COMMENT
Food and Health 2025;7(2):11. https://doi.org/10.53388/FH2025011

Inhibitory mechanism of flavonoids on dietary advanced glycation end products formation in food models

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Abstract: Advanced glycation end products (AGEs) are complex compounds formed through interaction of carbonyl groups from saccharides with amino groups in amino acids, proteins, lipids and nucleic acids, mainly via Maillard reaction. Studies have shown that AGEs can accumulate in the body and lead to neurodegenerative diseases, cardiovascular diseases, inflammatory responses, diabetes, and other diseases. This comment will provide a review of the inhibitory mechanism of flavonoids on dietary AGEs formation in food models and aims to provide a theoretical basis for the development of new therapeutic strategies and drugs.

Keywords: flavonoid compounds; advanced glycation end-products; inhibitory mechanism; reactive carbonyl species

Background

Advanced glycation end products (AGEs), a series of stable compounds, are generated by non-enzymatic reactions between reducing sugars and macromolecules such as proteins, lipids, or nucleic acids [1]. They are categorised as endogenous, which are formed within the body through the reaction of internal reducing sugars or di-carbonyl products with free amino groups in proteins or amino acids and exogenous, which are mainly derived from dietary intake [2]. Studies have shown that most AGEs in human body originate from protein-bound AGEs, and then digested as oligopeptide-AGEs in the body, which bind to AGE receptors on the cell surface, causing neurodegenerative and cardiovascular diseases, inflammatory responses, diabetes and so on [3]. AGEs inhibitors include synthetic and natural inhibitors, the currently used synthetic inhibitors are found to bring a series of side effects to patients after clinical, such as malignant tumors, influenza, vasculitis [4]. Therefore, the study of natural inhibitors to inhibit AGEs with no or little toxic side effects has become one of hot spots in the food field. Flavonoids are important functional components of foods and have various positive effects on health. Based on a C6 (A-ring) -C3 (C-ring) -C6 (B-ring) skeleton, they are classified as four classes : flavones (—C2 = C3—), flavanones (—C2—C3—), flavonols (—C3—OH), and iso-flavonoids (—C3—B-ring) [5]. In polyphenols, flavonoids were proved to have strong inhibition ability on AGEs formation. The structural formulas of some typical flavonoid with different substituents are shown in Figure 1.

This comment reviews recent advances in inhibition of flavonoid compounds on AGEs formation, highlighting the regulatory mechanism and future potential for developing novel and natural inhibitors against AGEs formation.

Mechanisms of AGEs Inhibition by flavonoids

Given the diverse structures and functions of flavonoids, mechanisms underlying the inhibition of AGE formation vary. Several categories of potential mechanisms and action sites have been posited, including covering glycation sites on proteins, chelating metal ions, scavenging oxidative free radicals, capturing reactive carbonyl species (RCS), reducing blood sugar levels, inhibiting aldose reductase, regulating AGE receptors, improving insulin resistance, reducing blood lipids, decreasing AGE cross-linking, and protecting the glyoxalase detoxification system (Figure 2) [6].

Covering glycation sites on proteins

Non-enzymatic glycation substantially alters protein structure and function, affecting hydrophilicity, α-helix and β-fold ratios, leading to the change in the tertiary structure of protein [1]. The change potentially affects enzyme activity or ligand-binding affinity. Some flavonoids competitively bind to proteins through hydrogen bonds or van der Waals forces, preserving protein structural integrity and inhibiting non-enzymatic reaction [7]. Harris et al. tested 17 flavonoid plant extracts using fluorometric and immunohistochemical methods, revealing that they all reduced AGEs formation to varying degrees, with most extracts showing half-inhibitory concentrations (IC50) of 0.40 μg/mL–38.6 μg/mL [8].

