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Impacts of dietary advanced glycation end products on health: associated diseases and mitigation strategies

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ABSTRACT: Dietary advanced glycation end products (AGEs) or glycotoxins, arising from the Maillard reaction in foods, undergo biotransformation into biological AGEs through gastrointestinal digestion and absorption, subsequently accumulating in virtually all organs and tissues via the bloodstream. Currently, extensive attention is being paid to the safety and health hazards associated with dietary AGEs. This article presents an exhaustive investigation of the physicochemical properties and formation of AGEs, as well as diseases linked to AGEs, including diabetes, cardiovascular disorders, kidney diseases, neurodegenerative conditions, obesity, gut microbial-associated diseases and food allergies. Furthermore, this review highlights the existing research limitations and offers prospects for future mitigation strategies targeting AGEs. As the results, AGEs intake through diet could significantly contribute to their accumulation, which due to dietary AGEs could undergo biotransformation into biological AGEs through gastrointestinal digestion and absorption, subsequently accumulating in organs and tissues via the bloodstream, therefore accumulate in various organs and tissues in human body, lead to complicated chronic diseases such as diabetes, cardiovascular disorders, kidney diseases, neurodegenerative conditions, obesity, gut intestinal microbial-related diseases and food allergies. Furthermore, the mitigation strategies mainly include dietary modifications aimed at reducing AGEs intake, such as food processing at lower temperatures, consuming plant-based and antioxidant-rich foods, and employing processing methods like steaming or boiling instead of frying or grilling. By these dietary AGEs mitigation strategies, individuals can help reduce their intake and accumulation of AGEs, potentially lowering their risk of AGEs-related diseases and promoting overall health and longevity, which could provide better understanding of the diet AGEs related diseases and mitigation approaches.

Keywords: Advanced glycation end products; Dietary; Diseases; Food processing; Mitigation strategy

1. Introduction

With the advancement of food processing, continuous emergence of new food ingredients and rapid development of international food trade, the modern food industry has provided consumers with more processed foods with appealing colors and good tastes. Among the various processing employed in the food industry, thermal processing stands out as a widely utilized technique that enhances the palatability and

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consistency of food products, prolongs the shelf life, and improves food safety. Thermal processing entails a cascade of non-enzymatic and chemical reactions (Geng et al., 2024; Tian et al., 2023). Notably, in 1912, Louis Camille Maillard found that the heating of glycine and glucose gives rise to an artificial meat aroma and a brown substance (Yang et al., 2023). Subsequently, in 1953, this phenomenon was designated as the Maillard reaction (MR) (Feng, Berton-Carabin, Fogliano, & Schroen, 2022). The MR predominantly manifests during the preparation of thermal processed foods, such as baking, frying and grilling, which giving foods with desirable flavor, color and antioxidant properties, while MR also induces alterations in the protein structures, especially for the amino acids with free amino groups, therefore diminishing the nutritional value of processed foods.

During the Maillard reaction, a range of detrimental substances such as advanced glycation end products (AGEs), acrylamide (AA), heterocyclic amines (HAs), 5-hydroxymethylfurfural (5-HMF), furan and others are generated. Among which, AGEs are compounds formed in the body when protein combine with sugar, when they accumulate with high levels in various human tissues including plasma, blood vessels, skin, eye, kidney and the heart, they increase the risk of many diseases (Arshi, Chen, Ikram, Zillikens, & Kavousi, 2023; Wang, Jiang, & Zhao, 2024). The formation of AGEs contributes to increased levels of oxidative stress and reactive carbonyl stress, as well as upregulation of inflammatory factor expression. Additionally, it is plausible that AGEs can induce insulin resistance and inflict damage upon the vasculature. Reports indicate that a substantial portion, exceeding 12%, of dietary AGEs undergo direct absorption by the intestine, subsequently entering the bloodstream and forming pools of AGEs within the body (Jia, Guo, Zhang, & Shi, 2023). Consequently, the deleterious effects of dietary AGEs on human health demand considerable attention and cannot be dismissed.

Given the accumulation of AGEs and their protein adducts at various glycation sites, extensive research has been conducted to explore the link between AGEs and human diseases. Recent investigations have highlighted the crucial role played by receptor for AGEs (RAGE) during the pathogenic process mediated by the AGEs-RAGE axis, with RAGE acting as a linkage between AGEs and diseases. Activation of RAGE on immune cells by AGEs and AGEs protein adducts can initiate a cascade leading to the generation of a significant amount of reactive oxygen species (ROS). The AGEs-RAGE induced ROS pathway subsequently triggers the activation of inflammatory cells and prompts the release of RAGE ligands, including S100 protein or HMGB1 (Demirer, & Fisunoğlu, 2024), thereby disrupting immune balance and resulting in cell damage and the formation of lesions. Notably, the AGEs-RAGE axis has also been implicated in cancer development (Lin, Wu, Lu, Hsia, & Yen, 2016). Furthermore, AGEs-protein conjugates can induce the activation of various cellular signaling pathways through RAGE, thereby impacting the physiological function of immune cells (Iacobini, Vitale, Pesce, Pugliese, & Menini, 2021; Paparo et al., 2024; Sharma, Kaur, Sarkar, Sarin, & Changotra, 2021). Additionally, AGEs can elicit cross-linking and stiffening of tissues such as tendons, intervertebral discs, skin, arteries and vaginal tissues (Weli et al., 2017). These effects contribute to the understanding of the intricate relationship between AGEs and disease pathogenesis.

In light of the connection between oxidative stress, chronic inflammation and various diseases were related to AGEs, recent researches have focused on the formation of AGEs, inhibiting their hazard and eliminating AGEs. Numerous studies have evaluated the inhibitory effects of both synthetic compounds and natural substances on the formation of AGEs. While certain synthetic substances demonstrate strong inhibition of AGEs formation or decomposition through cross-linking, they may also induce adverse side effects (Chen, Lin, Bu, & Zhang, 2018; Feng et al., 2023; Peng, Ma, Chen, & Wang, 2011; Sarmah & Roy, 2022). In contrast, natural substances are generally safer for human consumption. Consequently, there has been growing interests in evaluating the impacts of specific plant extracts and related phenolic components on inhibiting AGEs formation. These substances perform potent anti-glycation effects primarily due to their robust anti-oxidant activity (Chibane, Degraeve, Ferhout, Bouajila, & Oulahal, 2019; Maqsood, Benjakul, & Shahidi, 2013; Peng, Ma, Chen, & Wang, 2011). Considering their safety and efficacy, natural substances with strong inhibitory effects on AGEs formation are highly promising as functional foods or preventive substances for AGEs-related diseases and disorders. This review presents an overview of the formation mechanism and physiological toxicity of AGEs, elucidates approaches to inhibit dietary AGEs formation, which could provide novel insights into the prevention and treatment of dietary AGEs related diseases.

2. The physicochemical properties of AGEs

In the past few decades, Maillard reaction (MR) have been extensively employed in food processing to enhance the flavors and colors of food, which leading to the formation of AGEs as byproducts (Fallavena, Rodrigues, Marczak, & Mercali, 2022). AGEs are intricate and durable compounds formed during the Maillard reaction between amino compounds (e.g. proteins and amino acids) and carbonyl compounds (e.g. reducing sugars) (Chen et al., 2022; Peng, Ma, Chen, & Wang, 2011; Song, Liu, Dong, Wang, & Zhang, 2021). Therefore, gaining a comprehensive understanding of the physicochemical properties of AGEs is pivotal in addressing their detrimental impacts on health.

2.1 The formation of AGEs

AGEs are a series of compounds that generated during Maillard reactions involving sugars and proteins (Nevin et al., 2018). The amino acid residues that are most commonly involved in the formation of AGEs are lysine, arginine and the N-terminal region of proteins (Dhayalan & Jeltsch, 2022; Tian, Liu, Sun, Fu, & Yang, 2018). The process of AGEs formation includes a series of complex reactions, beginning with Schiff bases and Amadori products. During the Amadori rearrangement process, α-dicarbonyl groups can react with the free amino groups of lysine and arginine on proteins, resulting in the formation of AGEs compounds (Balparda et al., 2023; Li et al., 2022).

