	MGO	↓ MGO significantly by 11.84-31.65% in 24 h	HPLC	[137]
<i>Gelidium amansii</i> polysaccharides	MGO	↓ MGO significantly by 47.0-61.2% in 8 h	HPLC	[133]
Ergothioneine	ACR	↓ ACR significantly by 40.0-80.0% in 5 min-1 h	HPLC-DAD	[131]

Table 6. In vitro studies of food bioactives and/or metabolites on RCS/AGE modulation.

BSA-glycation inhibition assays				
Compound	Chemical model	Results	RCS/AGE detection	Ref.
GCG	BSA-MGO	↓ AGE ~97% by trapping MGO	HPLC, Fluorescence spectrophotometry	[234]
EGCG, 2 flavonalkaloids	Fructose/glucose-BSA	↓ AGE with IC ₅₀ of 11.7, 10.3-25.3 μM (aminoguanidine 228.8 μM)	ELISA	[235]
EC, ECG, EGC, EGCG	Glucose-BSA, alcoholic Env. (22%, v/v)	↓ total AGE, CML, CEL levels by trapping MGO	HPLC, Fluorescence spectrophotometry	[236]
Apple flower	Fructose/glucose-BSA-MGO	MGO trapping efficacy of 97.90% with undiluted apple extract When added in cookies, ↓ MGO by 11.82%, 57.33% and 60.36% with apple flower added at 1.0%, 2.5% and 5.0% levels, whilst ↓ AGEs fluorescence by 11.18%, 22.05% and 44.77%, respectively	HPLC-DAD	[183]
Myricetin, myricitrin, dihydromyricetin	Fructose-BSA-	↓ α-Dicarbonyl by 90.29%, 75.00% and 89.01% ↓ AGEs formation significantly 3.90, 4.07 and 4.10 times higher than aminoguanidine (22.25%)	Fluorescence spectroscopy	[98]
2,3,5,4'-tetrahydroxystilbene 2-O-β-d-glucoside	HAS-MGO	↓ AGE formation significantly in the human serum albumin (HAS)-MGO assay	LC-MS	[102]

Oxyresveratrol, piceatannol, resveratrol	BSA-ACR and BSA-MGO	↓ AGE formation with IC ₅₀ of 5.95 mM, 0.19 mM, and 5.71 mM,	Fluorescence spectrophotometry	[103]
Emodin	BSA-MGO	↓ AGE formation with IC ₅₀ of 0.08±0.01 mM	Fluorescence spectrophotometry	[105]
Curcumin	PBS-HNE	↓ HNE-protein modification by 65%	ELISA	[122]
<i>Auricularia auricula</i> polysaccharide	Fructose-BSA	↓ AGEs formation significantly in a dose-dependent manner	Fluorescence spectrophotometry	[132]
<i>Gelidium amansii</i> polysaccharides	Glucose-BSA	↓ Fructosamine significantly by 55.3% ↓ AGEs formation significantly by 44.5-58.4%	Fluorescence spectrophotometry	[133]
<i>Actinidia arguta</i> polysaccharide	Glucose-BSA	↓ AGEs formation significantly by 29.6-59.3%	Fluorescence spectrophotometry, ELISA kit	[136]
<i>Diaphragma Juglandis</i> Fructus polysaccharide	Fructose/glucose-BSA-MGO	↓ Fructosamine and AGE formation significantly for total fluorescent AGEs and four specific fluorescent AGEs (crossline, vesperlysine, pentosidine, and arylidine)	Fluorescence spectrophotometry	[137]

Cell studies

Compound	Compound class	Cell line	Concentration	Disease/bioactivity	Organ-signalling pathway	Results	Ref.
EGCG from tea, phloretin in apple, 6-shogaol, and 6-gingerol from ginger	Flavonoid-flavan-3-ol and non-flavonoid-stilbene	Human retinal epithelial cells	10-100 µM	Diabetes and its related complications	Modulation of key regulating detoxifying enzymes <i>via</i> regulation of Nrf2 function	↓ MGO-induced cytotoxicity	[112]
EGCG from tea, phloretin in apple, and 6-gingerol from ginger	Flavonoid-flavan-3-ol and non-flavonoid-stilbene	HRPE cells	0-25 µM	Diabetes	-	↓ AGEs accumulation ↓ AR ↓ AGE formation in high glucose conditions	[112]
Hesperetin	Flavonoid-flavanone	Immortalized human lens epithelial cells	50 and 100 µM	Cataracts	Eye	↓ AGE- and CML-modified lens proteins	[75]
Didymin	Flavonoid-flavanone	INS-1 cell	50 µM	Impaired glucose tolerance	Pancreas	↑ Insulin secretion at high glucose treatment	[237]
Didymin	Flavonoid-flavanone	INS-1 cell	50 µM	Impaired glucose tolerance	Pancreas	↑ Insulin secretion ↓ Postprandial glycemia ↓ Inflammation and apoptosis	[77]
Didymin	Flavonoid-flavanone	HepG2 cell	10-30 µM	Diabetes	Liver	↑ α-Glucosidase ↓ Insulin sensitivity ↓ AGE ↓ AR	[78]
Quercetin	Flavonoid-flavanol	SH-SY5Y cell	5, 10, and 20 µmol/L	Hyperglycemia	Brain, Nrf2/ARE/GLO I	↑ p-Nrf2, PKC, and ARE ↓ p-GSK-3β	[82]

						↑ GLO I activity	
Phloretin in apple	Flavonoid-dihydrochalcone	Endothelial cells	100 μ M	Anti-inflammatory effect	RAGE/p38 MAPK/NF- κ B pathway	Phloretin-MGO adduct on phloretin's protective effects	[87]
Phloretin and phloridzin in apple peel and flesh	Flavonoid-dihydrochalcone	Colon CCD-18Co cell line	10-50 μ M phloretin	Chronic diseases-inflammation-driven impairment of intestinal function, antioxidant activity, anti-inflammatory, and antiglycation	Colon	↓ Generation of advanced glycation end products (AGEs), ↓ PGE ₂ , IL-8 generation, and AGE development	[90]
6-Shogaol	Non-flavonoid-stilbene	Human gingival fibroblast cell line	2.5-15 μ M	Periodontitis and diabetes mellitus	-	↓ AGEs-induced ROS activity ↑ HO-1 and NQO1 levels compared with the AGEs-treated cells ↓ RAGE, IL-6, and ICAM-1 and the phosphorylation of p38, ERK and p65	[110]
6-Gingerol and 6-shogaol from ginger	Non-flavonoid-stilbene	HEC line (EA hy926)	10 μ M of ginger extract, 6-gingerol, and 6-shogaol	Endothelial dysfunction and inflammatory stress	↓ Ninjurin-1, TNFR1, and NADPH oxidase subunits expression	↓ Expression of cellular TNFR1 and RAGE ↑ Level of soluble RAGE in HEC exposed to TNF α	[111]
Tectochrysin	Flavonoid-flavone	SW480 and HCT116 human colon cancer cells	<i>In vitro</i> : 1, 5, and 10 μ g/mL <i>In vivo</i> : 5 mg/kg	Colon cancer	NF- κ B	↓ The growth of SW480 and HCT116 human colon cancer cells ↑ Expression of DR3, DR4, and Fas ↑ Pro-apoptotic proteins ↓ Activity of NF- κ B Tectochrysin binds directly to the p50 unit <i>In vivo</i> , ↓ tumour weights and volumes	[238]
<i>Auricularia auricula</i> polysaccharide	Macromolecule	CML-induced HK-2 cell model	0.05, 0.1, and 0.2 mg/mL	Diabetes and renal failure, anti-glycosylation, anti-cell fibrosis	Kidney, RAGE/TGF- β /NOX4	↓ RAGE/TGF- β /NOX4 ↓ FN1, α -SMA expression (critical fibrogenesis-associated molecules)	[132]
<i>Auricularia auricula-judae</i> polysaccharide	Macromolecule	HepG2 cell	0.2, 0.5 mg/mL	Anti-glycation	-	↓ AGEs formation significantly in short- and long-term glycosylation	[135]

Table 7. *In vivo* studies of food bioactives and/or metabolites on RCS/AGE modulation.