Chelating metal ions

Metal ions such as Fe^{2+}, Fe^{3+}, Cu^{+} and Cu^{2+}, play a role in non-enzymatic glycation due to their oxidative catalytic ability. They can catalyse the oxidation of sugars, proteins, nucleic acids and other compounds involved in AGEs production under aerobic conditions in foods or physiological environment, promoting free radical and carbonyl compound generation. For instance, glucose can produce enol radicals during catalysis by metal ions. Amino groups in protein or peptide chains readily form complexes with reducing metal ions and undergo conversion into carbonyl compounds when exposed to hydrogen peroxide, thereby accelerating protein oxidation [9]. Flavonoids often exhibit robust chelating abilities for metal ions, inhibiting their catalytic oxidation ability to reducing sugars, lipids, and proteins, thereby preventing AGEs formation [7].

Clearing oxidative free radicals and capturing RCS

In non-enzymatic glycation reaction, reducing sugars, proteins, lipids and other molecules can be oxidized to promote the formation of AGEs. Oxidative free radicals play important role in accelerating oxidative reaction [1]. Most AGEs inhibitors alleviate protein glycation and cross-linking by scavenging free radicals, further preventing AGEs formation. Flavonoids can inhibit AGE formation by inhibiting reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, clearing oxidative free radicals, and alleviating oxidative stress. RCS, crucial precursors of AGEs, display high reactivity due to carbonyl functional groups. Many flavonoids exhibit notable capture of RCS, inhibiting AGEs formation dose-dependently [10]. Figure 3a showed the typical luteolin-MGO adducts at different positions.

In general, flavonoids often inhibit AGEs formation through a combination of scavenging free radicals and capturing RCS. As shown in Figure 3b, the phenolic hydroxyl group in the flavonoids play an important role in their clearing free radical ability (blue), and the active sites of RCS trapping are marked in red. On the one hand, flavonoids can significantly inhibit Maillard reaction, caramelization, and lipid oxidation pathways due to their strong antioxidant activity, further reduce AGEs formation [11]. On the other hand, RCS lack

Food and Health 2025;7(2):11. https://doi.org/10.53388/FH2025011

electrons, while flavonoid can donate electrons, and they are prone to form adduct products via nucleophilic reactions [4]. Meanwhile, after scavenging free radicals, the B ring in flavonoids is epoxidized to form quinone, but flavonoids can continue to form adduct with RCS in some active sites of A-ring [12]. More than 63% of RCS have been trapped by pyro-di-quinone generated via epicatechin oxidation [13]. Liu et al. reported for the first time that the adduct of quercetin and MGO formed by nucleophilic reaction still retain the free radical scavenging capacity [14]. Song et al. also demonstrated that the cyanidin-3-O-glucoside could trap acrolein to form mono- and di-adducts at room temperature, and C-3-G-ACR adduct exhibited a more remarkable DPPH clearing ability than ascorbic acid [15]. Additionally, some investigations have confirmed that the capturing rate on RCS was significantly related to the flavonoids' structures. Flavonoids are more conductive to trapping RCS and thus reduce AGEs formation when C2–C3 positions in the C-ring of flavonoids are double bonds in comparison to single bonds. For example, quercetin (Figure 1 (20)) and luteolin (Figure 1 (14)) have better methylglyoxal (MGO) capture efficiency than epicatechin [16]. The C ring in chalcone is opening, which can ensure the integrity of the tri-hydroxyl structure of the A-ring, so it has a stronger RCS scavenging ability. For example, the scavenging ability of phloretin (Figure 1 (23)) and maclurin ((Figure 1 (24)) on RCS is much greater than that of quercetin (Figure 1 (20)) and hesperetin ((Figure 1 (10)), and the scavenging ability of cardamomin (Figure 1 (25)) is stronger than that of alpinetin (Figure 1 (7)) [17].

Other mechanism

Regulating AGE receptors

AGEs, through stimulation of oxidative stress via AGE receptor-related signalling, play a crucial role in diabetic complications. Blocking AGE binding and expression with AGE receptors through plant extracts is an effective means of inhibiting AGE formation. Flavonoids can regulate key AGE receptors, such as RAGE and AGER1. For instance, kaempferol (Figure 1 (17)) reduces AGE-stimulated elevation of RAGE and cyclic adenosine phosphate in hepatocytes [18].