The Hodge pathway, which is the classical pathway for AGEs formation, can usually be divided into three stages: initiation, propagation and advanced stage (Velichkova, Foubert, & Pieters, 2021). During the first stage (initial stage), reducing sugars (aldoses and ketoses) undergo nucleophilic addition reactions with amino groups, creating aldehydes and ketoimines (Schiff bases) (Aganovic et al., 2021; Poulsen et al., 2013; Solis-Calero, Ortega-Castro, Frau, & Munoz, 2015). Subsequently, the unstable and reversible Schiff bases

undergo Amodori or Heins rearrangement under acid-base catalysis. This generates 1-amino-deoxyketone or 2-amino-deoxyformaldehyde adducts, which are relatively stable Amodori or Heins products. Afterwards, Amodori products can convert into active dicarbonyl products (e.g. 3-deoxyglucosinone (3-DG), glyoxal (GO), and methylglyoxal (MGO)) during the reproductive phase. Among which, the formation of 3-DG occurs through non-oxidative rearrangement and hydrolysis reactions of Amodori products, whereas MGO and GO are produced from other methods.

In addition, the Amadori products may undergo metal-ion-mediated catalysis and oxidation to generate amines, while the sugar groups undergo dehydration to generate deoxyglucosone (DG). Moreover, these initial glycation products are prone to oxidative (glycation) and non-oxidative degradation, cleavage and covalent bonding, resulting in the formation of various stable compounds and protein cross-links, collectively referred to as AGEs. In the late stage, protein molecules undergo intermolecular or intramolecular heterocyclic cross-linking and cleavage, leading to protein denaturation and irreversible damage. Furthermore, AGEs can also be directly formed from Amadori products through rearrangement under oxidative and non-oxidative conditions.

In the Namiki oxidation pathway, initial products in the form of unstable Schiff bases undergo direct conversion into oxidized aldehydes (glycation). Furthermore, the Wolf pathway characterizes the process wherein reducing sugars automatically oxidize to form AGEs under metal catalysis (Bai, Li, Liang, Xia & Bian, 2023; Taghavi, Habibi-Rezaei, Amani, Saboury, & Moosavi-Movahedi, 2017). These pathways produce intermediate products, including dicarbonyl groups (e.g. MGO, GO, 3-DG) and free radicals. Moreover, the oxidation of polyunsaturated fatty acids through the lipid oxidation pathway may result in the production of GO or MGO, alongside advanced lipoxidation end products (ALEs). Although the Amadori product may not be a precursor, AGEs can still be generated via the reaction of pre-amador product and post-amador product (Makita et al., 1992; Velichkova, Foubert, & Pieters, 2021). Figure 1 illustrates the MR mechanism and process of AGEs formation.

As mentioned above, the various sources of α-dicarbonyl compounds influence the diversity of AGEs formation pathways and structures (Sarmah & Roy, 2022). AGEs are formed by covalent bond and can bind to the free amino groups on proteins, which generated highly stable and irreversible AGE structures. Once AGEs and their protein addition products are formed during food processing, general the stability is very high and irreversible.

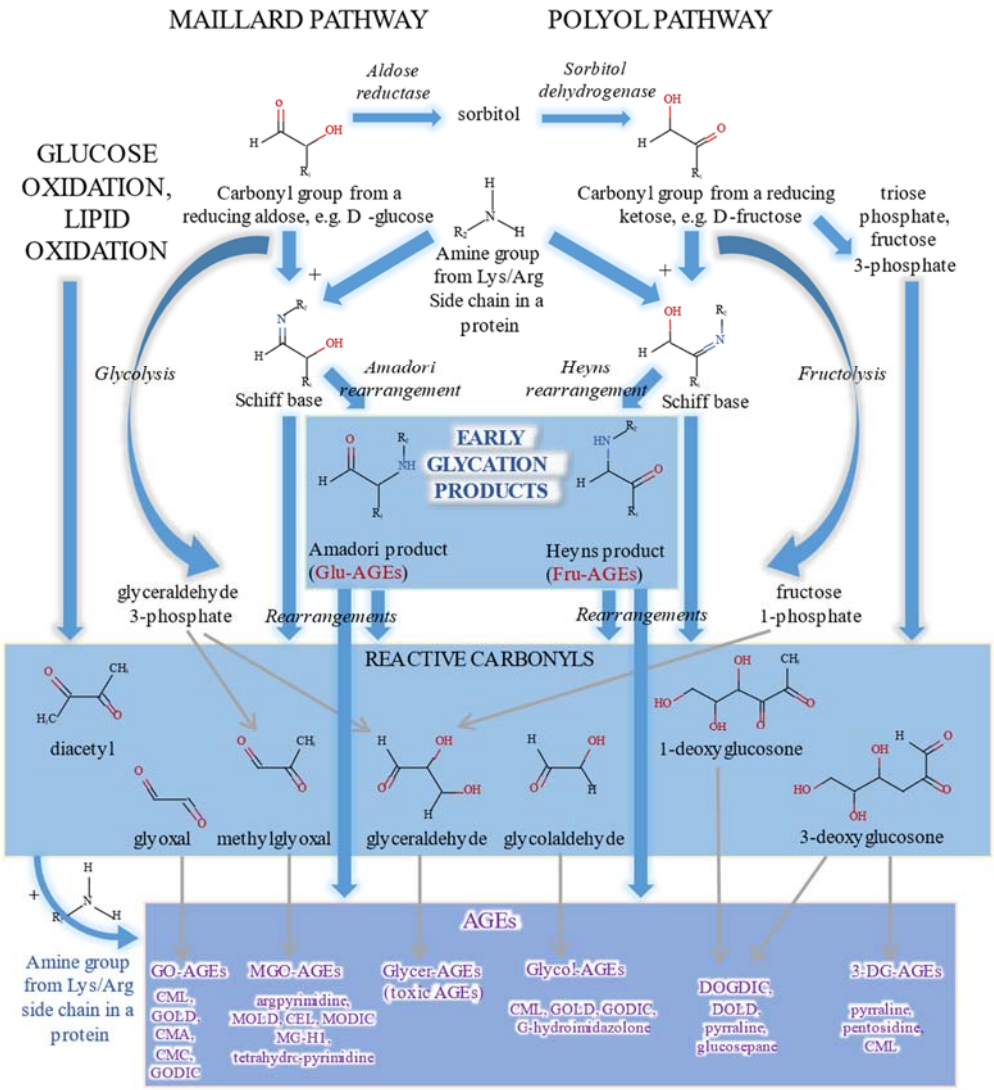

Figure 1 A formation scheme for AGEs is presented, including abbreviations for the following types: Glu-AGEs (glucose-derived), Fru-AGEs (fructose-derived), GO-AGEs (glyoxal-derived), MGO-AGEs (methylglyoxal-derived), Glycer-AGEs (glyceraldehyde-derived), Glycol-AGEs (glycolaldehyde-derived), and 3-DG-AGEs (3-deoxyglucosone-derived).

2.2 The classification of AGEs

Currently, there is limited understanding regarding the structure and characteristics of AGEs. Only a few AGEs have clearly defined structural characteristics. Up to now, more than 40 types of AGEs have been identified, which can be categorized into three main groups. The first group comprises AGEs that consist of lysine residues, including N^{ε}-(Carboxymethyl) lysine (CML), N^{ε}-(Carboxyethyl) lysine (CEL), pyrroline, and substituted lysine. The second group encompasses AGEs containing arginine residues, such as carboxymethyl arginine, imidazolinylornithine and arginine (Tian et al., 2023). The third group consists of cross-linked compounds, some of which exhibit fluorescence absorption properties and contain heterocyclic structures. Examples of common cross-linking AGEs include pyrazine (cross-linked between two lysine residues), glyoxal lysine dimer (GOLD, an imidazole cross-linked compound), methylglyoxal lysine dimer (MOLD), and DOLD (Tian et al., 2023). Additionally, certain AGEs may also undergo cross-linking between lysine and

arginine residues, for instance, pentoside (PTD), pentosinane and glucosepan (Biemel, Reihl, Conrad, & Lederer, 2002; Lederer & Buhler, 1999).

Numerous AGEs have been discovered in both food substrates and organisms, leading to their categorization into two types: biological AGEs and dietary AGEs. Biological AGEs, also known as endogenous AGEs (eAGEs), are formed through enzymatic reactions between reducing sugars or dicarbonyl compounds and nitrogen-containing groups in the physiological environment. For instance, when collagen encounters freely circulating glucose, it generates endogenous AGEs (Lasker, 2011). On the other hand, dietary AGEs (dAGEs) arise from non-enzymatic reactions of reducing sugars and nitrogen-containing groups in food (Zhang, Dong, et al., 2021). Upon consumption, dAGEs can enter systemic circulation, making food the primary external source of AGEs in the human body. Table 1 provides an overview of AGEs levels in various factory-produced and homemade foods. Within the gastrointestinal tract, dietary AGEs can convert into biological AGEs through digestion and absorption, accumulating in multiple organs (Zhang, Wang, & Fu, 2020). This implies that consuming food with a high dietary AGE content can increase physiological toxicity similar to that of biological AGEs (Liang, Chen, Li, Li & Yang, 2020). While some of the AGEs consumed through food undergo metabolism by the kidneys, others are absorbed by the body. According to Yuan et al. (2023), these AGEs gradually accumulate over time. Excessive accumulation of AGEs exacerbates oxidative stress and inflammation, resulting in chronic diseases such as diabetes, atherosclerosis, cardiovascular disease, Alzheimer's disease, and even cancer metastasis. Therefore, AGEs pose harm to the human body (Boveris & Fraga, 2004; Licastro et al., 2005; Yamagishi, Fukami, & Matsui, 2015).