Compound	Animal model (age, sex)	Animal model for what symptom/disease	Study dosage & duration	Results	Ref.
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Phloretin from apple and 6-gingerol from ginger	Male, 4-5-week-old C57BL/6J mice	Diabetic/prolonged hyperglycemia	Phloretin 25 and 75 mg/kg and 6-gingerol 25 and 75 mg/kg for 16 weeks	↓ Plasma glucose, alanine aminotransferase, aspartate aminotransferase, AGEs, and insulin levels ↓ The levels of AGEs and CML, <i>via</i> ↓ Nrf2 pathway ↑ GSH/GSSG ratio, HO-1, and glyoxalase 1 in liver tissue	[116]
Tea polyphenols	Aged T2DM rats	Memory function-synaptic plasticity	Tea polyphenols 75, 150, and 300 mg/kg groups 300 mg/kg group-faecal microbiota transplantation→aged T2DM model group	Tea polyphenols 300 mg/kg corrected the gut dysbacteriosis, ↓ intestinal permeability reduction and peripheral/central inflammation, and ↓ the hippocampal TLR4/NF-κB signalling pathway	[61]
Tea polyphenols	Male Sprague-Dawley rats (300 ± 20 g, <i>n</i> = 60)	Aged T2DM rat model-memory function-endoplasmic reticulum stress-mitophagy	Tea polyphenols 75, 150, 300 mg/kg groups (<i>n</i> = 10, respectively) for 9 weeks	Ameliorated mitophagy by ↓ p-mTOR (S2448), P62 and ↑ HSP60, PINK1 and Parkin, the ratio of LC3II/LC3I, co-localization of LC3 and HSP60, and ↑ autophagosomes and autolysosomes Tea polyphenols 30 mg/kg ↓ ERS by ↓ p-PERK, p-eIF2α, ATF4, GRP78, and restoring the ER structure	[62]
EGCG from tea, phloretin from apple, and 6-gingerol from ginger	Male, 5-week-old C57BL/6J mice	Diabetic complications affecting eyes, nerves, blood vessels, and kidney	EGCG at 25 and 75 mg/kg, phloretin at 25 and 75 mg/kg, and 6-gingerol at 25 and 75 mg/kg for 16 weeks	↓ RAGE expression	[112]
Quercetin	Male, 6-week-old CD-1 mice	Dicarbonyl stress	1 Week, 183 mg/kg bw quercetin 6 Weeks, 93-367 mg/kg bw quercetin	↓ MGO concentration in plasma, kidney, liver ↓ AGE in kidney and liver ↑ AR expression Mono-MGO adducts were generated dose-dependently ↑ AR, GLO I, and GLO II in kidney and liver	[81]
Hesperidin	6 Months and 27-29-month-old C57BL/6 mice	Aging-induced cardiovascular disease	4 Weeks, 0.5% in diets	↓ Aortic stiffness ↓ AGE, NF- p65, and nitrotyrosine	[69]
Hesperetin	Male, 10, 25, 75-week-old C57BL/6 mice	Cataract	<i>Ex vivo</i> 100 uM hesperetin-treated mice lens	↓ AGE-modified lens proteins ↑ Lens elasticity	[75]
Didymin	Male, 4-week-old C57BL/6J mice	HFD-induced diabetes	20 Weeks, 0.8 mg/kg bw intraperitoneally in last 3 weeks	↑ Insulin level in blood plasma Mono-MGO adducts were generated dose-dependently AR, GLO I, and GLO II ↑ in kidney and liver	[237]

Myricetin	CD-1 mice	Dicarbonyl stress	100 mg/kg bodyweight (bw) for once after fasting overnight	Myricetin and its methylated metabolites were found in urine and feces, and dose-dependently trapped MGO	[94]
Myricetin	Wistar rats	Cardiac damage	21 days, 25 and 50 mg/kg	↓ oxidative stress and inflammation (NF-κB, IL-6, IL-10) ↑ GSH and antioxidant enzyme catalase activities ↓ lipid peroxidation, hydrogen peroxide	[95]
Emodin (<i>Polygonum cuspidatum</i> extract, PCE)	Male, 7-week-old Sprague-Dawley rats	STZ-induced diabetic nephropathy	16 Weeks, 100 or 350 mg/kg bw PCE	Restored protein levels to normal ↓ podocyte loss and apoptosis ↓ caspase-3, MGO expression, oxidative stress	[105]
Physcion	Male, 8-week-old C57BL/6 N mice	LPS-induced gliosis	3 Weeks, 30 mg/kg/day bw physcion	↓ TNF-α and IL-1β ↑ Nrf2 and HO-1 expression ↑ presynaptic protein SNAP-23 and postsynaptic protein PSD-95	[106]
Myricetin	CD-1 mice	Dicarbonyl stress	100 mg/kg bodyweight (bw) for once after fasting overnight	Myricetin and its methylated metabolites were found in urine and feces, and dose-dependently trapped MGO	[94]
Myricetin	Wistar rats	Cardiac damage	21 days, 25 and 50 mg/kg	↓ oxidative stress and inflammation (NF-κB, IL-6, IL-10) ↑ GSH and antioxidant enzyme catalase activities ↓ lipid peroxidation, hydrogen peroxide	[95]
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Physcion	Male, 8-week-old C57BL/6 N mice	LPS-induced gliosis	3 Weeks, 30 mg/kg/day bw physcion	↓ TNF-α and IL-1β ↑ Nrf2 and HO-1 expression ↑ presynaptic protein SNAP-23 and postsynaptic protein PSD-95	[106]
Phloretin from apple and 6-gingerol from ginger	Male, 4-5-week-old C57BL/6J mice	Diabetic/prolonged hyperglycemia	Phloretin 25 and 75 mg/kg and 6-gingerol 25 and 75 mg/kg for 16 weeks	↓ Plasma glucose, alanine aminotransferase, aspartate aminotransferase, AGEs, and insulin levels ↓ The levels of AGEs and CML, <i>via</i> ↓ Nrf2 pathway ↑ GSH/GSSG ratio, HO-1, and glyoxalase 1 in liver tissue	[116]
6-Gingerol from rhizomes of <i>Zingiber officinale</i>	Male, albino rats	Doxorubicin-induced cardiac damage	6-Gingerol at 10 mg/kg (it was dissolved in distilled water with 0.5% Tween 80 by gastric gavage)	↓ Caspase-3 ↓ NF-κB ↑ Serum sRAGE in doxorubicin-injected rats	[118]
6-Gingerol from ginger	Male, 6-week-old Wistar rats	STZ injection induced diabetes and developed vascular complications	6-Gingerol (0.3-3 μM) or (1-1,000 μM) in AGE test	↓ AGE effects on blood vessels ↑ Vasoconstriction in diabetic aortae ↑ NO generation and GC stimulation	[117]

