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Review
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DIETARY ADVANCED GLYCATION END PRODUCTS (D-AGEs): FORMATION, DETECTION, AND HEALTH IMPLICATIONS

Seda UFUK[1], Melek ZOR[2*], Memnune ŞENGÜL[3], İsa Arslan KARAKÜTÜK[3]

[1]*Artvin Directorate of Provincial Agriculture and Forestry, 08000, Artvin, Türkiye*
[2]*Department of Gastronomy and Culinary Arts, School of Tourism and Hotel Management, Ağrı İbrahim Cecen University, 04100 Agri, Türkiye*
[3]*Department of Food Engineering, Faculty of Agriculture, Ataturk University, 25240 Erzurum, Türkiye*

Abstract: Advanced glycation end products (AGEs), also known as glycotoxins, are harmful compounds formed through non-enzymatic reactions between reducing sugars such as glucose, ribose, and fructose and amino groups in proteins, lipids, or nucleic acids. While AGEs are naturally produced in the body during normal metabolism (endogenous AGEs), they are also ingested through external sources, primarily via diet and smoking (exogenous AGEs). The formation of dietary AGEs (d-AGEs) is significantly influenced by food composition and processing factors, including heat exposure, cooking duration, humidity, pH, food additives, marination, and cooking methods. Higher temperatures and longer cooking times notably increase AGE levels in foods. These compounds are associated with various physiological toxicities and contribute to aging and the development of chronic diseases. This article explores the mechanisms of d-AGEs formation, their transport and toxic effects in the body, methods for detecting them, and strategies to inhibit their formation or intake. By raising awareness and providing practical inhibition methods, this work aims to reduce the health risks posed by dietary AGEs and support public health efforts.

Keywords: Maillard reaction, Browning reaction, Amadori products, Advanced glycation end products

***Corresponding author:** Department of Gastronomy and Culinary Arts, School of Tourism and Hotel Management, Ağrı İbrahim Cecen University, 04100 Agri, Türkiye
E mail: mzor@agri.edu.tr (M. ZOR)

Seda UFUK https://orcid.org/0000-0001-6250-6670
Melek ZOR https://orcid.org/0000-0002-5795-218X
Memnune ŞENGÜL https://orcid.org/0000-0003-3909-2523
Isa Arslan KARAKÜTÜK https://orcid.org/0000-0002-0317-2882

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1. Introduction

Advanced glycation end products (glycotoxins) are formed as a result of the non-enzymatic reactions of carbonyl groups of reducing sugars such as glucose, ribose, fructose, and others and the terminal amino groups of proteins, lipids or nucleic acids (Wu et al., 2013; Perrone et al., 2020; Vıcıl and Ulutaş, 2020). AGEs are a heterogeneous group of molecules that can form during the oxidation of lipids and proteins, Maillard reactions, and food processing (Yaman, 2021). AGEs, which have a yellow-brown color, are molecules that can alter the structure of proteins in both plasma and tissues (Demirel and Yıldıran, 2018). The main precursors of AGEs formed during the Maillard reaction steps are glyoxal (GO), 3-deoxyglucosone (3-DG) and methylglyoxal (MGO) (Çatak and Balcı, 2022). Advanced glycation end-products (AGEs) were originally identified by their ability to emit specific fluorescence and form cross-links between amino acids, such as crosslines, vesperlysines, and pentosidine. However, researchers have since discovered that other compounds like Nε-(carboxymethyl) lysine (CML), pyrraline, MG-H1 (a product of methylglyoxal), Nε-(carboxyethyl) lysine (CEL), and argpyrimidine, are also considered AGEs, even though they do not form cross-links or emit fluorescence (Takeuchi et al., 2024). In Figure 1, the formation of reactive dicarbonyl compounds and resultant AGEs is illustrated. Sensory differences and browning occur in foods as a result of the Maillard reaction that happens during food processing such as grilling and frying (Wang et al., 2013; Öztürk and Garipoglu, 2022).

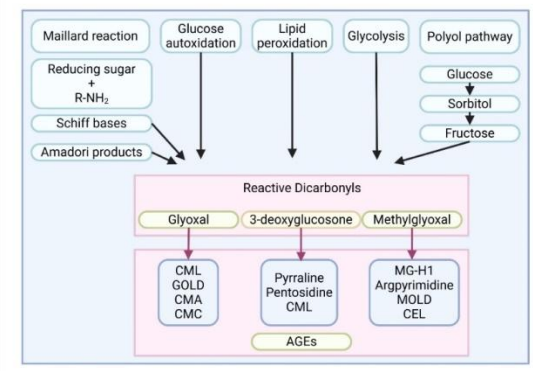

Figure 1. Formation of reactive dicarbonyls and AGEs (Nowotny et al., 2015).

In the presence of excessive reducing sugars, biomolecules undergo a non-enzymatic reaction known as glycation, which involves proteins, lipids, and nucleotides. This process leads to the formation of covalent bonds between biomolecules and reducing sugars, termed Schiff bases. Through various reactions, such as rearrangement, oxidation/reduction, and cyclization, this process leads to the production of irreversible and heterogeneous compounds known as advanced glycation end-products (AGEs). These AGEs are frequently found as modified forms of aminoacids such as lysine, arginine, and cysteine (Lee et al., 2024). Fructosyllysine (FL) and Nϵ-(carboxymethyl)lysine (CML) are among the most abundant and widely studied Amadori products and advanced glycation end-products (AGEs) found in foods. FL is formed from the reaction between glucose and lysine, while CML can arise either through the rearrangement of FL or via reactions between lysine and reactive carbonyl compounds like glyoxal or 3-deoxyglucosone. Other common AGEs in foods include compounds such as pyrraline, Nϵ-(carboxyethyl)lysine (CEL), hydroxymethylfurfural (HMF), and Nδ-(5-hydro-5-methyl-4-imidazolone-2-yl)ornithine (van Dongen et al., 2022). The most frequently measured and best-studied AGEs are derivatives of carboxyethyl-lysine (CEL), carboxymethyl-lysine (CML) and methylglyoxal (MGO) (Vasilj et al., 2023). These AGEs are commonly studied not only because of their prevalence in biological systems but also due to their strong association with the development and progression of chronic diseases, particularly diabetes-related complications. CML and CEL are stable end-products that accumulate in long-lived proteins and tissues, making them reliable indicators of cumulative glycation and oxidative stress (Peyroux and Sternberg, 2006; Ott et al., 2014).

While dietary AGEs are naturally present in foods, their formation significantly increases with high-temperature cooking, low moisture, prolonged heat exposure, the presence of trace metals, and higher pH levels; these dietary AGEs and ALEs are important for consumer risk assessment because they can be absorbed through the gastrointestinal tract, potentially raising the body's overall AGE levels (Srey et al., 2010). Therefore, cooking techniques such as roasting, grilling, and frying produce notably higher levels of dietary AGEs (dAGEs) compared to methods such as stewing, boiling, steaming, and poaching (Vasilj et al., 2023). It is observed that cooking methods in dry heat increase the formation of AGE compared to cooking methods in moist heat. It is indicated that the formation of AGE can be reduced by using high humidity, lower cooking temperatures, shorter cooking times, or acidic components such as vinegar or lemon juice (Akın and Özbek, 2022).