Based on the available evidence, it appears that exogenous low molecular mass (LMM) glycation products exhibit bioavailability, leading to enhanced dicarbonyl pressure and protein cross-linking, thereby contributing to the formation of endogenous AGEs. Conversely, the bioavailability of exogenous high molecular mass (HMM) glycation products seems to be limited. Interestingly, these HMM glycation products may instead bind to RAGE and have detrimental effects on health (Figure 2). This suggests that the binding of AGEs to RAGE in relevant tissues is more likely to stem from endogenous glycation products.

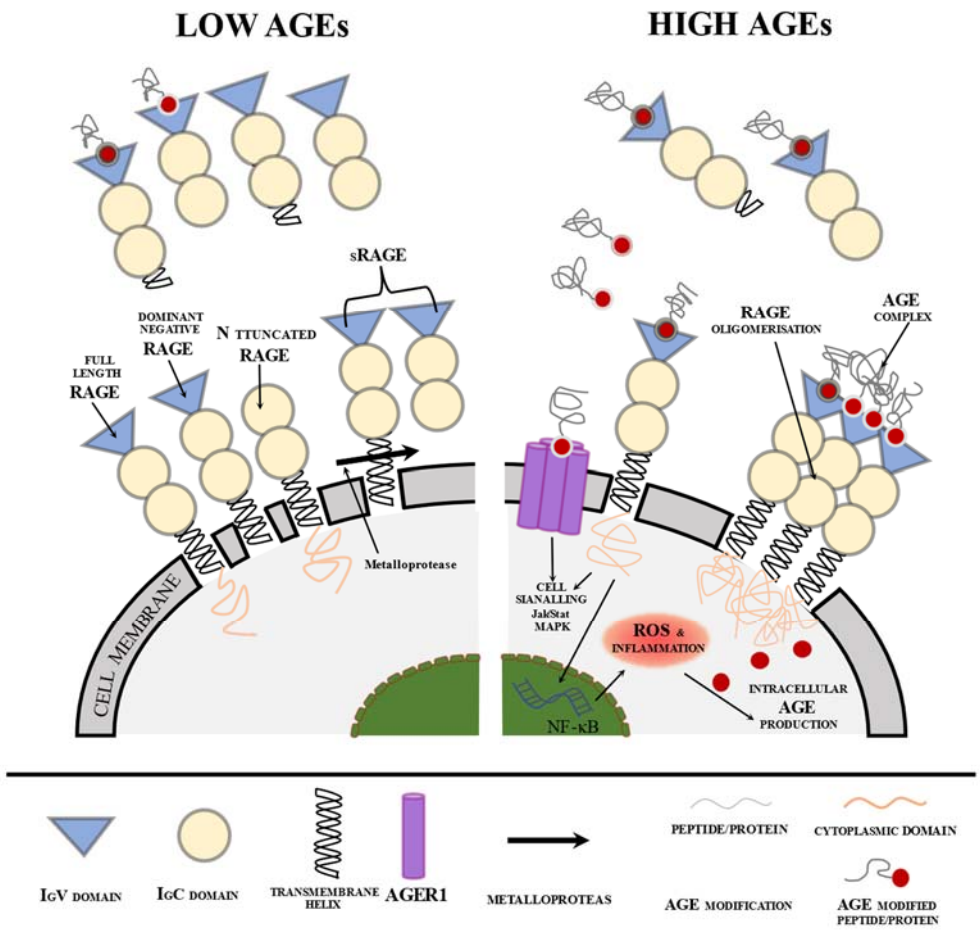

Figure 2 Isoforms of the receptor for Advanced Glycation End products (RAGE) and their interactions with downstream pathways activated by AGEs are examined. Technical abbreviations are explained upon first use. RAGE is a member of the immunoglobulin superfamily of receptors and a multi-ligand receptor. It includes various isoforms, such as full-length RAGE, dominant-negative RAGE, and N-truncated RAGE, which are membrane-bound. Additionally, RAGE has soluble, secreted and cleaved isoforms, with the cytoplasmic domain being necessary for RAGE signalling. The secreted isoforms are considered to work as decoys, binding to RAGE ligands and hindering their binding to the membranous forms of RAGE, which triggers downstream signalling. In an environment low in AGE (left), circulating sRAGE acts as a decoy receptor, binding to circulating RAGE ligands like AGEs and avoiding their binding to membranous isoforms of RAGE. In a high advanced glycation end-products (AGEs) environment, circulating soluble receptor for AGEs (sRAGE) levels are often reduced or the sRAGE capacity is fully saturated. As a result, it is no longer sufficient to inhibit receptor for AGEs downstream signalling.

2.3 The absorption of dietary AGEs

Dietary AGEs are typically digested and absorbed in the gastrointestinal tract, exerting an impact on consumers' health. The concentration of dietary and circulating free AGEs has been found to have a strong correlation with this effect (Nie, Li, Qian, Ying, & Wang, 2022; Sergi, Boulestin, Campbell, & Williams, 2021; Yuan et al., 2023). Consequently, the measurement of free AGEs serves as a crucial indicator of dietary AGEs intake, while plasma protein-bound AGEs are more reflective of endogenous AGEs (Sebekova & Sebekova, 2019; Zhang, Wang, & Fu, 2020). Estimating the absorption rate of AGEs in a regular diet becomes challenging due to their diverse nature, as well as identifying reasonable carriers for their delivery (Khalid, Petroianu, & Adem, 2022). However, absorption rates and mechanisms of specific AGEs such as CML, CEL, pentosidine, and pyrrolidine have been documented. Based on their chemical characteristics, an absorption rate of approximately 10%-30% has been observed (Suravajjala, 2012).

AGEs can exist in the gastrointestinal tract in two forms: as free molecules such as amino acids and small peptides weighing less than 5 kDa, or as high molecular weight complexes that bind to proteins (Baugreet et al., 2019; Poulsen et al., 2013; Zhao et al., 2017). The absorption of AGEs in their free form differs from that of bound AGEs. For instance, free CML, can be absorbed through simple diffusion, while dipeptides require peptide transporters that also facilitate the transport of pyrrolidine dipeptides (Snelson & Coughlan, 2019). As a result, the absorption of AGEs in the form of individual amino acids or dipeptides is more efficient than the absorption of AGEs bound to proteins. This is evident from the higher presence of CML in feces when protein-bound CML is consumed (Delgado-Andrade, 2016).

The same principle also applies to pentoside as well. When pentoside was extracted from brewed coffee (in its free form), it exhibits a higher absorption rate compared to baked goods, where pentoside exists in the form of protein-bound AGEs (Tagliazucchi & Bellesia, 2015). It is worth noting that modifying AGEs can impede protein digestion, making lower molecular weight AGEs more readily absorbed than protein-bound AGEs (Delgado-Andrade, 2016; van Dongen et al., 2022). However, even though AGEs bound to proteins can still be absorbed, their absorption rate is reduced.

3. AGEs related diseases

In recent decades, there has been a growing interest in understanding the impact of AGEs on health (Lin, Wu, & Yen, 2018; Luo, Zhang, Ho & Li, 2022). Accumulating evidence has demonstrated a close association between the accumulation of AGEs and various diseases. These diseases generally include complications of diabetes, cardiovascular diseases, kidney diseases, neurodegenerative diseases, obesity, intestinal microbial-related diseases and food allergies (Freund, Chen, & Decker, 2018; Garcia-Sanchez, Miranda-Diaz, & Cardona-Munoz, 2020). However, further comprehensive research is needed to determine whether AGEs directly induce these diseases or if they simply manifest as accompanying symptoms. Additionally, it is worth noting that AGEs can potentially induce oxidative stress and damage tissues by generating ROS (Aghadavod et al., 2016; Ung et al., 2017).