			2 Weeks of STZ injection to confirm diabetes, and an additional 8 weeks to develop vascular complications		
Curcumin	6-week-old mice	HFD-induced cardiac protein glycation	0.75% curcumin diet for 16 weeks	↓ glycation levels of three proteins (ACO2, NDUFS7, and DLAT)	[123]
Curcumin	HFD/STZ-induced T2DM mice	T2DM	800 mg/kg for 4 weeks	↓ liver injury ↓ AGE-RAGE axis ↓ PI3K/Akt and NF-κB	[124]
Curcumin	Male, Sprague–Dawley mice	HFD/STZ-induced T2DM hepatic and pancreatic pathophysiology	10, 50 mg/kg body weight for 6 weeks	↓ hepatic inflammation significantly ↓ phosphorylation of Akt and MAPK	[125]
<i>Auricularia auricula-judae</i> polysaccharide	<i>C. elegans</i>	Anti-glycation, anti-aging	0.5 mg/mL	↑ Lifespan by 32.9% under high sugar stress	[135]
Glutathione, carnosine	Dawley rats overexpressing human SOD1 ^{G93A}	Amyotrophic lateral sclerosis		↓ HNE levels in liver and muscles	[130]

2.1. Flavonoids

2.1.1. Flavonoids in tea and tea polyphenols

Tea polyphenols demonstrate significant modulatory effects on MR-derived RCS and AGEs.^[51] A comprehensive review in 2022 has documented these properties across key compounds: (+)-catechin, epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC), epigallocatechin gallate (EGCG), gallicocatechin gallate (GCG), theaflavins, quercetin, flavoalkaloids, and various tea extracts (green tea, black tea, pu-erh tea, fuzhuan tea, and matcha).^[3]

Catechins, characterized by two fused hydrocarbon rings, are structurally divided into esterified (EGCG, ECG) and non-esterified (EGC, EC) subtypes. EGCG was first identified as an RCS-trapping agent in 2007.^[52] The multiple aromatic hydroxyl groups confer potent free radical scavenging activity and mitigate oxidative stress.^[53] EGCG forms adducts with one or two molecules of GO and MGO at physiological conditions at C6 and C8 positions on its A-ring, crucially protecting pancreatic β -cells from damage.^[54] EGCG could also trap other RCS, such as ACR, and important RCS precursors like dehydroascorbic acid (DHAA).^[55, 56] The gallic acid moiety enhances EGCG's antioxidant capacity and inhibits glucose-metabolizing enzymes (α -amylase, α -glucosidase).^[57] Similar carbonyl-trapping activity occurs in other tea polyphenols, for instance, EGC, ECG, and EC traps DHAA.^[58]

In addition to directly scavenging RCS, recent studies suggested that tea polyphenols can trap MR intermediates called Amadori rearrangement products (ARPs, early-stage RCS precursors), and their degradation derivatives (deoxypentosone). This trapping occurs through the formation of adducts at the C6/C8 positions on EGCG's A-ring, thereby effectively suppressing downstream RCS and AGE generation.^[44, 59]

Chemical models demonstrated that tea polyphenols or extracts reduce RCS/AGE content primarily through trapping effects.^[3] *In vitro* and *in vivo* studies (rats/mice/*C. elegans*) illustrated that tea polyphenols suppress AGE formation and downregulate RAGE expression, thereby alleviating inflammation, nephropathy, and related pathologies. This protective effect operates through three key mechanisms: (1) promoting the Kelch-like ECH-associated protein 1-nuclear factor erythroid 2-related factor 2 (KEAP1-Nrf2) pathway, inducing overexpression of the detoxifying enzyme heme oxygenase-1 (HO-1) to scavenge ROS; (2) inhibiting the mitogen-activated protein kinase-C-Jun N-terminal kinases (MAPK-JNK) and mitogen-activated protein kinase-nuclear factor-kappa B (MAPK-NF- κ B) signalling cascades; and (3) suppressing the transforming growth factor- β (TGF- β) pathway. Collectively, these actions reduce downstream pro-inflammatory mediators, including cytokines like interleukin (IL)-6 and tumour necrosis factor-alpha (TNF- α), as well as enzymes like cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and matrix metalloproteinases (MMPs).^[3]

Recent studies (2022–present) have expanded the understanding of tea polyphenols' effects on RCS/AGE modulation and associated health benefits. Ultraviolet fluorescence analysis demonstrated dose-dependent

AGE reduction in gluten-glucose systems, with 0.5g/100mL tea polyphenols.^[60] *In vivo*, 300 mg/kg tea polyphenols improved memory in aged T2DM rats by correcting gut dysbiosis, restoring intestinal barrier function, and suppressing hippocampal TLR4/NF- κ B-mediated inflammation. Fecal microbiota transplantation confirmed these benefits, upregulating synaptic plasticity markers SYN, PSD-95, NMDAR1, and GluR1.^[61] Another study demonstrated memory enhancement through endoplasmic reticulum stress-mitophagy pathways in hippocampal neurons.^[62] Besides, two cohort studies, including 7,931 Chinese participants and 5,998 UK participants, revealed consistent biological age attenuation in regular tea drinkers. Transitioning to tea consumption reduced biological aging by approximately 0.3 years, with optimal benefits at ≥ 3 cups or 6-8g tea leaves daily.^[63]

However, current research on tea polyphenols exhibits significant methodological gaps. Chemical models and *in vitro* studies rarely establish complete evidence chains from quantifying RCS, ARPs, and AGEs to analyzing RAGE expression, signalling pathways, and downstream cytokines/enzymes. *In vivo* studies lack similar systematic progressions. Further studies should integrate all elements to construct complete mechanistic evidence. Previous clinical trials have confirmed health benefits of tea consumption, such as reduced biological aging; these studies report broad population-level associations involving complex dietary mixtures (e.g., Mediterranean diets).^[64] However, there is a lack of direct correlation between tea polyphenols and RCS/AGE modulation in clinical trials. Further investigations deserve to further directly link tea polyphenols to a wide range of RCS/AGE-related complications.

2.1.2 Flavonoids in citrus spp.

Citrus fruits are the world's second-largest dietary source of flavonoids after tea, which are bioactive compounds characterized by a distinctive C₆-C₃-C₆ backbone formed by two aromatic rings (A and B) connected through a three-carbon heterocyclic bridge.^[65] These flavonoids, particularly the abundant flavanones characterized by a saturated C2-C3 bond in their core structure, are primarily present as glycosides (e.g., hesperidin, narirutin, didymin, neohesperidin, naringin). The abundant glycosides, particularly hesperidin, are absorbed and converted to aglycones in the gastrointestinal tract.^[66-68] The aglycones (e.g., hesperetin, narigenin) exhibit significant therapeutic potential, including anticancer, cardiovascular, anti-inflammatory, and antibacterial properties.^[69-71]

Mitigation of age-related and diabetic complications by citrus flavonoids is extensively investigated, and a key mechanism is counteracting advanced glycation end-products (AGEs).^[72] Latest studies have shown that hesperetin traps reactive carbonyls such as ACR, while its derivative, hesperetin dihydrochalcone as a widely used sweetener, can trap 4-hydroxynonenal (4-HNE).^[73, 74] Structurally, hesperetin traps ACR to form mono-adducts at C6 or C8 positions on its A-ring, forming ring structures with the C5- or C7-hydroxyl group, respectively.^[73] Besides, hesperetin preserves lens elasticity by inhibiting AGE formation and enhancing protective chaperone proteins, potentially delaying presbyopia and cataract progression.^[75] In aged mice (27-29 months), hesperidin reversed arterial stiffening and inflammation by suppressing AGE accumulation in perivascular adipose tissue with increased levels of NF- κ B p65 and nitrotyrosine *ex vivo*.^[69]