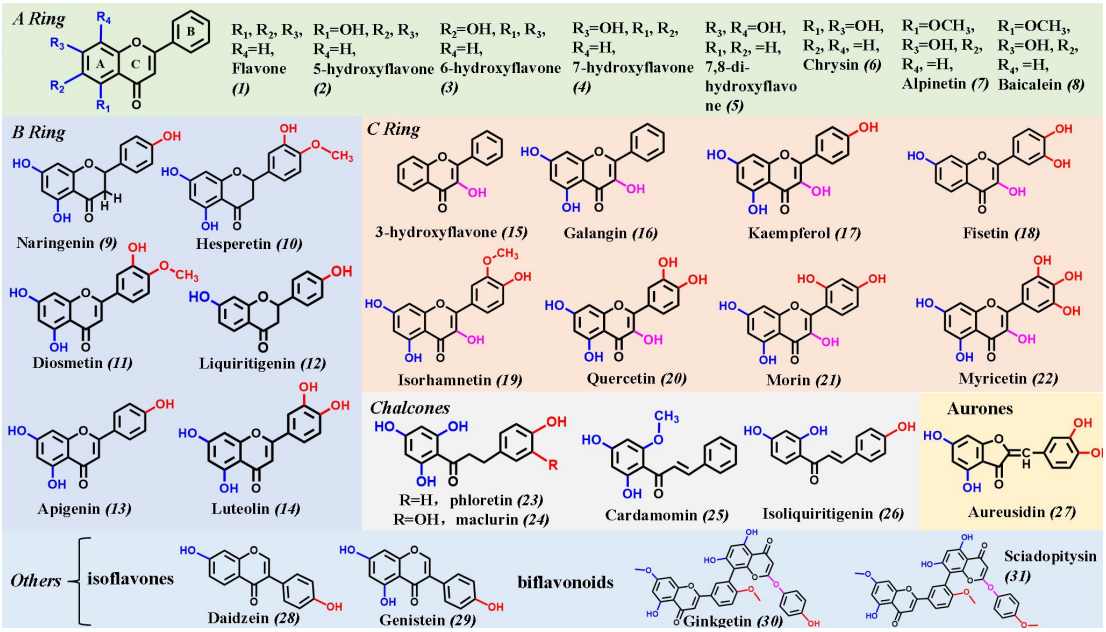

Figure 1 The structurally similar flavonoids with different characteristics

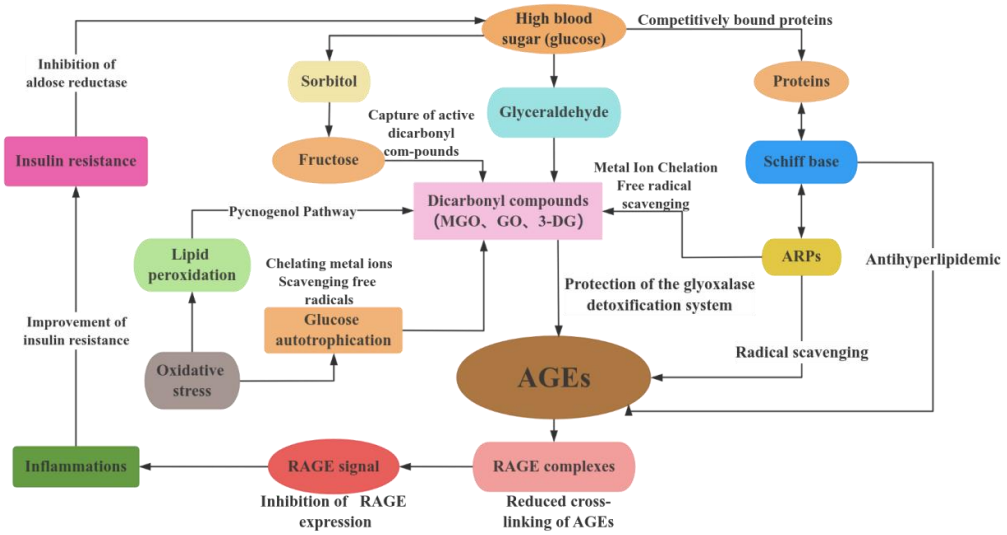

Figure 2 Mechanisms of AGE inhibition by plant extracts. ARPs, Amadori rearrangement products; 3-DG, 3-deoxyglucosone; GO, glyoxal; MGO, methyl glyoxal; AGEs, advanced glycation end-product.