Foods that are high in protein and fat, as well as processed and ultra-processed foods, tend to have high AGE content, especially when prepared at high temperatures and low humidity (Mendes et al., 2024). Heating times and different cooking methods play a crucial role in the formation of AGEs in foods. For example, 100 g of boiled chicken breast contains 1210 kU of CML, while the same amount of chicken, when fried at 450°F for 15 minutes, contains 5828 kU of CML (Vasilj et al., 2023). Food items with the highest levels of AGEs per gram include processed foods like crackers, chips, and cookies. The reason behind this is the thermal processing of these foods and the addition of components such as vegetable oil, butter, eggs, cheese, and nuts, which markedly accelerate the formation of AGEs (Sharma et al., 2015; Hu et al., 2022). Due to conflicting findings, there is no consensus on the AGE content in solid and liquid fats (Vasilj et al., 2023). In their study, Hu et al. (2022) stated that the proportions of sucrose, butter, and egg in butter cookies demonstrated a positive correlation with AGEs, highlighting that sucrose significantly promoted the formation of HMF and 3-deoxyglucosones (3-DG) (Figure 2). In addition to these findings, Hu et al. (2022) reported that the high levels of sucrose and butter in cookies were particularly favored by panelists due to their appearance, taste, and aroma.

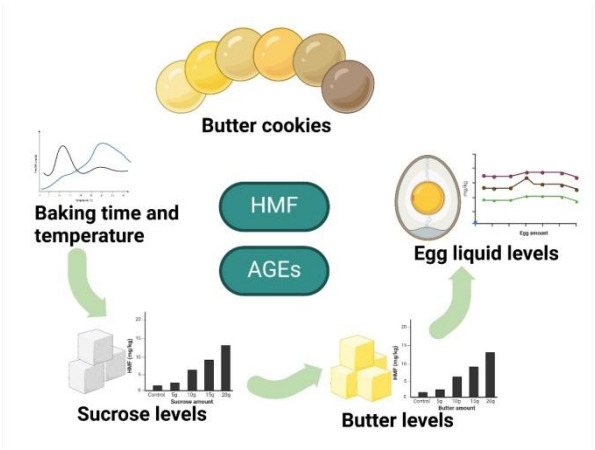

Figure 2. The roles of various factors in the formation of AGEs and HMF in butter cookies (Hu et al., 2022; Created in BioRender. Karakütük, I. (2025b) https://BioRender.com/e31j367)

2. Formation of d-AGES

In 1953, scientist Hodge divided the Maillard reaction into 3 different stages. In the first stage the aldehyde group of reducing sugar react with amino group of protein to form an unstable complex known as a Schiff base adduct which over several days rearrange to form a product called Amadori product. The second stage, known as the intermediate stage, involves the transformation of the Amadori product into reactive dicarbonyl compounds such as glyoxal (GO), (3-DG) and methylglyoxal (MGO). In the late stage of glycation, the final irreversible and colored compounds, known as AGEs, are formed (Ho et al., 2010; Khan et al., 2020; Erim et al., 2022). The process of AGE formation is shown in Figure 3.

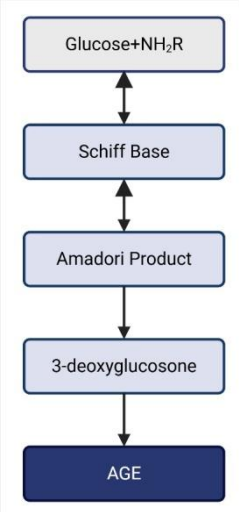

Figure 3. The formation of AGEs (Akın and Özbek, 2022; Created in BioRender. Karakütük, I. (2025c) https://BioRender.com/i45b405)

Due to the considerable variations in AGE structures in vivo and their formation through complex reactions like dehydration, condensation, oxidation, and rearrangements, only a limited number of AGE structures have been identified so far. The structures of highly cytotoxic AGEs are still unknown. Four types of glyceraldehyde-derived advanced glycation end-products (GA-AGE) structures have been identified by means of proteomic analyses. These include pyridinium compounds derived from GA (GLAP), MG-H1, trihydroxytriazine, and argpyrimidine (Takeuchi et al., 2024).

The amino acids lysine, histidine, and arginine in proteins are more susceptible to glycation. Among reducing sugars, glucose demonstrate the lowest glycation rate, whereas sugars like fructose, glyceraldehyde-3-phosphate, trehalose, and glucose-6-phosphate have higher rates of glycation (Akın and Özbek, 2022).

3. Endogen and Exogenous AGEs

There are basically two types of AGEs, which are endogenously produced and exogenously taken (Öztürk and Garipoglu, 2022). Endogenous AGEs are formed naturally within the body, with their levels increasing significantly under conditions such as hyperglycemia and oxidative stress. AGEs can also be obtained from external sources, particularly food, in which case they are referred to as dAGEs (Vasilj et al., 2023). AGEs can occur endogenously as a result of a series of complex enzymatic reactions in the organism. In addition, AGEs can be exposed exogenously through smoking or through food and therefore exogenous AGEs are called dAGEs (Yılmaz and Karabudak, 2016; Öztürk and Garipoglu, 2022).

The main source of exogenous AGEs is diet and occurs commonly in complex foods rich in sugar and fat content. Exogenous AGEs are formed rapidly and in large amounts by non-enzymatic reactions during food processing like frying, baking and caramelization (Kuzan, 2021). The composition of foods, duration of exposure to heat, humidity in the environment, pH, food additives, marination, temperature and cooking methods are factors that affect the formation of AGEs. As temperature and time increase, the content of AGEs also increases accordingly (Yılmaz and Karabudak, 2016; Çatak and Balcı, 2022; Demirer and Yardımcı, 2022). The AGE content of meat products or oils that have been subjected to high heat processing, such as roasting or frying, is higher than carbohydrates that have been boiled for a long time (Yılmaz and Karabudak, 2016). Additionally, exogenous AGEs formed during the heat processing of foods are more chemically diverse than endogenous AGEs produced within the body. This greater heterogeneity of dietary AGEs makes it more difficult to fully understand their biological effects (Öztürk and Garipoglu, 2022). Many studies have shown that the highest AGE compounds in foods are found in high-fat foods such as chips, crackers and cookies (Yaman, 2021).