Citrus flavonoids also improve glucose homeostasis and insulin resistance as a key strategy against glycation damage.^[76] Didymine features a flavanone core with a 7-*O*-rutinose glycoside and a methoxy group at the B ring's C4' position. It protects pancreatic β -cells from lipotoxicity by enhancing mitochondrial function through the activation of nuclear respiratory factor 1 (NRF1) and cytochrome c oxidase subunit IV (COX-IV), thereby restoring glucose-stimulated insulin secretion.^[77] It also alleviates insulin resistance in hepatocytes by inhibiting protein tyrosine phosphatase 1B (PTP1B), leading to the upregulation of the phosphatidylinositol 3-kinase /protein kinase B/glycogen synthase kinase-3 β (IRS-1/PI3K/Akt/GSK-3 β) pathway and restoring glucose uptake.^[78]

Besides flavanones, quercetin, a prominent flavonol, is particularly effective at trapping reactive dicarbonyls like MGO and GO at its A-ring C6 and C8 positions. The trapping capacity (over 90% of MGO within 24 hours) is enhanced by its unique C-ring structure, compared to other flavonoids such as epicatechin and luteolin.^[79] A clinical study suggested that quercetin's longer half-life ($t_{1/2}$ =12h) *in vivo* contributes to superior MGO trapping compared to other flavonoids.^[80] Beyond direct trapping, quercetin and its metabolite isorhamnetin upregulate key detoxification enzymes, including glyoxalase I/II and aldose reductase, via pathways such as Nrf2/ARE, thereby reducing AGE accumulation.^[81, 82] Finally, α -glucosidase inhibitors help manage diabetes by controlling carbohydrate hydrolysis. Citrus flavanones are effective inhibitors; for instance, didymine (IC₅₀: 8.28 μ g/mL) is twice as potent as narirutin due to its C4' methoxy group.^[83] Flavonoids inhibit the enzyme by binding its amino acid residues, offering an additional mechanism for managing postprandial hyperglycemia.^[84]

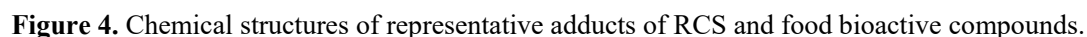
2.1.3 Flavonoids in apple

Flavonoids in apple, notably phloretin and phloridzin (phloretin glucoside), demonstrated potent anti-inflammatory and antioxidant properties by targeting RCS and AGEs. Research confirms their effectiveness across diverse cell models, including endothelial, colon, retinal, and human gingival fibroblasts.

Naturally abundant in apples, phloridzin belongs to the dihydrochalcone family, a subgroup of phenylpropanoids featuring the classic C₆-C₃-C₆ structure. It is hydrolysed by intestinal enzymes to form its aglycone phloretin, which undergoes phase II metabolism to produce glucuronide conjugates that circulate in blood at micromolar concentrations.^[85] Under physiological conditions (pH 7.4, 37 °C), both phloretin and phloridzin effectively trapped GO and MGO and formed adducts with mono- and di-GO/MGO molecules. Phloridzin demonstrated a scavenging efficiency of over 70% for MGO and 60% for GO, and phloretin showed higher capture efficiency than arginine and lysine.^[86] The reactive trapping sites for GO and MGO were the C3 and C5 positions of the A ring on both compounds.^[86]

In human umbilical endothelial cells (HUVECs), phloretin inhibited AGE formation by trapping MGO to form a di-MGO-phloretin adduct, identified for the first time as 2-hydroxy-1-(2,4,6-trihydroxy-3-(1-hydroxy-2-oxopropyl)-5-(3-(4-hydroxyphenyl)-propanoyl)phenyl)propan-1-one.^[87] Phloretin inhibited AGE-induced inflammation by blocking the RAGE/p38 MAPK/NF- κ B pathway.^[87] AGEs activate RAGE, the main receptor for AGEs, and subsequently trigger nicotinamide adenine dinucleotide phosphate [NAD(P)H]

Myricetin is another natural flavonoid widely found in fruits (such as berries and grapes), vegetables (from families including Myricaceae, Polygonaceae, and Primulaceae), and beverages like tea and wine.^[91] Similar to resveratrol (belonging to the stilbene subgroup of non-flavonoid polyphenols), myricetin can directly trap RCS, specifically MGO and ACR.^[92-94] Compared to galangin, kaempferol, and quercetin, myricetin exhibited the strongest scavenging ability by trapping 98.24% and 94.44% of ACR within 24h of simulated physiological conditions and 1h at 100 °C, respectively.^[93] The results suggested that an increased number of phenolic hydroxyl groups on the B ring enhances flavonol's trapping efficacy.^[93] The ACR and MGO were conjugated with myricetin at C6 or C8 positions on the A-ring to form mono-ACR/MGO adduct, but show differences in di-ACR/MGO adduct formation. One ACR binds at the A-ring C6 or C8 position and further forms a ring with the hydroxyl group at the A-ring C7 position, and the second ACR binds at the B-ring C2' position, while two MGO bind at the C6 and C8 positions on the A ring, as shown in Figure 4.^[93, 94] Besides, two methylated (B ring) metabolites of myricetin also trapped MGO at the C8 position on the A ring.^[94]



Myricetin and its derivatives, myricitrin and dihydromyricetin, exhibited promising antioxidant, anti-inflammation, anticancer, and antiglycation properties.^[95, 96] *In vivo* studies showed that myricetin can serve as a prophylactic treatment for alleviating cardiac damage caused by 2-fluorouracil, a strong anti-cancer drug. This was achieved by suppressing oxidative stress, inflammation, and cardiotoxicity biomarkers, such as significantly elevated GSH and antioxidant enzyme catalase activities, and significantly decreased lipid peroxidation, hydrogen peroxide, and inflammatory intermediate (NF- κ B, IL-6, IL-10) levels.^[95] Besides, various *in vivo* studies have revealed that myricetin has played a dual action against diabetes by preventing hyperglycemia via suppressing saccharide digestion/absorption and stimulating insulin production (possibly through GLP-1 receptors), and in the meantime, by alleviating associated complications via defending endothelial cells against hyperglycemic oxidative damage.^[96] Two myricetin-derived flavonols, myricetin-3-*O*-(2''-*O*-galloyl)- α -L-rhamnoside and myricetin-3-*O*-(4''-*O*-galloyl)- α -L-rhamnoside, showed the strongest antiglycation capacity as a mixture isolated from *Eugenia pyriformis* leaves.^[97] Compared to myricetin derivatives, i.e., myricitrin and dihydromyricetin, myricetin exhibited predominant antiglycation activity in the bovine serum albumin (BSA)-fructose glycation reaction system. Myricetin inhibited the formation of high molecular weight AGEs by 85% at 40 μ mol/L by preventing the conversion of α -helix to β -sheet and reducing cross-linking structure formation.^[98]