3.1 AGEs and diabetic complications

Hyperglycemia is an endocrine disorder that can affect multiple organs such as the eyes, blood vessels, kidneys, and nerves (Vijaykrishnaraj & Wang, 2021). In addition, it is also the basis of micro and macro complications such as diabetes neuropathy (neurons), diabetes retinopathy (eyes), diabetes cardiomyopathy (kidney and heart), liver disease and fat accumulation (Filla & Edwards, 2016; Vijaykrishnaraj & Wang, 2021; Pedreanez, Robalino, Tene, & Salazar, 2024). One of its main mechanisms is to emphasize the role of AGEs and inflammatory signals (Singh & Agrawal, 2022). Diabetes retinopathy (DR) is an eye complication, which is more vulnerable to hyperglycemia, leading to the damage of photoreceptors and blood vessels on the retina, leading to decreased vision (Tonade & Kern, 2021). In addition, diabetes neuropathy is due to the influence of uncontrolled hyperglycemia on the central nervous system (CNS), resulting in changes in neurochemical signals across the blood brain barrier (Vijaykrishnaraj & Wang, 2021). Diabetes cardiomyopathy (DCM) is characterized by cardiovascular and pulmonary complications caused by elevated

blood sugar levels, leading to hypertension and heart diseases (Battiprolu, Gillette, Wang, Lavandero, & Hill, 2010).

Type 2 diabetes (T2DM) is a metabolic disease characterized by chronic elevation of circulating blood glucose levels, resulting from insulin resistance and dysfunction of islet cells (Reifsnyder et al., 2022). Insulin resistance, the main feature of T2DM, is characterized by delayed response of target tissues to insulin. Research has shown that AGEs can activate the JNK and IKK/NF-κB signaling pathways, thereby confirming the association between AGEs and insulin resistance (Khalid, Alkaabi, Khan, & Adem, 2021). The AGEs-RAGE axis further induces oxidative stress, which is implicated in the development of insulin resistance (Abell, 2010; Nagalievska, Petryn, & Sybirna, 2022). Animal models and human studies have demonstrated that high dietary AGE levels during fetal development can initiate metabolic reprogramming that ultimately leads to the development of T2DM, independent of genetic susceptibility (Fernandez-Twinn & Ozanne, 2010; Fowden, Giussani & Forhead, 2005; Martin-Gronert & Ozanne, 2012). The detrimental effects of dietary AGEs on insulin signaling in humans have also been confirmed (Rains & Jain, 2011). Mitochondrial bioenergy dysfunction is a plausible mechanism linking AGEs overload and insulin resistance (Berlanga-Acosta et al., 2020). Furthermore, AGEs may exert harmful effects on pancreatic islet cells and promote cell apoptosis through the production of ROS. Therefore, AGEs contribute to islet cell dysfunction, which is another major factor in the pathogenesis of T2DM (Shu et al., 2011).

A low AGEs diet can have a positive impact on insulin resistance, fasting insulin, total cholesterol, and low-density lipoprotein (Dessein, Shipton, Stanwix, Joffe, & Ramokgadi, 2000; Posadas-Romero et al., 2004). Using a low AGEs diet is a practical method to reduce the incidence of risk factors for metabolic syndrome in adults, especially in diabetes patients (Tamura, Omura, Toyoshima & Araki, 2020). The formation of diabetes involves AGEs and RAGE. Indyk, Bronowicka-Szydelko, Gamian & Kuzan (2021) emphasized the correlation between AGEs and RAGE with common biomarkers of the disease, such as creatinine, glomerular filtration rate, and glycated hemoglobin. The interaction of AGEs-RAGE can also trigger cellular oxidative stress, thereby activating various pathways, including p21ras, mitogen activated protein kinase (MAPK), or protein kinase C (PKC) (Safi, Qvist, Kumar, & Ismail, 2013; Sruthi & Raghu, 2021). The disruption of endothelial cell cohesion by AGEs can lead to oxidative stress, which can have a negative impact on barrier function (Dobi et al., 2021). Figure 3 depicts the role of dietary AGEs in innate and adaptive immunity.

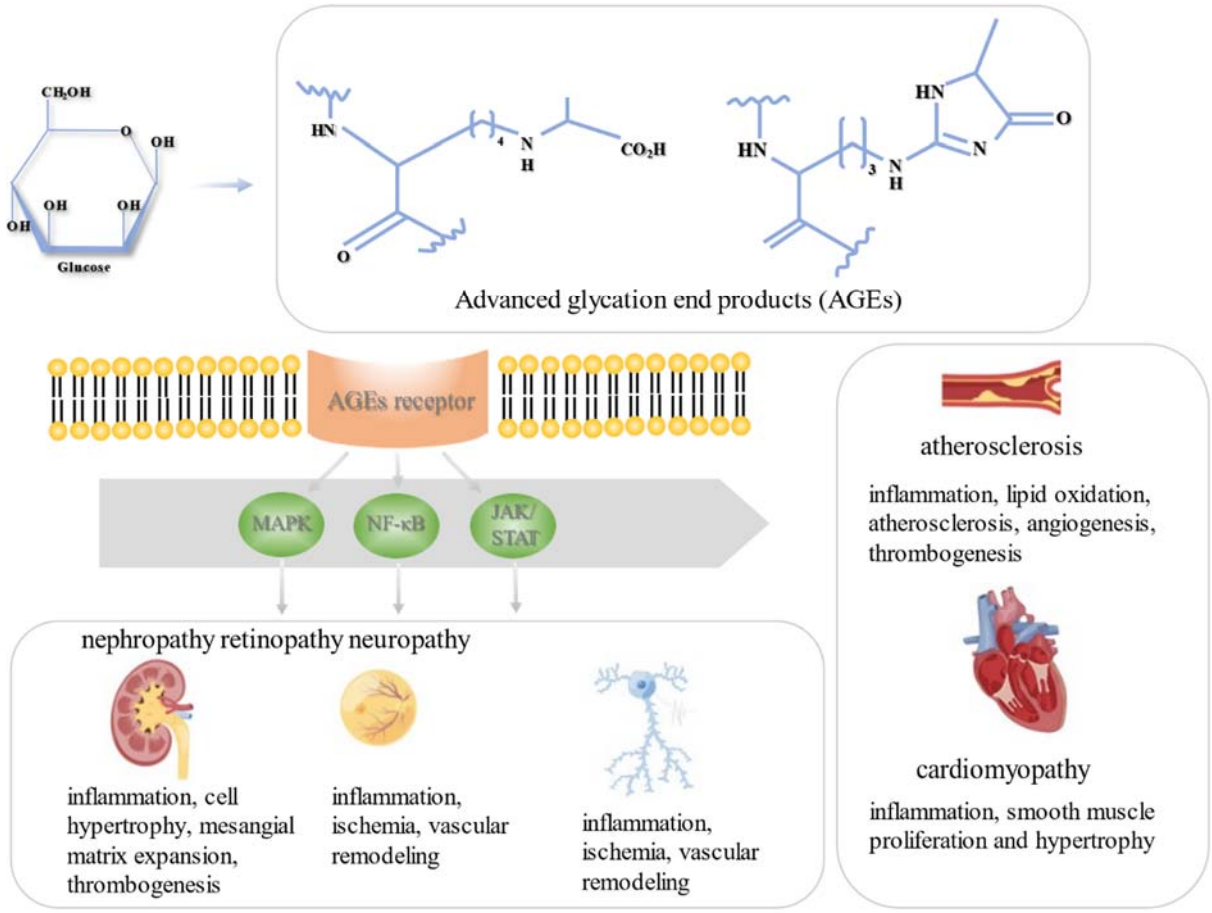

Figure 3 Role of Dietary Advanced Glycation End Products (AGEs) in Innate and Adaptive Immunity. Dietary advanced glycation end products (dAGEs) could affect innate immunity by interacting with RAGE or binding to AGE receptors that internalize ligands. This can impact several diseases through related pathways. RAGE regulates the MAPK NF-κB signaling pathway. After binding to the ligand, RAGE phosphorylates its downstream MAPK, activating NF-κB protein. This, in turn, enters the nucleus to promote the transcriptional expression of inflammatory factors.

3.2 AGEs and cardiovascular diseases

AGEs play a crucial role in inducing complications of microvascular diabetes by binding to extracellular matrix proteins, resulting in changes in the elasticity, structure, and function of blood vessels (Mengstie et al., 2022). Moreover, the interaction between AGEs and RAGE leads to vascular inflammation, peripheral cell apoptosis, damage to the blood tissue barrier, and increased permeability (Rungratanawanich, Qu, Wang, Essa, & Song, 2021). Irrespective of the presence or absence of hyperglycemia, AGEs can worsen cardiovascular complications (Mapanga & Essop, 2016). The accumulation and exposure to AGEs can cause oxidative stress and aggravate inflammation, leading to the oxidation of low-density lipoprotein (LDL) and subsequent damage to cardiovascular health (Zhang, Li, et al., 2021). Within blood vessels, accumulated AGEs can interact with monocytes, endothelial cells, and smooth muscle cells, resulting in cellular dysfunction, tissue damage, and arteriosclerosis (Aronson & Rayfield, 2002; Doran, Meller, & McNamara, 2008). Additionally, higher levels of circulating AGEs are positively correlated with the incidence rate of cardiovascular disease, as well as the severity of coronary atherosclerosis and coronary artery disease (Borissoff et al., 2013; Frysz et al., 2022).