Animal-derived foods, including beef, fish, cheese, poultry, and eggs, are noted to include the highest levels of AGEs per 100 grams of food. Vegetables and fruits generally contain lower levels of AGEs compared to meat (Vasilj et al., 2023). The number of AGEs per serving (5 grams) in fat is generally higher compared to other food groups. Despite the lower AGE content in the meat group compared to the fats, the consumption quantity of the meat group is generally higher. Hence, a significant portion of the AGE intake originates from the meat group. It has been determined that when animal-derived foods are cooked using dry heat, there is an increase in AGE levels. Under the influence of heat, reducing sugars like glucose-6-phosphate within muscle cells react with the amino groups present in the structure of meat, resulting in an observed increase in AGE levels. It has been found that cheeses with higher fat content, such as Parmesan cheese, exhibit higher levels of AGEs compared to cheeses with lower fat content, such as mozzarella cheese. While cooking is known to promote the formation of new AGEs in foods, uncooked items like cheese can still contain high levels of AGEs. It is believed that the reason for this lies in the pasteurization process and the aging period applied to cheese (such as culturing or ripening), during which AGE formation occurs (Demirel and Yıldıran, 2018).

The total amount of AGEs in the body comprises both endogenously formed AGEs and exogenously consumed AGEs through factors such as tobacco smoke, pollution, and certain foods (Ruiz et al., 2020).

The same situation applies to animals kept as pets and consuming commercially produced feeds. The nutritional value and digestibility of amino acids, particularly lysine, in feed ingredients and diets vary depending on the applied heat treatment (Almeida, 2013). It has been observed that broiler chickens and piglets fed with heat-damaged soybean meal experience a decrease in live weight and carcass weight compared to those fed with untreated soybean meal.

Furthermore, it has been determined that the adverse effects of heat damage on performance can be partially alleviated by adding crystalline aminoacids to the feeds (Almeida et al., 2014). In another study, it was observed that in cattle fed with heat-treated feeds, the formation of AGEs and MRP as a consequence of heating was also detected in the milk of the animals. However, cattle that did not consume processed feeds exhibited lower levels of glycated protein content in their milk (Schwarzenbolz et al., 2016).

4. Physiological Toxicity of d-AGES

Advanced Glycation End Products (AGEs) are harmful compounds commonly found in modern diets, particularly in processed foods, and have significant health effects. It was previously thought that the absorption of dietary AGEs was low and therefore had no significant effect on human health. However, recent studies have shown that AGEs taken with diet are absorbed in the body and may have significant negative consequences on human health (Demirel and Yıldıran, 2018). The formation of endogenous AGEs is a normal metabolic process, however when excessively high levels of AGEs accumulate in tissues and the bloodstream, they can have pathogenic effects (Sharma et al., 2015; van Dongen et al., 2022). AGEs accumulate in healthy aging individuals, and this accumulation is more significant at high glucose concentrations. While the accumulation of AGEs in tissues is primarily linked to microvascular and macrovascular damage observed in diabetes, but it is also associated with other conditions including atherosclerosis, end-stage renal disease, Alzheimer's disease, rheumatoid arthritis, cataracts, sarcopenia, and various degenerative ophthalmic diseases, as well as vascular dementia, Parkinson's disease, and several other chronic diseases (Luevano-Contreras and Chapman-Novakofski, 2010). The excessive accumulation of AGEs in body tissues contributes to high levels of oxidative stress and inflammation. Especially, it significantly leads to the pathogenesis of various chronic diseases like chronic kidney diseases, type 2 diabetes, and cardiovascular disorders (Uribarri et al., 2007; Shen et al., 2020; Akın and Özbek, 2022).

AGEs contribute to the pathogenesis of chronic diseases associated with aging. These compounds and their precursors are naturally produced in the body during the aging process, but they are also found in heat-treated foods and cigarette smoke, leading to further AGE accumulation. Excessive endogenous production of AGEs has been linked to proinflammatory processes involved in conditions like atherosclerosis, insulin resistance, and vascular complications of diabetes. Though, there is less understanding regarding the effects and metabolic destiny of AGEs derived from the diet (Kellow and Coughlan, 2015). Furthermore, AGEs are known as potential endocrine decayers due to their ability to intervene in hormone signaling (Qiang et al., 2024).

In Figure 4, the binding of AGEs to RAGE, triggering a series of pro-inflammatory and pro-metastatic cellular signaling pathways, has been illustrated (Peterson and Ligibel, 2024).

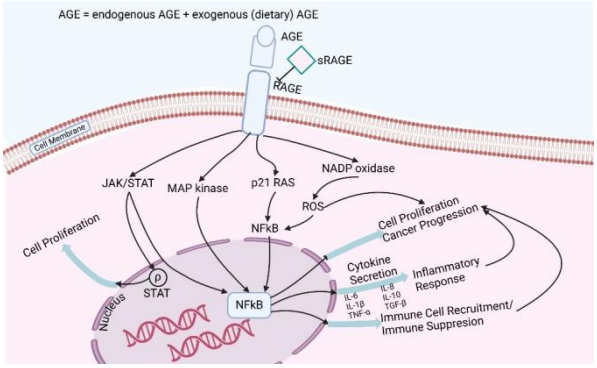

Figure 4. The binding of AGEs to RAGE, triggering a series of pro-inflammatory and pro-metastatic cellular signaling pathways (Peterson and Ligibel, 2024)

It is estimated that individuals consume between 25 to 75 mg of AGEs and 500 to 1200 mg of Amadori products daily through their diet (Öztürk and Garipoglu, 2022). However, the precise extent to which dietary AGEs are absorbed in the digestive system and enter circulation remains unclear (Luevano-Contreras and Chapman-Novakofski, 2010).

Some of the exogenous AGEs ingested with food are absorbed in the intestines and enter circulation, where they can accumulate in cells and tissues. Excessive accumulation of AGEs can lead to various health disorders. About 10% of AGEs consumed through diet are absorbed into circulation. Recent systematic reviews of clinical studies suggest that dAGEs may increase the risk factors associated with chronic diseases like inflammation, oxidative stress, and insulin resistance (Çatak and Balcı, 2022). The pathological effects of AGEs occur through two different mechanisms: AGE receptor-mediated and AGE receptor-independent pathways. The former involves direct cross-linking of AGEs with body proteins, leading to structural deformity, while the latter induces inflammation through AGE-sensitive receptors (Erim et al., 2022).

Scientific evidence suggests that AGEs contribute to cancer risk and outcomes by promoting inflammation, increasing reactive oxygen species, and causing metabolic dysregulation. Additionally, they play a role in shaping the tumor microenvironment (Peterson and Ligibel, 2024). Figure 5 illustrates diseases arising from various potential mechanisms triggered by the formation of AGEs and their associated health complications (Anwar et al., 2021). It is reported that AGEs exert harmful effects on cellular functions through a range of mechanisms, including the production of free radicals, alteration of enzyme activity, degradation of proteins or lipids, oxidation of lipids or nucleic acids, carbonyl stress, or interaction with AGE receptors on the cell surface (Singh et al., 2014).