2.2 Other polyphenols

2.2.1. Polyphenols in foti

Known as foti in North America and heshouwu in China, *Polygonum multiflorum* has a long history in traditional medicine for anti-obesity, antioxidant, anti-inflammatory, and anti-aging activities.^[99] The therapeutic potential stems from abundant polyphenols, primarily stilbenes and anthraquinones, remaining as the key focus of ongoing research, with newly identified compounds consistently falling within the two polyphenol subgroups.^[99] Oxyresveratrol (a stilbene) and various stilbene glucosides alongside anthraquinones emodin and physcion are common constituents in foti.^[100, 101] Under simulated physiological conditions, the key bioactive compound *trans*-2,3,5,4'-tetrahydroxystilbene 2-*O*- β -D-glucoside (THSG) from foti can efficiently suppress AGEs formation in a dose-dependent manner by trapping more than 60% of MGO within 24h, with C4 and C6 on the A ring serving as the primary trapping sites. THSG's AGE inhibitory efficacy outperformed resveratrol and pterostilbene.^[102] Oxyresveratrol showed better inhibition capacity of AGE formation than aminoguanidine by trapping MGO and ACR at positions C4 and C6 in a chemical model, and also combated carnosine in reducing AGE accumulation and increasing collagen expression and epidermis stratification in a 3D skin model.^[103, 104] Emodin, an anthraquinone with three hydroxyl groups, also exerted better MGO scavenging results than aminoguanidine, with half of the IC₅₀.^[105] Although emodin presented better MGO-trapping capacities than other anthraquinones with two hydroxyl groups (e.g., physcion), the exact mechanism remains under investigation.^[105] Similarly, physcion attenuated neuroinflammation, oxidative stress, and memory impairments via TLR-4/NF- κ B signalling, as well as reduced lipid accumulation and prevented obesity in mouse models, but the direct relation with AGE formation remains unknown.^[106, 107]

2.2.2 Polyphenols in ginger

The main active ingredients in dried and fresh ginger are 6-shogaol and 6-gingerol, respectively. 6-Shogaol outperforms 6-gingerol in potency and effectiveness due to its α,β -unsaturated ketone structural skeleton, but 6-gingerol retains significant antioxidant, anti-inflammatory, and anticancer properties via its phenolic hydroxyl group.^[108] In human gingival fibroblasts exposed to AGEs, 6-shogaol demonstrated multifaceted protection by reducing AGE-induced ROS activity and suppressing IL-6/ICAM-1 expression and elevating antioxidant enzymes HO-1 and NAD(P)H quinone dehydrogenase 1 (NQO1). It also concurrently inhibited RAGE expression and blocked phosphorylation of p38, extracellular signal-regulated kinase (ERK), and p65 kinases, collectively alleviating AGE-induced inflammation through MAPK/NF- κ B pathways.^[109, 110] A human endothelial cell study (EA.hy926) revealed that both 6-gingerol and 6-shogaol (10 μ M) reversed endothelial dysfunction and inflammatory stress by upregulating eNOS, tumor necrosis factor receptor 1 (TNFR1), and NAD(P)H-quinone oxidoreductase subunits.^[111] 6-Shogaol uniquely decreased cellular TNFR1 and RAGE expression while increasing soluble RAGE (a key decoy receptor) during TNF- α exposure, highlighting its superior therapeutic potential in vascular inflammation. Similarly, 6-shogaol and 6-gingerol reduced MGO-induced cytotoxicity by affecting key enzymes and upregulating Nrf2 expression in human retinal epithelial cells.^[112] In human retinal pigmented epithelial cells (HRPE), pretreatment with 6-gingerol significantly reduced AGE accumulation, showing potent antiglycative properties by suppressing aldose reductase activity and preventing AGE formation.^[113] The protective effects of 6-shogaol and 6-gingerol have also been demonstrated in animal models with diabetic and cardiac damage.^[114, 115] In C57BL/6J mice fed with high-fat diets (HFD) for 16 weeks, 6-gingerol (75 mg/kg) and phloretin (25 mg/kg) reversed HFD-induced suppression of nuclear Nrf2 while significantly lowering insulin, plasma glucose, and alanine aminotransferase levels. The administration of 6-gingerol, as well as phloretin, reduced AGE accumulation and suppressed RAGE and CML levels by activating the Nrf2 pathway, elevating hepatic GSH/GSSG ratios, and upregulating HO-1 and GLO-1.^[116] Meanwhile, in STZ-diabetic Wistar rats, 6-gingerol (0.3-3 μ M) uniquely alleviated aortic vasoconstriction not through AGE reduction but by directly countering AGE-induced vascular damage via nitric oxide-mediated vasodilation and guanylate cyclase stimulation.^[117] In a rat model with doxorubicin-induced heart damage, oral gavage of 6-gingerol significantly reduced cardiac inflammation and cell death by suppressing NF- κ B and caspase-3 expression and boosting soluble RAGE levels.^[118]

The α -carbon of the carbonyl group, also the β -carbon of the benzene ring, is the main binding site of both 6-shogaol and 6-gingerol to form mono-MGO adducts.^[119]

2.2.3 Polyphenols in turmeric

Curcumin, the principal curcuminoid belong to diarylheptanoids from turmeric (*Curcuma longa* L.), exhibits potent anti-glycation activity through direct RCS trapping and modulation of AGE-induced cellular damage. The α,β -unsaturated β -diketone moiety enables effective scavenging of MGO and ACR. LC-MS/MS

studies confirmed that curcumin traps ACR, forming mono-ACR (CMA-1) and di-ACR adducts, with CMA-1 structure elucidated by NMR at the C4 position.^[120] Curcumin demonstrates synergistic RCS scavenging with quercetin. In grilled chicken wings, the combination accelerated ACR adduct formation (CMA-1 and QDA), yielding greater ACR reduction and confirming synergism ($CI < 1$).^[120] The latest study revealed that curcumin, along with another nine diarylheptanoids reported for the first time, effectively trapped MGO and inhibited the formation of AGEs. Natural deep eutectic solvents (NADES) further enhance the stability and solubility of diarylheptanoids during the extraction from turmeric.^[121]

Besides, Curcumin also exhibits protective effects against HNE, as alkali-solubilized curcumin (in 5 mM NaOH, pH 11) was found to inhibit HNE-protein modification by 65% *in vitro*.^[122] However, structural confirmation for curcumin-HNE adducts does not yet exist, nor does other RCS. Further investigations on unverified curcumin-RCS-adducts are needed

Recent proteomic analysis in high-fructose diet-fed mice revealed that curcumin selectively prevents glycation of three specific cardiac proteins, including ACO2 (tricarboxylic acid cycle), NDUFS7 (mitochondrial respiratory chain), and DLAT (pyruvate dehydrogenase complex), suggesting targeted protection of energy metabolism pathways.^[123] The hepatoprotective effects of curcumin have been further elucidated in HFD/streptozotocin (STZ)-induced T2DM models. Curcumin treatment attenuated liver injury by modulating the AGE-RAGE axis and restoring metabolic homeostasis, with metabolomics analysis revealing alterations in galactose, glycine, serine, threonine, and nicotinate metabolism.^[124] Similarly, in another HFD/STZ-induced T2DM rat model, oral administration of curcumin nanoparticles for 6 weeks significantly alleviated hepatic inflammation by decreasing phosphorylation of p38-MAPK pathway molecules, while concurrently restoring the decreased phosphorylation of AKT pathway.^[121, 125-129]

2.3 Macromolecules

2.3.1 Amino acids, peptides, and derivatives

Latest studies have revealed that amino acids and peptides also possess dicarbonyl trapping capacities. Beyond the initial discovery of EGC-ACR and EC-MGO/GO formed *in vivo* following tea consumption, theanine, an amino acid primarily found in tea, has demonstrated remarkable RCS scavenging activity under both simulated physiological and food processing conditions.^[55, 92]