AGEs also contribute to the development of cardiovascular diseases. The correlation between the experimental results and the blood parameters (e.g. high-density lipoprotein cholesterol, uric acid) of patients receiving treatment in diabetes clinics supports this claim (Su et al., 2011; Zhang, Zhao, Lu, Meng, & Zhou, 2023). AGEs are associated with specific pathophysiological processes of the vascular condition, such as a gradual decrease in arterial wall elasticity (arterial stiffness) (Gelzinsky, Filipovsky, Mayer, Mlikova-Seidlerova, & Mares, 2022; Mayer et al., 2021). In the bloodstream, AGEs can interact with endothelial cells through RAGE, resulting in vascular complications (Banarjee, Sharma, Bai, Deshmukh, & Kulkarni, 2018). Furthermore, AGEs can trigger oxidative stress in brain microvascular endothelial cells, leading to increased blood vessel permeability (Liu et al., 2022). Additionally, RAGE and Toll-like receptor 4 (TLR4) exhibit numerous similarities, including shared ligands and signaling pathways, which can induce inflammation, thrombosis, and oxidation (Wei, Zhang, Li, Wang, & Yao, 2023).

AGEs mainly induce arterial injury and exacerbate the progression of atherosclerotic plaque by activating cell receptor-dependent signaling pathways (Singh, Siva, & Ravichandiran, 2022; Wasim et al., 2022). The interaction between AGEs and RAGE, a transmembrane signal receptor presents in all cell types crucial to atherosclerosis, alters cellular activity, enhances gene expression, and promotes the release of inflammatory substances. Ultimately, this leads to arterial wall damage and plaque formation (Ahmed, 2005; Xiao et al., 2020). This review aims to analyze the role of AGEs in the occurrence, development, and instability of atherosclerosis. AGEs interact with their transmembrane receptor in endothelial cells, smooth muscle cells, and platelets, initiating intracellular signaling that causes endothelial damage, altered vascular smooth muscle cell function, and modified platelet activity (Basta, Del Turco, & De Caterina, 2004; Kosmopoulos, Drekolias, Zavras, Piperi, & Papavassiliou, 2019). Table 2 displays the relevant structures of RAGE receptors.

Table 2 Structural components of AGEs receptors studied in relation to dietary AGEs including RAGE, galeclin-3, SR-A and CD36

AGEs Receptor	Structure	AGEs Binding Sides	Forces for AGEs Interaction
RAGE	EC: one V-type domain, two C-types domains and a short transmembrane domain. IC: cytoplasmic tail.	V-type domain	Electrostatic interactions.
Galectin-3	Component of AGEs-R complex has a carbohydrate rocognition domain (CRD) and a carbohydrate binding site (CBS).	CBS	Hydrophilic interactions via hydrogen bonds, and hydrophobic intoractions, specifically the CH-n interaction explains binding to loctins and lipopolysaccharides.
SR-A	EC: scavenger recoptor cysteine-rich structure (SRCR), collagenous domain, α-helical coiled coil, and spacer as well as an intracellular cytoplasmic.	Collagenous domain	For specific AGEs unknown. All ligands are macromolecular and polyanionic. For apo-A and apo-E, amphipathic α-helix suggestsd as a potential recognition motif. Dual cation-binding site proposed as main domain for ligand binding via SR-A, hence electrostatic interactions.
CD36	Two transmembrane domains, an EC loop with glycosylation sites and two short IC tails.	Hydrophobic binding pocket located at the highly glycosylated	Electrostatic interactions, via a positively charged moiety that binds to negatively charged ligands, basod on studies with diacylglycerol and

	sites	oxidized low density lipoprotein as ligands.

Note: AGEs: Advanced glycation end products; RAGE: Receptor for AGEs; SR-A: Class A scavenger receptor; CBS: carbohydrate binding site.

A previous study found that, the α-dicarbonyl derived AGEs are associated with cardiovascular disease in the elderly population, while are not associated with healthier middle-aged and elderly populations (Lamprea-Montealegre et al., 2022). Another study found that AGEs only have adverse effects on the cardiovascular system in the presence of significant dicarbonyl and oxidative stress (Cianfruglia, Morresi, Bacchetti, Armeni, & Ferretti, 2020). According to another reports, further research on α-dicarbonyl derivatives may bring potential new strategies for preventing cardiovascular disease in high-risk elderly populations (Schalkwijk & Stehouwer, 2020). According to this meta-analysis, higher levels of AGEs measured by skin spontaneous fluorescence were significantly associated with a higher overall risk of MACE (major adverse cardiovascular events), and AGEs were closely associated with nonfatal and fatal cardiovascular events (Chen, Huang, Liu, & Zhou, 2022; Planas, Simo-Servat, Hernandez, & Simo, 2022). AGEs is an important biomarker for predicting the occurrence of MACE.

3.3 AGEs and kidney diseases

The accumulation of AGEs in the kidneys has been associated with increased oxidative stress and inflammation, ultimately leading to renal failure (Wojtaszek, Oldakowska-Jedynak, Kwiatkowska, Glogowski, & Malyszko, 2021; Wu et al., 2021). Acute or chronic kidney disease, as well as end-stage renal failure, can impair the clearance of AGEs (Mosenzon et al., 2022). Consequently, due to a decrease in the glomerular filtration rate, glomerular and tubular cells are exposed to potentially harmful AGEs for an extended period (Chevalier, Thornhill, & Chang, 2000). These alterations may result in impaired renal function, hasten the onset and progression of kidney disease, along with an elevation in circulating AGEs levels (Baylis, 2009; MacIsaac, Ekinci, & Jerums, 2014). The interactions between AGEs and RAGE in the kidneys promote the activation of connective tissue growth factor (CTGF), transforming growth factor-beta (TGF-β), mitogen-activated protein kinase (MAPK), nuclear factor-kappa B (NF-κB), and protein kinase C (PKC) pathways, leading to increased oxidative stress, inflammation, and fibrosis (Lu, Zhong, Liu, Xiang, & Deng, 2019; Oltean, Coward, Collino, & Baelde, 2017). These processes can result in damage to the kidney capsule, glomerular hypertrophy, proteinuria, and eventual progression to end-stage renal failure. Figure 4 demonstrates that the high-mobility group box 1 (HMGB1) ligand of RAGE enhances the activation of extracellular signal-regulated kinase 1/2 (ERK1/2), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1), all of which contribute to renal inflammation and the development of kidney disease, including refractory cases (Dong, Zhang, Huang, & Deng, 2022; Rungratanawanich, Qu, Wang, Essa, & Song, 2021).