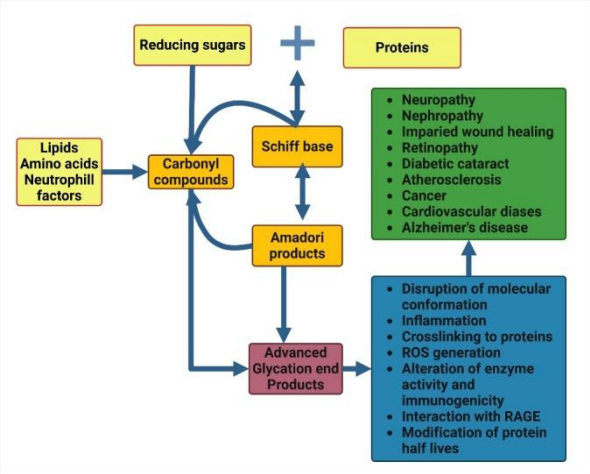

Figure 5. The diseases arising from various potential mechanisms triggered by the formation of AGEs and their associated health complication (Anwar et al., 2021; Created in BioRender. Karakütük, I. (2025e) https://BioRender.com/l87g434)

(Chilelli et al., 2013) reported that the effects of AGEs on diabetes primarily occur through two pathways. The first pathway involves AGEs directly causing cellular damage leading to pancreatic β-cell injury and disruption of insulin regulation. The second pathway entails AGE modification of mitochondrial respiratory chain proteins triggering the formation of reactive oxygen species (ROS) and establishing a vicious inflammatory cycle.

In diabetes, the chronic high-glucose environment encourages the formation of AGEs. These AGEs accumulate in diabetic bones, leading to increased non-enzymatic cross-linking within collagen fibrils. This disrupts intrafibrillar mineralization and causes disorganized mineral deposition on collagen fibrils, ultimately weakening bone strength. By inhibiting AGE formation, guanidines significantly enhance the microstructure and biomechanical strength of diabetic bone and accelerate bone fracture healing (Gao et al., 2024).

Glycation products and their receptors are frequently linked to higher morbidity and disease severity in various infectious conditions. For instance, a meta-analysis by Chen et al. (2019) revealed an association between HbA1c levels and Helicobacter pylori infection. Research by Sprenger et al. (2017) found a significant increase in fluorescent AGEs in the skin of individuals infected with HIV-1. Andrades et al. (2012) demonstrated that plasma levels of CML and CEL were related to the severity of sepsis. Moreover, lower serum levels of soluble RAGE (sRAGE) have been correlated with both acute and chronic morbidities in children with bronchiolitis (Patregnani et al., 2021). Furthermore, sRAGE is being explored as a potential biomarker for sepsis and late-onset neonatal infections (Zolakova et al., 2016).

In addition to all this information, it is important to mention the therapeutic possibilities related to glycation, which include: (1) treatment with anti-RAGE antibodies, (2) treatment with soluble RAGE (AGE receptor) and (3) use of AGE inhibitors and (4) AGE blockers. Such strategies can notably decrease the occurrence of processes that cause diabetic complications (Bronowicka-Szydełko et al., 2024).

5. Transport of d-AGES

Studies have shown that the majority of free CML in the body is directly related to the dietary intake of dCML (Tessier et al., 2016). The total amount of AGE in an individual's body is expressed as the sum of endogenously produced AGE and exogenously produced AGE (Prasad et al., 2019). The reason AGEs cause diseases is that they bind abnormally to proteins in the body, disrupting their structure and rendering them unable to perform their functions, which consequently leads to the development of diseases (Karaköse, 2023). For these reasons, thoroughly understanding the absorption process and metabolism of AGEs in the body is of vital importance to comprehend how they affect diseases.

It has been determined that nearly 10% of the advanced glycation end-products (AGEs) present in food and drinks are absorbed by the body. Nevertheless, only one-third of these are excreted through urine and feces. The absorbed fraction remains within the body for a duration of up to 72 hours (Erim et al., 2022). Research conducted on adults reveals that approximately 10% of dietary-derived advanced glycation end-products (AGEs) are absorbed, with two-thirds of the absorbed AGEs enduring within the body and one-third being eliminated through gastrointestinal processes or urinary excretion (Akın and Özbek, 2022).

The elimination of AGEs from the body occurs through urine, and this also provides information about how much AGE has accumulated in the body. Although the excretion amounts of dAGEs vary among individuals, this variability significantly affects the diseases they may have. It is believed that when urinary excretion decreases, individuals may have diabetes and kidney disease (Karaköse, 2023).

6. Inhibition Methods of d-AGES

The association of AGEs with ailments occurs through increased oxidative stress by means of AGE-RAGE activation and/or suppression of the body's defense systems. Considering the detrimental effects of AGEs on health, reducing dietary AGE intake is the most appropriate method to prevent AGE-related health issues (Yalçın and Rakıcıoğlu, 2022).

The pathways of glyoxalase, aldehyde dehydrogenase, aldose reductase and carbonyl reductase are defense mechanisms developed against methylglyoxal (MGO) formation in living organisms.

The glyoxalase system plays a pivotal role within cellular contexts as the main detoxification system used against MGO and other reactive carbonyl compounds (Vıcıl and Ulutaş, 2020). Alagebrium chloride, irbesartan, aspirin, carnosine, metformin, and calcium antagonists represent often utilized synthetic inhibitors of AGEs. Nonetheless, the use of synthetic AGE inhibitors may cause symptoms such as anemia, vomiting, dizziness, liver damage, gastrointestinal disorders, and headache (Khan et al., 2020; Zhou et al., 2020). It has been reported that there is a strong connection between exposure to AGE (Advanced Glycation End-products) and impaired intestinal barrier function. One of the most well-known AGEs, the methylglyoxal-derived hydroimidazolone-1 (MG-H1), has been shown to increase intestinal permeability in the human colon carcinoma cell line Caco-2 and to impair intestinal barrier integrity in mice (Lim et al., 2022). Sprague-Dawley rats fed a high-AGE diet for 18 weeks exhibited a significant increase in colonic permeability, as demonstrated by histological changes and the downregulation of tight junction proteins (TJs) like Occludin and Zonula Occludens-1 (ZO-1) in the colonic tissue (Qu et al., 2017). A 24-week high-AGE diet significantly impaired the integrity of the intestinal barrier, enhancing the movement of luminal molecules across the intestinal epithelium. This disruption was linked to a down-regulation of tight junction proteins (TJs), including Occludin and Claudin-1, in mice (Snelson et al., 2021).