For the first time, theanine-ACR/MGO/GP adducts were identified, alongside epigallocatechin gallate-ACR/methylglyoxal conjugates. To date, three distinct theanine-ACR adducts have been characterized, with their formation highly dependent on temperature. At 37°C, mono-ACR (THE-ACR) and one di-ACR adduct (THE-2ACR-1) predominated, whereas at 100°C, two di-ACR adducts (THE-2ACR-1 and THE-2ACR-2) became dominant. Structural analysis confirmed that ACR attaches specifically to the C2-amino group of theanine.^[55, 92]

Carnosine, a dipeptide comprising alanine and histidine, serves not only as a metal-ion chelator but also as an effective scavenger of RCS.^[45, 46] Its protective capacity is exemplified against two toxic lipid-derived RCS: ACR and HNE. ACR is one of the most toxic RCS generated by lipid oxidation and during tobacco

combustion, wood burning, and high-heat cooking. HNE is also a cytotoxic lipid peroxidation product and an RCS that can cause cell death. Carnosine can directly trap ACR and HNE to form mono-adducts through covalent binding. As illustrated in Figure 4, both its terminal amino group and imidazole ring nitrogen attack the electrophilic carbonyl groups of these RCS, yielding stable adducts.^[47] Human studies in overweight or obese individuals (n=29) confirmed that these adducts undergo efficient renal clearance, appearing exclusively in urine while remaining undetectable in plasma.^[47] Another study also suggested the mono-HNE adduct formation through the imidazole ring nitrogen.^[130]

Glutathione, a tripeptide comprising glutamate, cysteine, and glycine, can directly trap HNE through the thiol group, forming a mono-HNE adduct.^[130] The adducts of carnosine and glutathione with HNE were quantified in the liver and muscle of transgenic rats, indicating the detoxification of the two peptides in lipid-peroxidation related aging and disease progression.^[130] Ergothioneine, a thiol-derivative of histidine primarily found in mushrooms, is also proven to react with ACR, forming mono-adducts (EGT-ACR-1 and EGT-ACR-2). The binding site is at the thiol group, trapping ACR significantly by 40.0-80.0% in 5 min-1 h.^[131]

Advanced analytical techniques, particularly NMR-based verification, have increasingly confirmed the capacity of various food-derived bioactives to trap RCS. However, further investigation is needed to identify novel bioactive compounds with validated adduct formation. Additionally, systematic comparisons of their relative RCS reactivity are essential to identify the most effective candidates and to better reflect the behaviour within complex food matrices.

2.3.2 Polysaccharides

Polysaccharides have exhibited promising anti-glycation effects, primarily and positively correlated with their antioxidant activities by scavenging free radicals and ROS.^[132] *Gelidium amansii* (Tengusa-agar, a marine red alga) polysaccharides exhibited MGO trap rates of 47.0% to 61.2% for MGO within 8 h.^[133] Astragalus polysaccharides can reduce AGE formation by protecting insulin function, boosting insulin secretion, and enhancing glucose and lipid metabolism.^[134] In parallel, recent *in vitro* studies elucidated that degraded polysaccharides from *Auricularia auricula-judae* (also known as wood ear) had a dose-dependent suppression of AGE generation.^[135] Similarly, polysaccharides from *Auricularia auricula* and *Actinidia arguta* (hardy kiwi) inhibited AGE formation primarily by blocking protein carbonyl group formation and protecting protein thiol groups instead of scavenging dicarbonyl compounds. These suggest their antiglycation effects likely stem from antioxidant activity.^[132, 136] On the other hand, polysaccharides from *Diaphragma Juglandis* Fructus (dried woody septum of walnut hull) displayed AGE-inhibiting capacity by MGO trapping, free radical scavenging, and BSA binding.^[137]

3. Medicines and pharmaceuticals for RCS/AGE modulation

For decades, drug development has actively targeted endogenous RCS or AGEs. While some candidates succeeded, like prescription medicine metformin and promising pyridoxamine, others became cautionary failures, including aminoguanidine, alegebrum, and derivatives PTB/C-16/C-36/TRC4149/TRC4186 (failed

to be AGE crosslink breakers). Aminoguanidine, along with metformin and pyridoxamine, and a series of AGE crosslink breaker attempts will be discussed in the following to provide some hints to relieve RCS and AGE stress.

3.1 Aminoguanidine

As the first clinically tested AGE inhibitor, aminoguanidine proved that inhibiting AGE formation could combat diabetic complications. Unlike diabetes medicines decrease levels of blood sugar or glycated hemoglobin/collagen, aminoguanidine specifically targets AGE formation, suppressing fluorescent crosslinks in collagen by halting late-stage glycation reactions in animal studies.^[138] Effective RCS scavenger aminoguanidine has two reactive sites: a hydrazine group (-NHNH₂-) and dicarbonyl-trapping guanidino group [-NH-C(=NH)NH₂-].^[139] Aminoguanidine is a pharmacological agent for AGE formation inhibition, and can rapidly trap reactive carbonyls (like metformin does), forming amino-triazine derivatives that stop glycation.^[140] While it blocks multiple damage pathways, including crosslinking, lipid peroxidation, free radicals, and even oxidant-induced apoptosis, aminoguanidine cannot inhibit post-Amadori AGE formation. This limitation explains why aminoguanidine cannot compete with pyridoxamine (a form of vitamin B6) in early kidney disease trials.^[48, 49] Moreover, the drug development of aminoguanidine was discontinued due to severe side effects, including anemia, crescentic glomerulonephritis leading to severe kidney damage, and kidney failure.^[49]

3.2 Metformin

Beyond its established role as a first-line therapy for T2DM treatment, metformin (dimethylbiguanide) also functions as a reactive dicarbonyl scavenger. The guanidino group of metformin can bind with the carbonyl group of α -dicarbonyl compounds (DCs) to form unique triazepin-like adducts, thereby reducing plasma DC levels.^[141] However, the primary metformin-MGO reaction product is identified as (*E*)-1,1-dimethyl-2-(5-methyl-4-oxo-4,5-dihydro-1*H*-imidazol-2-yl)guanidine, a five-membered imidazolinone, rather than the expected trizaepinone.^[142]

MGO, derived from pyruvic acid and multiple metabolic pathways, is a highly reactive agent with a glycation activity approximately 20,000-fold faster than that of glucose, enabling it to readily bind with DNA, proteins, and lipids.^[143] Clinically, elevated MGO levels are consistently observed in T2DM patients. The primary modulator of MGO is GLO1, the glutathione-dependent enzyme that maintains the critical balance between reduced (GSH) and oxidized (GSSG) glutathione forms. Besides direct trapping of DCs, metformin actively improves the GSSG/GSH ratio in diabetes, tackling MGO metabolism to reduce oxidative stress while enhancing GLO1 activity through increased glutathione availability for MGO detoxification.^[144, 145] Similar to other findings, metformin treatment in hypertriglyceridemic rats reduced α -dicarbonyl accumulation and boosted cardiac GLO1 expression in the myocardium.^[146] These results suggested that adequate GSH levels drive the glyoxalase system's optimal detoxification of reactive carbonyls.^[147] Metformin further activates redox-sensitive transcription factors, such as Nrf2, activator protein 1 (AP-1), and NF- κ B, to upregulate GLO

I transcription and restore key antioxidant defence enzymes, including glutathione-S-transferase and catalase.^[146, 148] Notably, metformin's efficacy is tissue-specific: while it offers significant cardiac benefits, high renal lactate levels abolish metformin's dicarbonyl stress reduction in kidney cells, explaining weaker kidney improvement.^[143]