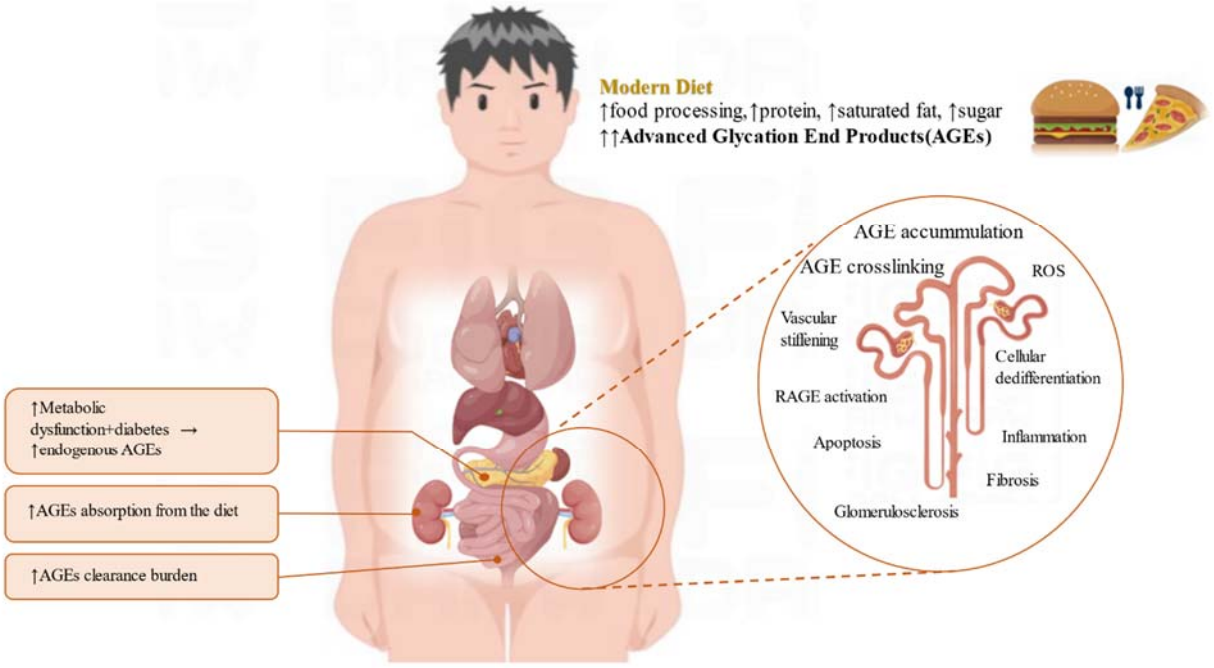

Figure 4 Etiology of AGE-related Diseases in Modern Dietary Patterns. The kidney, a major site for AGE clearance, is particularly vulnerable to damage from AGEs. Increased circulating AGEs correlate with the risk of chronic kidney disease (CKD) and all-cause mortality. Additionally, individuals with significant renal function loss show a higher AGE burden, especially with uraemia. Some evidence suggests that reducing AGEs through dietary changes or pharmacological inhibition could benefit CKD.

Patients with chronic kidney disease (CKD) are more susceptible to oxidative stress and chronic inflammation, which can increase the synthesis of AGEs (Modaresi, Nafar, & Sahraei, 2015; Podkowinska & Formanowicz, 2020; Watanabe et al., 2008). As the renal clearance function decreases in CKD patients, there is an accumulation of AGEs. This accumulation, along with the decline in renal function, contributes to increased all-cause mortality (Molinari et al., 2023; Steenbeke et al., 2022). These AGEs are considered non-traditional risk factors and play a significant role in the progression of cardiovascular disease in CKD patients (Hirsch, Lau, Kushwaha, & Yong, 2023; Steenbeke et al., 2022). The interaction between AGEs and their receptors on the cell surface, known as RAGE, enhances cell function through the activation of NF-κB and disrupts the balance leading to increased production and release of inflammatory cytokines (Bopp et al., 2008; Steenbeke et al., 2022).

The changes in the AGEs-RAGE axis have been found to be associated with the development of various chronic kidney diseases (Steenbeke et al., 2022). Soluble RAGE (sRAGE) acts as a decoy receptor, inhibiting the activation of membrane-bound RAGE and mitigating AGEs-RAGE related toxicity (Zgutka, Tkacz, Tomasiak, & Tarnowski, 2023). The ratio of AGEs to sRAGE, particularly sRAGE alone, may serve as a valuable prognostic indicator for kidney disease (Le Bagge, Fotheringham, Leung, & Forbes, 2020). Nephropathy is another common complication of diabetes (Pearce, Simo, Lovestam-Adrian, Wong, & Evans, 2019). Research has identified two mechanisms by which toxic AGEs (tAGEs) contribute to kidney disease: (1) inducing apoptosis of human interstitial cells, (2) stimulating the secretion of vascular endothelial growth factor (VEGF) and monocyte chemotactic protein-1, leading to increased filtration and microalbuminuria (Yamagishi & Matsui, 2011).

3.4 AGEs and neurodegenerative diseases

The brain is a highly specialized organ that governs motor, behavioral, neurocognitive, and executive functions with strict regulation (Foldi, Morris, & Oldfield, 2021). However, unlike other tissues such as the liver and kidneys, the brain generally lacks defensive or protective enzymes and proteins. Consequently, oxidative stress in the brain can increase as a result of aging or prolonged exposure to detrimental substances like alcohol (ethanol), high-fat diets rich in n-6 fatty acids, and sugary beverages, leading to the generation of AGEs (Rungratanawanich, Qu, Wang, Essa, & Song, 2021; Svegliati-Baroni et al., 2019). This process contributes to the escalation of oxidative damage, further fueling the development and progression of neurodegenerative diseases (Alves et al., 2021; Kubis-Kubiak, Rorbach-Dolata, & Piwowar, 2019).

Similar to AGEs, RAGE are also significantly expressed in various brain regions, including the cerebral cortex, hippocampus, cerebellum and substantia nigra, during the development of neurodegenerative diseases (Crichton, Dexter, & Ward, 2008; Gasparotto et al., 2019; Silvin & Ginhoux, 2018). Activated microglia produce and release AGEs albumin, which induces upregulation of RAGE in neurons and neuronal cell death, thus contributing to neurodegenerative diseases (Bayarsaikhan et al., 2015; Byun et al., 2012). The accumulation of AGEs and their interaction with RAGE can also induce reactive glial hyperplasia and activate the NF-κB-mediated pro-inflammatory pathway, resulting in cellular stress, glial proliferation, and ultimately, neuronal degeneration (Dong, Zhang, Huang, & Deng, 2022; Iacobini, Vitale, Pesce, Pugliese, & Menini, 2021; Manigrasso, Juranek, Ramasamy, & Schmidt, 2014). It is believed that the AGEs-RAGE axis is associated with the pathophysiological processes of dementia (Chen et al., 2021; Sharma, Kaur, Sarkar, Sarin, & Changotra, 2021). However, the relationship between this system and the risk of dementia onset, if present, is limited to the short term (van Oijen et al., 2007).

A study targeting Alzheimer's disease patients demonstrated that the accumulation of AGEs accelerates the formation of Aβ (amyloid β-protein), tau, and amyloid precursor protein (APP). Furthermore, the study also discovered that the cross-linking of AGEs with Aβ and the excessive phosphorylation of tau contribute to an increase in these aggregates (Dubey et al., 2020; Rungratanawanich, Qu, Wang, Essa, & Song, 2021). Moreover, AGEs can impede the expression of SIRT1, activate inducible nitric oxide synthase (iNOS) and Caspase-3, resulting in neuronal apoptosis and/or degeneration, ultimately leading to glial proliferation (Alanazi et al., 2020; Shahcheraghi et al., 2023; Taurone et al., 2022). Mass spectrometry analysis has corroborated that one of the most prevalent AGEs-protein adducts in the brain is AGEs-albumin adduct, which induces overexpression of RAGE in primary neurons of the human AD brain (Buccellato, D'Anca, Fenoglio, Scarpini, & Galimberti, 2021; Zgutka, Tkacz, Tomasiak, & Tarnowski, 2023).

The formation of AGEs albumin adducts is influenced by oxidative stress and Aβ (Buccellato, D'Anca, Fenoglio, Scarpini, & Galimberti, 2021). Increased aggregation of Aβ leads to deterioration. Furthermore, Aβ is generated through the interaction between AGEs albumin and RAGE, subsequently promoting the formation of AGEs albumin adducts and forming a favorable feedback loop. The binding of AGEs albumin adducts and RAGE establishes a connection with neuronal apoptosis by activating the pro-apoptotic JNK and

Bcl-2 related protein X (Bax) pathway (Chrysanthou, Miro Estruch, Rietjens, Wichers, & Hoppenbrouwers, 2022; Xie, Mendez, Mendez-Valenzuela, & Aguilar-Hernandez, 2013). Apart from AGEs and AGEs adducts, HMGB1 and Aβ can also bind to RAGEs to activate NF-κB, ERK1/2, p38, JNK, PI3K, Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways, leading to neuronal cell death and neurodegeneration (Belinskaia, Voronina, Shmurak, Jenkins, & Goncharov, 2021; Chu, 2014). Additionally, cross-linked AGEs with Aβ also reduces the ability of microglia to clear plaques (Munch et al., 2003).

In the context of Parkinson's disease (PD), numerous studies have demonstrated the association between dietary AGEs and the formation of AGEs in the substantia nigra (Vicente Miranda, El-Agnaf, & Outeiro, 2016). The accumulation of AGEs in newly formed Lewis bodies during the early stages of PD suggests their potential involvement in promoting Lewis body formation during disease progression (McNaught & Olanow, 2003). Furthermore, α-AGEs cross-linked by synaptic nucleoproteins have been detected in the brains of PD patients and have been found to contribute to the aggregation of toxic oligomers of α-synuclein, a synaptic nucleoprotein (Al-Hilaly et al., 2016). Additionally, in the brain of PD patients, the interaction between RAGE and S100 leads to the activation of the NF-κB and TNF-α signaling pathway, resulting in dopaminergic neuronal death and subsequent neurodegeneration (Wang et al., 2020). Among the various AGEs products found in the brains of PD patients, AGEs albumin, synthesized by activated microglia, is the most abundant (Bayarsaikhan et al., 2015). Increased expression of RAGE induced by AGEs albumin aggregation has been shown to trigger apoptosis in primary dopamine neurons in the brain (Jiang, Wang, Tuo, Ma, & Xie, 2018).