Within the glyoxalase enzyme system, comprised of glyoxalase-1 and glyoxalase-2 enzymes, this system is recognized as the glyoxalase system. Located within the cytosol of cells, it contains α-ketoaldehydes as substrates, catalyzing them with catalytic amounts of GSH and Glo1 as cofactors. Reactive and non-cyclic α-ketoaldehydes are converted to α-hydroxy acids through the mediation of the glyoxalase system. Glyoxalase-1 catalyzes the isomerization of hemithioacetal, forming the structure of S-2-hydroxyacylglutathione. Hemithioacetal forms spontaneously in the presence of GSH. Glyoxalase-2, in contrast, converts the structure of S-2-hydroxyacylglutathione into α-hydroxy acids and simultaneously regenerates the GSH consumed in the step catalyzed by Glyoxalase-1 (Villanueva, 2017).

Numerous strategies have been explored to mitigate AGE interactions, including strategies to hinder AGE formation and AGE action, or disrupt pre-existing AGE cross-links.

Additionally, in response to oxidative stress, the AGE-RAGE signaling pathway triggers several intracellular pathways, culminating in the production of pro-inflammatory cytokines (for example; TNF-α, IL-6, and TGF-β), vascular adhesion molecules (like ICAM-1, VCAM-1, and ET-1), and reactive oxygen species (ROS), hence reinforcing vascular inflammation. Specifically, when human aortic endothelial cells (HAECs) are cultured under hyperglycemic conditions, oxidative stress ensues through AGE-RAGE signaling activation. This, in turn, upregulates MAPK pathways and prompts NF-κB and AP-1 activation. These transcription factors are later implicated in the elevation of gene expression for lysyl oxidase (LOX), an ECM enzyme, and endothelin-1 (ET-1), a vasoconstrictor protein. Subsequently, endothelial homeostasis is compromised, leading to cellular damage (Kosmopoulos et al., 2019) (Figure 6).

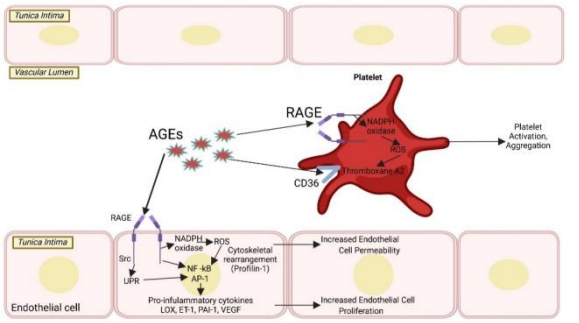

Figure 6. Effects of AGE-RAGE signaling in platelets and endothelial cell function (Kosmopoulos et al., 2019; Created in BioRender. Karakütük, I. (2025f) https://BioRender.com/m27q949)

Natural antioxidants and their alternatives are used as inhibitors of glycation reactions. It is stated that secondary metabolites abundant in fruits such as polyphenols also have inhibitory effects on AGEs (Zhao et al., 2022). In addition, the inclusion of these compounds can lead to results such as darker coloring in foods, increasing hardness and reduced taste compound production (Zheng et al., 2024). It has been reported that active compounds like miricitrin, ellagic acid, and quercitrin derived from *Drosera tokaiensis* tissue cultures exhibit strong inhibitory effects on AGEs (Tominaga et al., 2020). In addition, it should be considered that quercetin, catechin, and caffeic acid added at low concentrations have been reported to decrease food CML formation more than high concentrations, while high concentrations of polyphenols can increase hydrogen peroxide formation. In this case, hydrogen peroxide accelerates the formation of CML from Amadori products by generating hydroxyl radicals through Fenton reactions (Yalçın and Rakıcıoğlu, 2022).

In scientific terms, cooking is described as the transfer of energy from a heat source to food. This heat transfer aims to enhance the nutritional value and flavor of food, make it more digestible, and ensure the destruction of pathogenic microorganisms. Nevertheless, certain preparation and cooking methods may result in nutrient loss and a reduction in nutritional value, while some substances formed during cooking may render these foods harmful to health (Erim et al., 2022).

It has been reported that the number of AGEs in foods is associated with cooking methods and cooking temperature. Furthermore, there is a noteworthy correlation between the AGE content in foods and the fat content and MGO level.

The highest AGE compounds in foods are reported to be found in high-fat foods such as chips, crackers, and cookies (Uribarri et al., 2010).

When assessing the formation levels of AGEs based on cooking methods, the ranking typically proceeds as follows: oven roasting > deep frying > grilling > pan frying > boiling. Furthermore, the utilization of acidic marinades like tomato juice, vinegar, or lemon juice has been shown to potentially decrease AGE formation in meats by up to 50%. Notably, polyphenols, such as phenolic acids, flavonoids, stilbenes, and lignans, demonstrate anti-AGE properties (Akın and Özbek, 2022; Erim et al., 2022); Huang et al. (2024) demonstrated that resveratrol reduces oxidative stress and inflammation caused by AGEs in diabetic periodontitis through the NF-κB signaling pathway in AGE-stimulated human gingival fibroblasts (HGFs). Increasing the consumption of low-AGE foods such as whole grains, minimally processed dairy and meat products, fruits, and vegetables, while reducing the consumption of high-AGE foods such as grains, processed meat products, cheese, snack foods, and sugary beverages, decreases dietary AGE intake. Moreover, using moist heat cooking methods such as steaming, boiling, and simmering instead of dry heat cooking methods limits the formation of AGEs in foods. Polyphenols reduce AGE formation through mechanisms such as increasing antioxidant capacity, scavenging dicarbonyls, and breaking protein cross-links (Yalçın and Rakıcıoğlu, 2022).

7. Detection Methods

Many studies have been conducted to analyze AGEs in biological samples and foods, aiming to elucidate the main pathogenic mechanisms and understand whether the AGEs present in the human body originate from endogenous or exogenous sources (van Dongen et al., 2022).

A significant challenge in further exploring the risks associated with AGEs is the absence of a representative analytical system for detecting various AGEs in complex samples. Over the past decade, a range of separation and detection techniques have been employed to analyze AGEs. Separation methods include high-performance liquid chromatography-based techniques, such as ion pair chromatography, hydrophilic interaction chromatography, reverse phase liquid chromatography (RPLC and ion exchange chromatography). Detection methods used in these analyses include mass spectrometry (MS), fluorescence, and UV-Vis spectroscopy (Scheijen et al., 2016; Lee et al., 2024).

Various analytical methods have been employed to quantify the advanced glycation end-products (AGEs) content in foods. The majority of studies have assessed the concentration of Carboxymethyllysine (CML) in foods using enzyme linked immunosorbent assay (ELISA) based techniques (Kellow and Coughlan, 2015). Both food and blood contain numerous AGE metabolites that can be quantified using ELISA. Other techniques for measuring AGEs include liquid chromatography, particularly tandem mass spectrometry (LC-MS/MS), which is considered the gold standard for AGE detection. However, due to the complexity of this method, ELISA is typically preferred for AGE measurement. Determining the exact AGE content in food is a complicated process that involves homogenizing and extracting individual food items, followed by testing AGE metabolites in the supernatant using ELISA. This approach has contributed to the development of a database containing the AGE values for 550 common foods. The most accurate measurement of serum AGE is obtained from fasting blood samples, as consuming a meal rich in AGEs can elevate AGE levels. Among the most commonly measured metabolites are carboxyethyl-lysine (CEL), methylglyoxal (MG), and carboxymethyl-lysine (CML). CML is the primary metabolite used in AGE food databases and is frequently studied in relation to diet and serum AGE levels, particularly concerning cancer (Peterson and Ligibel, 2024).