MGO contributes to AGE formation, which is one of the key pathogenic mechanisms in diabetic complications and neurodegenerative diseases. *In vitro* studies demonstrated that when albumin bathes in α -dicarbonyls, metformin addition inhibited fluorescent AGE, suggesting that metformin suppressed AGE formation by reacting directly with α -dicarbonyls at the molecular level.^[141]

3.3 Pyridoxamine

Pyridoxamine, a bioactive vitamin B6 derivative developed in 2007, emerges as a promising AGE inhibitor and therapeutic candidate for diabetic complications. Pyridoxamine works as a metal-ion chelator and radical scavenger with clinical dosages of 200, 1200-2400, and 100-500 mg for diabetic retinopathy, atherosclerosis, and diabetic nephropathy, respectively.^[149-151] Pyridoxamine inhibits AGE formation through three main pathways: blocking oxidative degradation of MR intermediates (Amadori products), scavenging toxic glucose-derived carbonyl products, and trapping ROS.^[48] Specifically, in the post-Amadori pathways, pyridoxamine inhibits AGE generation by binding catalytic redox metal ions and interacting with protein or the Amadori moiety. Pyridoxamine's chemical structure features an aminomethyl group and a phenolic hydroxyl on the pyridinium ring, and it can directly trap RCS, such as GO and MGO, forming stable adducts such as GO-pyridoxamine (GOPM) and MGO-pyridoxamine (MGOPM), where the aminomethyl group serves as the primary reaction site.^[48] Pyridoxamine demonstrates therapeutic efficacy in hyperoxaluria and hyperlipidemia complications by reducing circulating toxic RCS and preventing protein-AGE modifications.^[138]

When targeting different glycation stages, pyridoxamine's antioxidant capacity strongly outperforms metformin in blocking early and intermediate AGE formation. But metformin takes the lead during post-Amadori glycation, showing stronger inhibition than both aminoguanidine and pyridoxamine. For late-stage AGE defence, both metformin and pyridoxamine deliver protection, though pyridoxamine emerges as the more promising therapeutic option based on overall performance.^[152]

3.4 Alegebrum and other AGE crosslink breakers

Alegebrum (4,5-dimethylthiazolium, also known as ALT-711) heads a list of failed AGE crosslink breakers, alongside compounds including *N*-phenylthiazolium bromide (PTB), 3-[2-(4-bromo-phenyl)-1-methyl-2-oxo-ethyl]-4,5,6,7-tetrahydro-benzothiazol-3-ium bromide (C-16), 3-benzyloxycarbonylmethyl-4-methyl-thiazol-3-ium bromide (C-36), 3-((2-(methylsulfonyl)hydrazino)carbonyl)-1-(2-oxo-2-(2-thienyl)ethyl)-pyridinium bromide (TRC4149), and 3-((2-(methylsulfonyl)hydrazino)carbonyl)-1-(2-oxo-2-(2-thienyl)ethyl)-pyridinium chloride (TRC4186).^[46, 50] The first reported AGE crosslink breaker was PTB in 1996. Capable of breaking covalent crosslinks, daily fluorescence administration of PTB (10mg/kg) for 4

weeks reduced immunoglobulin G (IgG) binding to red blood cells in diabetic rats, but eventually failed due to stability issues.^[153] Stable derivatives resulted in the development of alegebrium, which has acute preventive effects against MGO in Sprague-Dawley rats, reduced arterial stiffness in streptozotocin-induced diabetic rats, and improved impaired cardiovascular function in older rhesus monkeys.^[154-156] These promising results led to several clinical trials (even phase III) on chronic heart disease and renal dysfunction in individuals with and without diabetes, effects of individual exercise on diastolic heart failure, and the overall elderly population.^[157] However, all these studies were terminated due to failing to show significant results or financial reasons. C13 and C36 were reported in 2005 and 2007 as effective AGE crosslink breakers to reduce AGE accumulation in diabetic rats.^[158, 159] TRC4186 and TRC4149 exhibited dose-dependent AGE-breaking effects and reversed diabetic complications in *in vitro* and *in vivo* studies, and phase I clinical trials.^[160-163] However, no AGE crosslink breaker candidates have succeeded for pharmaceutical usage to date.

3.5 Benfotiamine

Discovered in 1999, benfotiamine acts as an AGE inhibitor by shunting glycation precursors into the pentose phosphate pathway. It advanced through Phase I/II trials for diabetic neuropathy (150-320 mg/day), diabetic nephropathy (900 mg/day), and Alzheimer's disease (600 mg/day).^[164-166] However, inconsistent results exist. In the diabetic peripheral nephropathy trial, benfotiamine failed to significantly lower plasma/urinary AGEs or improve endothelial/inflammatory markers versus placebos. Even after 12 weeks, it did not significantly affect hyperglycemia's vascular damage pathways.^[165] On the contrary, the latest phase IIa cognitive trial in 2023 suggested that oral benfotiamine safely improved cognition in early mild cognitive impairment and mild AD.^[166]

More synthetic compounds are related to glycation inhibition and the alleviation of diabetic complications, but lack direct clinical correlation with RCS/AGE suppression, including aspirin, diclofenac, buformin, inositol, kinetin, and others.^[20] These clinical setbacks underscore why food-derived natural compounds are emerging as a safer alternative, aligning better with health-conscious approaches. However, there is a lack of robust studies exploring natural compounds that break AGE-protein crosslinks or comparing their efficacy against established candidates as RCS/ARP trapping agents, metal-ion chelators, and free radical scavengers. Without this evidence, advancing these promising natural alternatives to clinical trials remains premature, making this an urgent priority for near-future investigation.

4. Bioavailability Improvement of Food Bioactives

The primary challenge for dietary bioactives is poor oral bioavailability, ranging from less than 1% to single-digit percentages. Specifically, the absolute bioavailabilities of curcumin and quercetin are less than 1% and 3.61%, respectively.^[167, 168] The poor availabilities are caused by low solubility, instability in the gastrointestinal tract, extensive phase I/II metabolism, and active efflux by intestinal transporters.^[169, 170]

4.1. Major Enhancement Strategies

To address the poor availability, major strategies are nano-delivery systems and biotechnological approaches. For nano-delivery systems, encapsulation in bio-based nanoparticles protects polyphenols and enhances absorption, including cyclodextrins, micelles, liposomes, solid lipid particles, nanoemulsions, polymeric nanoparticles, and phytosomes. Solid lipid nanoparticles and nanoemulsions improve the solubility of lipophilic compounds such as quercetin.^[171] Polymeric nanoparticles provide controlled release, and phytosomes increase membrane permeability for compounds such as silymarin.^[170, 172] While for biotechnological approaches, enzymatic hydrolysis converts poorly absorbed glycosides into more bioavailable aglycones. Fermentation with lactic acid bacteria similarly enhances isoflavone absorption.^[172] Besides, co-administration with absorption enhancers like piperine inhibits metabolism and efflux, increasing curcumin bioavailability.^[170]