Research has shown that an increase in circulating AGEs is associated with a decline in cognitive function and an increased risk of dementia over time (D'Cunha et al., 2022). Preliminary studies have also indicated that higher accumulation of AGEs in the brain may be linked to mental disorders, particularly depression and schizophrenia (Bradlow, Berk, Kalivas, Back, & Kanaan, 2022). The potential mechanisms underlying the impact of AGEs include heightened oxidative stress and neuroinflammation, both of which play significant roles in the pathogenesis of mental disorders and neurodegeneration (Pardillo-Diaz, Perez-Garcia, Castro, Nunez-Abades, & Carrascal, 2022). Moreover, reducing dietary intake of AGEs has been shown to enhance the effectiveness of treatment for neurological and psychiatric disorders (Foley & White, 2002).

The role of the NLRP3 (NLR Family Pyrin Domain Containing 3) inflammasome-mediated inflammation and sepsis in the pathogenesis of diabetic keratopathy (DK) is well established. Under normal circumstances, the NLRP3 inflammasome plays a crucial role in corneal wound healing and nerve regeneration (Wan et al., 2022). However, in diabetic patients, the sustained activation of the NLRP3 inflammasome results in delayed wound healing and impaired nerve regeneration (Zhou et al., 2022). Mechanistically, the accumulation of AGEs can stimulate excessive activation of the NLRP3 inflammasome through ROS production (Lara, Macias-Verde, & Burgos-Burgos, 2020). Moreover, inhibiting the

AGEs/ROS/NLRP3 inflammatory axis through genetic and pharmacological interventions has been shown to significantly promote corneal epithelial wound closure and nerve regeneration in diabetes (Li et al., 2023).

3.5 AGEs and obesity

A study conducted over a period of five years revealed that advanced glycation end products (AGEs) can contribute to weight gain among adults. Interestingly, even after adjusting for factors such as total energy intake, it was found that AGEs still have a significant impact on weight gain, suggesting a direct influence on energy balance (Cecil, Tavendale, Watt, Hetherington, & Palmer, 2008). The regulation of energy balance is controlled by the hypothalamus, and insulin, a hormone that suppresses appetite, plays a crucial role in this process (Wang & Cheng, 2018). Consequently, AGEs may disrupt the hypothalamus' ability to maintain energy balance through the development of insulin resistance (Nadal, Quesada, Tuduri, Nogueiras, & Alonso-Magdalena, 2017). In a survey conducted by Van Dongen et al. (2021), it was observed that mice fed with baked feed had relatively lower food intake compared to those fed with standard feed, while both groups exhibited similar weight gain. This suggests that aggregated AGEs might activate various pathways, including c-Jun N-terminal kinase (JNK), Iκ-B kinase (IKK), nuclear factor κB (NF-κB), and tumor necrosis factor α (TNF-α), leading to insulin and leptin resistance in the hypothalamus, hypothalamic dysfunction, imbalance in energy control, and subsequently, food consumption and weight gain. These factors ultimately contribute to obesity and metabolic syndrome (Chan, 2009). It is important to note that the relationship between dietary AGEs and weight gain is not strong. Lakdawalla and Philipson (2009) suggest that consuming dietary AGEs may not necessarily result in increased obesity.

3.6 AGEs and gut microbiota-associated diseases

The composition and function of gut microbiota are influenced by both endogenous and exogenous factors, with dietary AGEs playing a significant role in food consumption levels (Zmora, Suez, & Elinav, 2019). Upon ingestion, less than 30% of dietary AGEs are absorbed by the intestine, with less than 15% excreted through urine and feces. This suggests that the remaining unabsorbed AGEs might undergo degradation by gut microbiota (Chen & Yang, 2020). The gut microbiota produces specific degrading enzymes to break down AGEs and utilize the released energy (Clavijo & Vives Florez, 2018). Consequently, the presence of unabsorbed AGEs can influence the composition and quantity of gut microbiota (Li et al., 2022).

Furthermore, the composition of intestinal microbiota is closely linked to the development of several diseases, including type 2 diabetes, obesity, neurodegenerative diseases, and end-stage renal failure. It has been observed that AGEs play a significant role in influencing the composition of gut microbiota. Therefore, adopting a dietary strategy that restricts the intake of AGEs holds promise for enhancing the composition of gut microbiota and ameliorating disease-related conditions.

The presence of AGEs can have an impact on the composition of gut microbiota by promoting the growth of specific microbiota. This, in turn, can lead to a decrease in microbial diversity and potentially result in intestinal permeability (Hemmati et al., 2023). Accumulated AGEs may stimulate the production and release

of pro-inflammatory cytokines, harmful metabolites, and bacterial products. Consequently, this can increase intestinal permeability, disrupt the intestinal barrier function, and facilitate bacterial transport. Such processes can cause damage to intestinal epithelial cells and contribute to systemic endotoxemia, inflammation, and multiple organ damage (Chi et al., 2021; Compare et al., 2012; Kalyan et al., 2022). The modulation of intestinal microbiota regulated by AGEs has been implicated in the pathogenesis of various diseases, including type 2 diabetes, obesity, neurodegenerative diseases, and end-stage renal failure. Implementing dietary restrictions on AGEs has shown potential to optimize the composition of gut microbiota, leading to alleviation of disease conditions.

3.7 AGEs and food allergy

Through non-enzymatic reactions, carbohydrates have the ability to bind with proteins, nucleic acids, or lipids, resulting in the formation of compounds known as AGEs (Twarda-Clapa, Olczak, Bialkowska, & Koziolkiewicz, 2022). While endogenous formation of AGEs can occur, the Western diet is characterized by certain factors that significantly contribute to dietary AGE exposure. These factors include elevated levels of added sugar, protein dehydration during various processing techniques, high-pressure sterilization for prolonged product preservation, frying, microwave heating and reheating (Abdelwahed, Degobert, Stainmesse, & Fessi, 2006; Kopp, 2019).

Dietary AGEs have the ability to bind with RAGE, which are integral components of the endogenous risk detection network (Smith, Venter, O'Mahony, Canani, & Lesslar, 2023). RAGE is a critical element within this endogenous threat detection network, and its activation can be triggered by amyloid proteins as well as danger-associated molecular patterns (DAMPs) such as high-mobility group box 1 (HMGB1) and S100 proteins (Bergmann et al., 2022; Jozefowski, 2016; Lambert et al., 2021). The stimulation of RAGE can initiate various intracellular pro-inflammatory processes (Yang et al., 2019). A compelling association exists between the rise in food allergies observed in several Western countries and the increased consumption of dAGEs (Heuser, 2008). Epidemiological evidence, along with our expanding comprehension of immune processes influenced by the AGEs-RAGE axis, lend support to this perspective (Gasparotto et al., 2023; Smith, Masilamani, Li, & Sampson, 2017; Zhang, Wang, & Fu, 2020). The escalating intake of dAGEs aligns with current theories on the etiology of food allergies, including the hygiene hypothesis, the role of the gut microbiome in food allergies, epidermal barrier dysfunction, insufficient dietary diversity, limited dietary fiber, low vitamin D levels, and delayed introduction of high-risk foods in early infancy (Augustine, Kumar, Al Khodor, & van Panhuys, 2023; Lee, 2020; Lee, Song, Wu, Yu, & Zhang, 2020). HMGB1, recognized as a significant protein capable of alerting the immune system, shares receptor binding sites with AGEs. However, it remains uncertain whether the mechanism by which dAGEs induce food allergies is identical to that of HMGB1 (Zhang, Wang & Fu, 2020).

Further research is needed to identify the RAGE ligands involved in promoting RAGE-dependent responses (Perkins, Donnell, & Oury, 2021). The *in vitro* studies have demonstrated that protein-bound CML may contribute to RAGE activation, while heat-induced protein aggregation may also play a critical role

(Raupbach et al., 2023; Runde et al., 2014). Due to RAGE's ability to recognize various ligands characterized by folding and fibrillar formation, they can be classified as PRRs and activated by food ligands in innate immune responses. This, in turn, can lead to the development of non-communicable diseases (Noriega et al., 2022; Xie et al., 2020). Dietary AGEs can influence immune system activation by binding to galactose agglutinin 3, CD36, and SR-A. These receptor internalized ligands mediate the interaction between antigen-presenting cells (APCs) and the adaptive immune system, potentially promoting T-cell activation and leading to allergic reactions (den Haan, Arens, & van Zelm, 2014; Junker, Gordon, & Qureshi, 2020). Although there is limited research on dAGEs distorting T cells, there is sufficient evidence to suggest that APCs absorb and present dAGEs as food allergens.