The main factors contributing to a high AGE diet, adapted from dietary AGE analysis in the lung, prostate, colorectal and ovarian cancer screening trial, are represented by food groups in Figure 7 (Peterson and Ligibel, 2024).

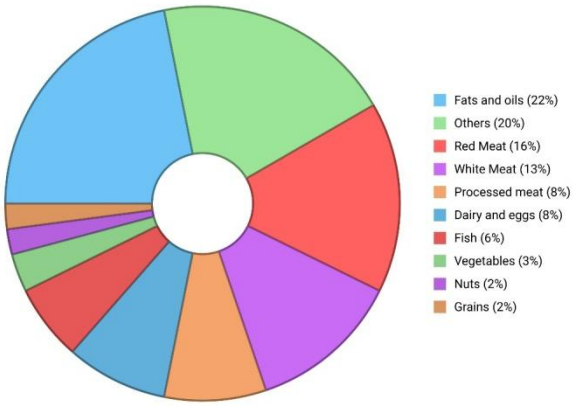

Figure 7. Contribution (%) of various food groups to dietary AGE intake (Peterson and Ligibel, 2024). *"Others" includes crackers, deserts, sugary drinks, and alcohol.

The use of various methodologies across several studies has resulted in inconsistent and conflicting findings. Currently, there is no universally accepted method for the accurate measurement of numerous advanced glycation end-product (AGE) moieties. Frequently employed techniques include chromatography, high-performance liquid chromatography (HPLC), fluorescence, and enzyme-linked immunosorbent assay (ELISA) (Peppa and Vlassara, 2005). Lee et al. (2024) developed a novel analytical method using RPLC-electrospray ionization (ESI)-MS to target 14 different AGEs, addressing challenges such as chromatographic separation difficulties due to the high hydrophilicity, diversity, and structural similarities of AGEs.

They achieved high sensitivity and accuracy by employing pre-column dansyl chloride derivatization, which helped overcome the limitations of previous methods. In their study, they demonstrated the method's broad applicability by successfully identifying AGEs in three types of foods (beer, coffee, and sausage) and six distinct glycated protein types. They concluded that this analytical system would provide valuable insights into the pathogenesis of AGE-related diseases.

8. Conclusion

In summary, the detrimental impacts of dietary advanced glycation end-products (d-AGEs) are of significant concern within the processed food sector. Studies indicate that d-AGEs play a pivotal role in fostering chronic conditions like diabetes, cardiovascular issues, and neurodegenerative diseases. Processing techniques employed in the food industry, including high-temperature cooking and prolonged storage, contribute to elevated levels of d-AGEs in processed foods. Efforts to minimize AGE formation should be increased by incorporating antioxidants comprising polyphenols in suitable proportions into foods with high AGE content and/or consumption levels, to sustain healthy eating habits and food preparation methods. Several inhibition methods, such as employing acidic components like lemon juice or vinegar, have shown potential in reducing the formation of d-AGE. Educating consumers about the detrimental effects of d-AGEs and reducing their consumption can lead to positive effects on public health.

Author Contribution

The contribution percentages of the authors' are given below. All authors have reviewed and approved the article.

	S.U.	M.Z.	M.Ş.	İ.A.K.
C	40	40	10	10
D	40	40	10	10
S	25	25	40	10
DCP	40	40	10	10
DAI	50	40	5	5
LS	50	30	10	10
WR	40	40	10	10
CR	30	40	15	15
SR	40	40	10	10

C= conceptualization, D= design, S= supervision, DCP= data collection and/or processing, DAI= data analysis and/or interpretation, LS= literature search, WR= writing, CR= critical review, SR= submission and revision, PM= project management, FA= funding acquisition.

Conflict of Interest Statement

The authors declare that there is no conflict of interest in this study.

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References

Akın Ö, Özbek YD. 2022. İleri glikasyon son ürünlerinin gebelik üzerine etkisi. Sakarya Üniversitesi Holistik Sağlık Dergisi, 5(1): 39-55.

Almeida F. 2013. Effects of the Maillard reactions on chemical composition and amino acid digestibility of feed ingredients and on pig growth performance. University of Illinois at Urbana-Champaign, Doctoral dissertation, Urbana, IL, USA, pp: 154.

Almeida FN, Htoo JK, Thomson J, Stein HH. 2014. Effects of balancing crystalline amino acids in diets containing heat-damaged soybean meal or distillers dried grains with solubles fed to weanling pigs. Animal, 8(10): 1594-1602.

Andrades ME, Lorenzi R, Nagai R, Moreira JCF, Ritter C, Dal-Pizzol F. 2012. Plasma glycation levels are associated with severity in sepsis. Eur J Clin Invest, 42(10): 1055-1060.

Anwar S, Khan S, Almatroudi A, Khan AA, Alsahli MA, Almatroodi SA, Rahmani AH. 2021. A review on mechanism of inhibition of advanced glycation end products formation by plant derived polyphenolic compounds. Mol Biol Rep, 48(1): 787-805.

Bronowicka-Szydełko A, Gostomska-Pampuch K, Kuzan A, Pietkiewicz J, Krzystek-Korpacka ML, Gamian A. 2024. Effect of advanced glycation end-products in a wide range of medical problems including COVID-19. Adv Med Sci, 69(1): 36-50.

Çatak J, Balcı E. 2022. Paketli keklerde ileri glikasyon son ürünleri öncüllerinin HPLC ile tespiti ve değerlendirilmesi. J Characterization, 2(1): 82-90.

Chen JH, Xing YL, Zhao LY, Ma HJ. 2019. The association between Helicobacter pylori infection and glycated hemoglobin A in diabetes: A meta-analysis. J Diabetes Res, 2019: 1-10.

Chilelli NC, Burlina S, Lapolla A. 2013. AGEs, rather than hyperglycemia, are responsible for microvascular complications in diabetes: A "glycoxidation-centric" point of view. Nutr Metab Cardiovasc Dis, 23(10): 913-919.

Demirel Y, Yıldıran H. 2018. İleri glikasyon son ürünleri ve böbrek hastalıkları. Gümüşhane Üniv Sağlık Bilim Derg, 7(1): 210-217.

Demirer B, Yardımcı H. 2022. İleri glikasyon son ürünlerinin diyabet komplikasyonları üzerine etkileri: Bir derleme. Beslenme ve Diyet Dergisi, 50(1): 101-108.