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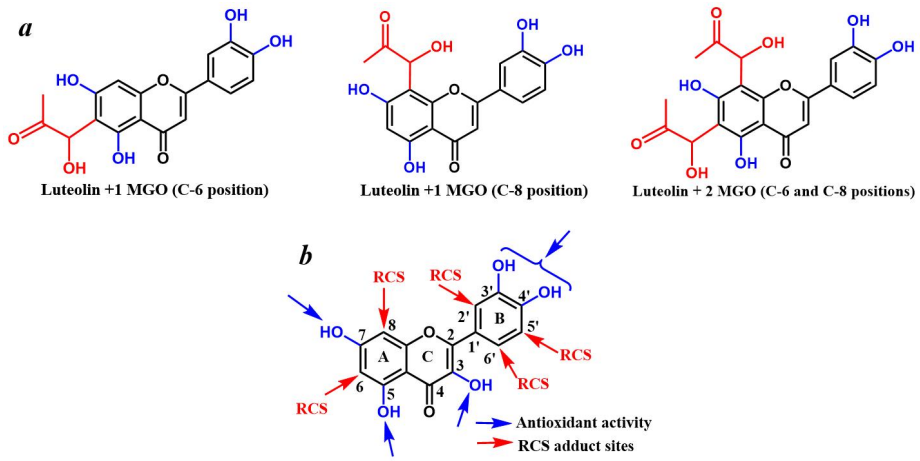

Figure 3 The typical luteolin-MGO adducts at different positions (a) and flavonoids' active sites of antioxidant activity and RCS trapping (b)

Reducing blood sugar and lipid levels

Elevated blood sugar in diabetic patients directly accelerates AGE formation. Therefore, reducing blood sugar and lipid levels is crucial for limiting AGE formation and accumulation. Many flavonoids exhibit strong ability to inhibit α-glucosidase and α-amylase in vitro with few side effects.

Inhibiting aldose reductase activity

As a key enzyme in the polyol pathway, aldose reductase converts glucose to fructose, and fructose is more easily transformed into RCS or AGEs. Therefore, inhibiting polyol pathway is a potential strategy for reducing AGE formation. Flavonoids have the activity to inhibit aldose reductase at different concentration [19].

Conclusion

In summary, intake of exogenous AGEs and production of endogenous AGEs can increase cellular AGE levels beyond a critical threshold, causing disease by promoting protein glycation, interacting with RAGEs, and inducing oxidative stress responses. Flavonoids are natural inhibitors in blocking AGE formation by covering protein glycation sites, chelating metal ions, eliminating free radicals, capturing RCS, and reducing blood sugar levels. Therefore, In the field of natural medicine, continuous research on flavonoids and their mechanisms of action is crucial, emphasising the importance of discovering new drugs while also considering their safety and efficacy. In the field of food processing and safety, high temperature cooking is an inevitable measure to pursue the pleasant flavour and colour of food. Hence, adding natural edible plants or spices and avoiding excessive sugar and oil are important strategy to control AGEs formation in food industry.

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Competing interests

The authors declare to have no conflict of interest.

Acknowledgments

This work was financially supported by the National Natural Science Foundation of China (Grant No. 32472468 and No. 32001817), the Fundamental Research Program of Shanxi Province (202303021221123).

Abbreviations

AGEs, Advanced glycation end products; RCS, reactive carbonyl species.

Citation

Jin MY, Li H. Inhibitory mechanism of flavonoids on dietary advanced glycation end products formation in food models. *Food Health*. 2025;7(2):11. doi: 10.53388/FH2025011.

Executive editor: Xiu-Jin Wei.

Received: 16 March 2025; **Accepted:** 26 March 2025**; Available online:** 28 March 2025.