4.2. Recent Studies in Bioavailability Enhancement of the Food Bioactives

A 2025 systematic review confirmed that nanoformulations (polymeric, lipid-based, metal nanoparticles) significantly enhance EGCG stability and pharmacological activity, with encapsulation efficiencies of 51–97%.^[173] Loaded nanoparticles demonstrated superior antioxidative, anti-inflammatory, and anticancer effects compared to free EGCG.^[173] For hesperidin, a systematic review of 69 formulation studies concluded that lipid-based nanosystems, polymeric nanoparticles, and phytosomes deliver the largest and most consistent improvements in hesperidin bioavailability.^[174] Cochleate formulations achieved 2.21-fold higher plasma concentrations and 25-fold greater exposure than plain API in rats.^[175] Besides, recent nanoemulsion formulations dramatically improved phloretin's oral bioavailability. A gelatin–alginate nanoparticle formulation (SAGP31) enhanced cardioprotective efficacy in myocardial ischemia models through ROCK II inhibition.^[176] Another mixed emulsifier-stabilized nanoemulsion achieved 2.72-fold higher AUC and demonstrated significant neuroprotection in cerebral ischemia/reperfusion injury.^[177] Low molecular weight chitosan bioconjugates of 6-shogaol and zingerone showed dramatically improved water solubility (11.59 and 17.67 mg/mL, respectively) and pH-dependent release profiles favorable for cancer therapy, with enhanced anticancer activity against HepG2 cells.^[178] For curcumin, a comprehensive 2025 review confirmed that nanocarrier systems (liposomes, polymeric nanoparticles, SLNs, nanoemulsions) address curcumin's poor water solubility (~11 ng/mL), rapid degradation, and extensive first-pass metabolism.^[179] A shellac nanoencapsulation system co-delivering curcumin and quercetin showed synergistic antioxidant activity and ~48% post-digestive bioaccessibility.^[127] Low molecular weight chitosan bioconjugates achieved 10.7 mg/mL water solubility and enhanced anticancer activity (IC₅₀ 14.0 µg/mL).^[178] However, clinical translation remains challenged, with a 2025 pharmacokinetic study reporting unconjugated curcumin plasma levels below 2 nM for most commercial formulations, still 100-fold lower than *in vitro* effective concentrations.^[129] Notably, piperine co-administration provided no bioavailability enhancement, and all products contained 13–33% less curcumin than claimed.^[129]

4.3. Current Nano-formulated Food Bioactive Market

So far, over 400 patented nano-polyphenols have been included in SciFinder® since 2000, with an increasing trend peaking in 2018. For potential application, the majority of 97 patents approved in 2019-2021 claimed to serve as pharmaceuticals or nutraceuticals (88%), with the rest as functional food (5%), cosmeceuticals (2%), and combinations (3%).^[180] The patented nano-polyphenols include various ones, and only berberine, catechins/EGCG/green tea, quercetin, resveratrol, rutin, silymarin, and polyphenol extracts have been launched in commercialized products in the forms of capsules/tablets, liquid, and cream/gel, respectively.^[180] Among these, curcumin is the most popular commercialized nano-polyphenol. From 2022-2026, an additional 56 patented nano-polyphenols have been included in SciFinder®, indicating the popularity of nano-polyphenols in the market.

4.4. Challenges for Nano-formulated Food Bioactives

Despite progress, challenges remain. First of all, the nanotoxicity concerns persist due to a lack of long-term accumulation studies.^[180] For instance, myricetin may also act as a pro-oxidant in the presence of metal ions, leading to oxidative stress and cellular damage, or even hepatic and renal toxicity with high dosage intake.^[181] What's more, a 2025 human dose-escalation study established Oral carnosine safety up to 10 g, with peak plasma concentrations within 1 h. However, adverse effects were reported when the dosage rose to 15g, including headache, nausea, and paraesthesia.^[182]

Besides, manufacturing scalability and reproducibility are difficult and costly, impeding the actual application.^[172] Regulatory frameworks for nano-formulated foods are still evolving, leaving the market without strict supervision.^[180] Significant inter-individual variability in metabolism and gut microbiota complicates predicting responses.^[169] Future success depends on rigorous clinical trials for enhanced bioavailability with measurable health outcomes.

5. Conclusion and Future Perspectives

Modulation of RCS and AGEs is crucial in today's health-conscious society, with natural bioactives and metabolites emerging as key candidates. This review systematically summarizes the inhibitory mechanisms of representative bioactives and metabolites, including polyphenols (flavonoid and non-flavonoid subclasses), macromolecules, and pharmaceuticals, to establish comparative references. Despite research in this emerging field continuing to expand, critical knowledge gaps remain before these solutions can be effectively implemented.

It is important to sort out the specific dietary or endogenous approach as the RCS/AGE reduction strategy for finding appropriate bioactives/metabolites and designing the subsequent research. For dietary applications, the primary goal is to lower RCS/AGE levels within food matrices. Current research relies heavily on chemical models to demonstrate reduction effects using purified compounds or extracts, with few studies probing deeper mechanisms such as specific RCS trapping sites (e.g., via NMR analysis of conjugates). Crucially, real-food applications remain scarce: a lack of data on how these compounds behave throughout full processing cycles or how the complex food components influence AGE formation, which thus requires further investigation.

Moreover, sensory impact presents another gap since bioactives often alter flavor profiles (aroma/taste), affecting consumer acceptance. For instance, while amino acids like tryptophan inhibit AGEs, they may introduce unwanted nutty or fruity notes; similarly, phlorizin-rich apple flower darkened cookies in trials.^[183] Current evaluations prioritize physical attributes (texture, color, moisture) or rough sensory feedback, underscoring the need for systematic sensory evaluation before and after bioactive integration.

On the other hand, endogenous approaches face distinct challenges. Many studies rely on simplified chemical models like BSA-protein systems to validate RCS/AGE modulation despite poor physiological relevance, as these aerobic environments do not reflect the body's anaerobic conditions. While high-accuracy instrumentation accelerates the discovery of novel polyphenols with potent antiglycation activity, their low bioavailability undermines *in vitro/in vivo* results and future practical application. Emerging solutions like nanotechnology and hydrogels show potential but remain hampered by high costs and complex formulations.^[185] Nanotoxicity is also a major concern and deserves long-term accumulation studies. Meanwhile, polyphenol catabolites persist longer and at higher plasma concentrations than the parent compounds, suggesting these metabolites deserve further focused investigation for endogenous RCS/AGE control.^[186]

In addition, critical research gaps demand attention across multiple aspects. Beyond polyphenols and macromolecules, expanding bioactive discovery to compounds like ginsenosides remains essential.^[187] Current AGE research focuses narrowly on CML, CEL, and pyrraline despite numerous identified AGEs, with detection limitations persisting. Transitioning from ELISA assay (limited to total AGEs/CML/CEL) to more precise LC-MS/MS analyses is increasing, but is also hindered by unavailable commercial AGE standards and the method's cost/time intensity, which warrants the development of a mature LC-MS database and new rapid detection technologies like molecular probes. Methodological challenges include accommodating source-dependent bioactive variability and enabling cross-study comparisons, where using universal references like aminoguanidine might be a good solution. Therefore, the following research are worthy to conduct: 1) provide stronger *in vivo* and clinical evidences directly linking bioactives to RCS/AGE modulation and disease outcomes, 2) elucidate mechanistic clarity for novel or unknown compounds like emodin/phycion, particularly their structural influence on conjugate formation and exact binding sites, and 3) validate emerging technologies' efficacy and scalability beyond lab-scale experiments. Finally, geographically-tailored dietary guidelines, potentially via real-time tracking apps, require development for diabetic populations at heightened RCS/AGE risks.

Declaration

Chi-Tang Ho is a senior editor, Shiming Li is a scientific editor, and Baojun Xu is an associate editor for Food Science and Human Wellness, and they were not involved in the editorial review or the decision to publish this article. All authors declare that there is no conflict of interest involved in this manuscript.

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