Erim B, Ergene E, Hecer C. 2022. Besin hazırlama ve pişirme yöntemlerinin ileri glikasyon son ürünleri üzerine etkisi. Aydın Gastronomy, 6(2): 275-281.

Gao QM, Jiang YY, Zhou DY, Li GF, Han YF, Yang JZ, Xu K, Jing YY, Bai L, Geng Z, Zhang H, Zhou GY, Zhu MR, Ji N, Han RN, Zhang YW, Li ZH, Wang CD, Hu Y, Su JC. 2024. Advanced glycation end products mediate biomineralization disorder in diabetic bone disease. Cell Rep Med, 5(9): 100966.

Ho SC, Wu SP, Lin SM, Tang YL. 2010. Comparison of anti-glycation capacities of several herbal infusions with that of green tea. Food Chem, 122(3): 768-774.

Hu H, Wang Y, Shen M, Huang Y, Li C, Nie S, Xie M. 2022. Effects of baking factors and recipes on the quality of butter cookies and the formation of advanced glycation end products (AGEs) and 5-hydroxymethylfurfural (HMF). Curr Res Food Sci, 5: 940-948.

Huang CY, Chen SH, Lin TC, Liao YW, Chang YC, Chen CC, Yu CC, Chen CJ. 2024. Resveratrol attenuates advanced glycation end product-induced senescence and inflammation in human gingival fibroblasts. J Dent Sci, 19(1): 580-586.

Karaköse D. 2023. Yüksek yağlı diyetle beslenen fare modellerinin yağ dokularında ileri glikasyon ürünlerinin incelenmesi. İstanbul Sabahattin Zaim Üniversitesi, Fen Bilimleri Enstitüsü, İstanbul, Türkiye, pp: 100.

Karakütük I. 2025a. Figure 1. Created in BioRender. https://BioRender.com/b07x896

Karakütük I. 2025b. Figure 2. Created in BioRender. https://BioRender.com/e31j367

Karakütük I. 2025c. Figure 3. Created in BioRender. https://BioRender.com/i45b405

Karakütük I. 2025d. Figure 4. Created in BioRender. https://BioRender.com/x24r992

Karakütük I. 2025e. Figure 5. Created in BioRender. https://BioRender.com/l87g434

Karakütük I. 2025f. Figure 6. Created in BioRender. https://BioRender.com/m27q949

Kellow NJ, Coughlan MT. 2015. Effect of diet-derived advanced glycation end products on inflammation. Nutr Rev, 73(11): 737-759.

Khan M, Liu HL, Wang J, Sun BG. 2020. Inhibitory effect of phenolic compounds and plant extracts on the formation of advance glycation end products: A comprehensive review. Food Res Int, 130: 108933.

Kosmopoulos M, Drekolias D, Zavras PD, Piperi C, Papavassiliou AG. 2019. Impact of advanced glycation end products (AGEs) signaling in coronary artery disease. BBA-Mol Basis Dis, 1865(3): 611-619.

Kuzan A. 2021. Toxicity of advanced glycation end products (Review). Biomed Rep, 14(5): 1-9.

Lee HHL, Ha SK, Kim Y, Hur J. 2024. Simultaneous analysis of advanced glycation end products using dansyl derivatization. Food Chem, 432: 137248.

Lim JM, Yoo HJ, Lee KW. 2022. High molecular weight fucoidan restores intestinal integrity by regulating inflammation and tight junction loss induced by methylglyoxal-derived hydroimidazolone-1. Mar Drugs, 20(9): 587.

Luevano-Contreras C, Chapman-Novakofski K. 2010. Dietary advanced glycation end products and aging. Nutrients, 2(12): 1247-1265.

Mendes NP, Cândido FG, Valente FX, Peluzio MDG, Juvanhol LL, Alfenas RCG. 2024. Dietary advanced glycation end products, body composition, and anthropometric measures: A cross-sectional analysis in women with excess body weight. Nutr Metab Cardiovasc Dis, 34(7): 1721-1730.

Nowotny K, Jung T, Höhn A, Weber D, Grune T. 2015. Advanced glycation end products and oxidative stress in type 2 diabetes mellitus. Biomolecules, 5(1): 194-222.

Ott C, Jacobs K, Haucke E, Santos AN, Grune T, Simm A. 2014. Role of advanced glycation end products in cellular signaling. Redox Biol, 2: 411-429.

Öztürk SA, Garipoğlu G. 2022. Determination of glyoxal and methylglyoxal bioaccessibility in pastas and noodles varieties by in vitro digestion method. J Characterization, 5(2): 102-110.

Patregnani JT, Fujiogi M, Camargo CA, Brooks BA, Hoptay CE, Mansbach JM, Teach SJ, Freishtat RJ, Hasegawa K. 2021. Serum soluble receptor for advanced glycation end products in infants with bronchiolitis: Associations with acute severity and recurrent wheeze. Clin Infect Dis, 73(9): e2665-e2672.

Peppa M, Vlassara H. 2005. Advanced glycation end products and diabetic complications: A general overview. Hormones, 4(1): 28-37.

Perrone A, Giovino A, Benny J, Martinelli F. 2020. Advanced glycation end products (AGEs): Biochemistry, signaling, analytical methods, and epigenetic effects. Oxid Med Cell Longev, 2020: 1-15.

Peterson LL, Ligibel JL. 2024. Dietary and serum advanced glycation end-products and clinical outcomes in breast cancer. BBA-Rev Cancer, 1879(1): 188786.

Peyroux J, Sternberg M. 2006. Advanced glycation endproducts (AGEs): pharmacological inhibition in diabetes. Pathol Biol, 54(7): 405-419.

Prasad C, Davis KE, Imrhan V, Juma S, Vijayagopal P. 2019. Advanced glycation end products and risks for chronic diseases: Intervening through lifestyle modification. Am J Lifestyle Med, 13(4): 384-404.

Qiang X, Liang SM, Lv YC, Wang XY, Zhang H, Zhan J. 2024. Advanced glycation end products (AGEs) impair the intestinal epithelial barrier via STAT3 activation mediated by macrophages. Food Chem Toxicol, 192: 113869.

Qu WT, Yuan XJ, Zhao JS, Zhang YX, Hu J, Wang JW, Li JX. 2017. Dietary advanced glycation end products modify gut microbial composition and partially increase colon permeability in rats. Mol Nutr Food Res, 61(10): 1700176.

Ruiz HH, Ramasamy R, Schmidt AM. 2020. Advanced glycation end products: Building on the concept of the "common soil" in metabolic disease. Endocrinology, 161(1).

Scheijen JLJM, Clevers E, Engelen L, Dagnelie PC, Brouns F, Stehouwer CDA, Schalkwijk CG. 2016. Analysis of advanced glycation endproducts in selected food items by ultra-performance liquid chromatography tandem mass spectrometry: Presentation of a dietary AGE database. Food Chem, 19: 1145-1150.

Schwarzenbolz U, Hofmann T, Sparmann N, Henle T. 2016. Free Maillard reaction products in milk reflect nutritional intake of glycated proteins and can be used to distinguish "organic" and "conventionally" produced milk. J Agric Food Chem, 64(24): 5071-5078.

Sharma C, Kaur A, Thind SS, Singh B, Raina S. 2015. Advanced glycation end-products (AGEs): An emerging concern for processed food industries. J Food Sci Technol-Mysore, 52(12): 7561-7576.

Shen CY, Lu CH, Wu CH, Li KJ, Kuo YM, Hsieh SC, Yu CL. 2020. The development of Maillard reaction, and advanced glycation end product (AGE)-receptor for AGE (RAGE) signaling inhibitors as novel therapeutic strategies for patients with AGE-related diseases. Molecules, 25(23).

Singh VP, Bali A, Singh N, Jaggi AS. 2014. Advanced glycation end products and diabetic complications. Korean J Physiol Pharmacol, 18(1): 1-14.

Snelson M, Tan SM, Clarke RE, de Pasquale C, Thallas-Bonke V, Nguyen TV, Penfold SA, Harcourt BE, Sourris KC, Lindblom RS, Ziemann M, Steer D, El-Osta A, Davies MJ, Donnellan L, Deo P, Kellow NJ, Cooper ME, Woodruff TM, Coughlan MT. 2021. Processed foods drive intestinal barrier permeability and microvascular diseases. Sci Adv, 7(14).

Sprenger HG, Bierman WF, Martes MI, Graaff R, van der Werf TS, Smit AJ. 2017. Skin advanced glycation end products in HIV infection are increased and predictive of development of cardiovascular events. AIDS, 31(2): 241-246.

Srey C, Hull GL, Connolly L, Elliott CT, del Castillo MD, Ames JM. 2010. Effect of inhibitor compounds on Nε-(carboxymethyl)lysine (CML) and Nε-(carboxyethyl)lysine (CEL) formation in model foods. J Agric Food Chem, 58(22): 12036-12041.

Takeuchi M, Suzuki H, Takeda K, Sakai-Sakasai A. 2024. Toxic advanced glycation end-products (TAGE) are major structures of cytotoxic AGEs derived from glyceraldehyde. Med Hypotheses, 183.

Tessier FJ, Niquet-Léridon C, Jacolot P, Jouquand C, Genin M, Schmidt AM, Grossin N, Boulanger E. 201

Tessier FJ, Niquet-Léridon C, Jacolot P, Jouquand C, Genin M, Schmidt AM, Grossin N, Boulanger E. 2016. Quantitative assessment of organ distribution of dietary protein-bound 13C-labeled Nε-carboxymethyllysine after a chronic oral exposure in mice. Mol Nutr Food Res, 60(11): 2446-2456.

Tominaga Y, Sugawa H, Hirabayashi K, Ikeda T, Hoshi Y, Nagai R. 2020. Extract containing multiple phenolic compounds inhibits the formation of advanced glycation end-products. Arch Biochem Biophys, 693.

Uribarri J, Cai W, Peppa M, Goodman S, Ferrucci L, Striker G, Vlassara H. 2007. Circulating glycotoxins and dietary advanced glycation endproducts: Two links to inflammatory response, oxidative stress, and aging. J Gerontol A Biol Sci Med Sci, 62(4): 427-433.

Uribarri J, Woodruff S, Goodman S, Cai WJ, Chen X, Pyzik R, Yong A, Striker GE, Vlassara H. 2010. Advanced glycation end products in foods and a practical guide to their reduction in the diet. J Am Diet Assoc, 110(6): 911-916.

van Dongen KCW, Kappetein L, Estruch IM, Belzer C, Beekmann K, Rietjens IMCM. 2022. Differences in kinetics and dynamics of endogenous versus exogenous advanced glycation end products (AGEs) and their precursors. Food Chem Toxicol, 164.

Vasilj M, Goni L, Gayoso L, Razquin C, Sesma MT, Etxeberria U, Ruiz-Canela M. 2023. Correlation between serum advanced glycation end products and dietary intake of advanced glycation end products estimated from home cooking and food frequency questionnaires. Nutr Metab Cardiovasc Dis, 33(9): 1768-1777.

Vıcıl S, Ulutaş E. 2020. Metilglioksal ve ileri glikasyon son ürünleri. Bozok Vet Sci, 1(1-2): 74-79.

Villanueva M. 2017. Glyoxalase 1 attenuates the effects of chronic hyperglycemia on explant-derived cardiac stem cells. Université d'Ottawa/University of Ottawa, Doctoral dissertation, Ottawa, Canada, pp: 134.

Wang H, Tu ZC, Liu GX, Liu CM, Huang XQ, Xiao H. 2013. Comparison of glycation in conventionally and microwave-heated ovalbumin by high resolution mass spectrometry. Food Chem, 141(2): 985-991.

Wu Q, Chen HY, Lv ZJ, Li SY, Hu B, Guan YF, Xie BJ, Sun ZD. 2013. Oligomeric procyanidins of lotus seedpod inhibits the formation of advanced glycation end-products by scavenging reactive carbonyls. Food Chem, 138(2-3): 1493-1502.

Yalçın E, Rakıcıoğlu N. 2022. Besinlerde oluşan ileri glikasyon son ürünlerine polifenollerin etkisi. Beslenme ve Diyet Dergisi, 50(2): 66-75.

Yaman M. 2021. İleri glikasyon son ürünlerinin (AGEs) öncüllerinin in vitro biyoerişilebilirliklerinin bazı gıdalarda belirlenmesi. Avrupa Bilim ve Teknoloji Dergisi, (27): 598-604.

Yılmaz B, Karabudak E. 2016. Besinlerdeki ileri glikasyon son ürünleri ve azaltma yöntemleri. Beslenme ve Diyet Dergisi, 44(3): 280-288.

Zhao WB, Cai PJ, Zhang N, Wu TT, Sun AD, Jia GL. 2022. Inhibitory effects of polyphenols from black chokeberry on advanced glycation end-products (AGEs) formation. Food Chem, 392.

Zheng XY, Ai BL, Zheng LL, Liu WY, Yang Y, Xiao D, Sheng ZW. 2024. Modulatory effects of tryptophan on advanced glycation end products formation and flavor enhancement in high-protein intermediate-moisture food during storage. LWT-Food Sci Technol, 197.

Zhou Q, Cheng KW, Xiao JB, Wang MF. 2020. The multifunctional roles of flavonoids against the formation of advanced glycation end products (AGEs) and AGEs-induced harmful effects. Trends Food Sci Technol, 103: 333-347.

Zolakova B, Zolak V, Hatok J, Matasova K, Nosal S, Zibolen M. 2016. Soluble receptor for advanced glycation end products in late onset neonatal infection. Bratisl Med J, 117(1): 15-18.