Therefore, the immunogenicity of dAGEs is believed to be dependent on the interaction between specific receptors of dAGEs and APCs (Kheirollahpour, Mehrabi, Dounighi, Mohammadi, & Masoudi, 2020). However, it should be noted that different studies have utilized diverse proteins and glycation processes, and the structural alterations of both AGEs and proteins have not been thoroughly characterized. Furthermore, the impact of digestion on glycated proteins and its effect on APCs remains largely unknown (Vetter, 2015).

Teodorowicz et al. (2017) proposed that the modification of dietary antigens with AGEs structures could potentially impact the immunogenicity of CD4 T cells and the IgE reactivity of food allergens found in various allergenic foods. This modification has the potential to reduce the IgE reactivity of food allergens, allowing for the development of hypoallergenic materials and foods that can be utilized in oral immunotherapy for food allergies (Gil, Fernandez-Rivera, Pastor-Vargas, & Cintas, 2023). However, caution must be exercised when altering the immunogen of food allergen AGEs as the induction of regulatory T cells is crucial for the effectiveness of oral immunotherapy (Romagnani, 2006). Further research is necessary to investigate the influence of AGEs on the gut microbiome in order to understand the relationship between AGEs and allergies (Johansson, Sjogren, Persson, Nilsson, & Sverremark-Ekstrom, 2011). Certain types of MR products have been shown to have the potential to promote beneficial microbiota, which may play a role in regulating allergies (Tan, Macia, & Mackay, 2023). It is important to note that MR products vary in composition, thus a detailed description of individual glycated compounds in experimental diets is essential to improve our understanding of the developmental and regulatory effects of AGEs on allergies (Smith, Masilamani, Li, & Sampson, 2017).

Huang et al. (2023) conducted a study on the precursors of AGEs using a two-step simulated gastrointestinal (GI) model. They investigated the impact of α-dicarbonyl compounds, namely methylglyoxal (MGO), glyoxal (GO), and 3-deoxyglucosinone (3-DG), on the glycation and digestion behavior of ovalbumin (OVA). The research findings indicate that α-dicarbonyl compound glycation hinders trypsin cleavage sites and obstructs specific spatial locations, thereby reducing the digestibility of OVA, particularly in the GO and MGO-OVA groups. Furthermore, the formation of AGEs is influenced by the type of precursor used and masks the epitope of OVA, counteracting the adverse effects of reduced digestion on its antigenicity (Huang et al., 2023). Additionally, the study observed significant alterations in the release patterns of peptides

in glycated OVA, including changes in the sequence and structure of well-known OVA protease-resistant epitopes (Shah et al., 2019). This research offers a new perspective on the impact of Maillard reaction products (MRPs) in heat-processed foods on nutrition and health, as well as their potential association with the regulation of egg allergies (Tessier & Birlouez-Aragon, 2012).

A high AGEs diet induced changes in the composition and structure of the gut microbiota in mice, ultimately resulting in insulin resistance. Specifically, the reduction of butyric acid bacteria appeared to negatively impact the intestinal epithelial barrier, leading to persistent low-grade inflammation and ultimately chronic inflammation, which in turn contributed to the development of insulin resistance (Atzeni et al., 2022; Ma et al., 2022).

Yu et al. (2023) conducted a systematic comparison of the effects of two common dietary AGE sources on OVA sensitization results *in vivo*. Their research focuses on various aspects of disease etiology and represents the first investigation of its kind. It has been observed that both types of AGEs affect the OVA sensitization mode through distinct mechanisms. OVA-specific AGEs tend to induce Th2-biased immune responses, while OVA non-specific AGEs are more likely to disrupt the intestinal barrier, leading to upregulation of RAGE and ecological imbalance of GM (gut microbiota) (Sherenian et al., 2021; Turcanu, Maleki, & Lack, 2003). This can be explained by allergen-dependent and allergen-independent pathways mediated by different forms of dietary AGEs. These pathways encompass innate signaling mechanisms regulated by various AGEs and their receptors, interactions between innate and adaptive immunity, as well as crosstalk between the host immune system and the microbiome (Berin & Sampson, 2013; Goncalves, Araujo, & Di Santo, 2018; Perusko et al., 2018). Given the conflicting results found in our current research on immune cell phenotypes and cytokine responses, further mechanistic studies investigating the biological correlation between specific types of dietary AGEs and allergen-specific immune responses are warranted in the future (Jeurink et al., 2019). To generate allergen-specific AGEs (i.e. OVA AGEs), OVA was glycated with methylglyoxal and heated to the standard AIN 93G diet to obtain allergen non-specific AGEs (Toda, Heilmann, Ilchmann, & Vieths, 2014). Different forms of AGEs were established using BALB/c mouse models, and their effects on clinical symptoms, specific antibodies, type 2 cytokines, GM composition, immune cell subpopulations, and gut barrier function were investigated (Gause, Rothlin, & Loke, 2020). Although OVA-AGEs with low levels of IgE binding *in vitro* did not reduce OVA sensitization, their induction of Th2 response *in vivo* was stronger than that of natural OVA (Nguyen et al., 2022). Both forms of AGEs increased spleen inflammation, exacerbating intestinal barrier disruption and gastrointestinal microbiota imbalance, particularly after exposure to unrelated AGEs (Ali & Kunugi, 2020). This study underscores the impact of dietary AGEs on food allergies and enhances our understanding of the biological effects of immunotoxic compounds in contemporary diets (Barlow et al., 2002).

Currently, there is no definitive conclusion regarding the interaction between AGEs and the immune system within the body. It is imperative for future human studies to elucidate the significance of these mechanisms in terms of both health and disease.

4. AGEs mitigation strategies

Upon human consumption, dietary AGEs tend to accumulate within various tissues, potentially contributing to AGEs-related ailments. Nevertheless, the presence of dietary AGEs in everyday food makes their avoidance impractical (Tian et al., 2023). Pironene and pentoside, which exhibit an absorption rate of 60-80%, represent the two primary forms of AGEs identified in the human body. These compounds predominantly consist of free amino acids, low molecular weight peptides, or high molecular weight peptides (Savoie, Gauthier, Marin, & Pouliot, 2005). Research indicates that individuals typically consume approximately 100-300 micromoles or 16000 AGEs kU per day through their diet (Vijaykrishnaraj & Wang, 2021). Consequently, individuals afflicted with chronic conditions such as diabetes and its associated complications should strive to minimize their dietary intake of AGEs (Martinon et al., 2021). The pressing task at hand is to discover effective strategies for preventing the formation of dietary AGEs, thereby resolving the issue at its source. Limiting the production of dietary AGEs can be achieved by selecting food ingredients with minimal AGEs content, modifying food production processes, and introducing exogenous supplements (Geng et al., 2024). The current approaches to inhibit dietary AGEs generation are as following.

4.1 Food processing methods

Food processing methods have a significant impact on the formation of AGEs in processed foods, with baking, frying and grilling having a greater effect compared to boiling (Uribarri et al., 2010). For instance, cooking or stewing chicken, pork, or beef can reduce the AGEs content to half than that of grilled meat. The generation of AGEs in the diet is influenced by two primary factors: high processing temperature and prolonged processing time (Goldberg et al., 2004). High-temperature, low-humidity, and prolonged processing methods such as frying and grilling can result in higher levels of AGEs production compared to low-temperature (Suleman et al., 2020). Moreover, the final number of AGEs largely depends on the moisture content of the food, processing techniques, processing temperature, processing time, and pH value (Shi et al., 2021). To mitigate the production of dietary AGEs during high-temperature cooking, pickling food or meat with acidic substances like vinegar or lemon juice is an effective method that can reduce AGEs generation by up to 50% (Sharma, Kaur, Thind, Singh, & Raina, 2015). Previous investigations have shown that processing techniques involving short heating times, low temperatures, high humidity, and immersion in acidic solutions can effectively limit the production of AGEs in processed foods (Rannou et al., 2016).

4.2 AGEs inhibitors

AGEs inhibitors may be a potential therapeutic strategy to prevent diabetes or other pathological complications. Currently, various potential AGEs inhibitors have been proposed, and some have even entered the clinical trial stage (Peng, Ma, Chen, & Wang, 2011). AGEs inhibitors can be categorized into two groups: synthetic compounds and natural products (Anwar et al., 2021). In general, AGEs inhibitors work by capturing or clearing intermediate products generated during the saccharification process, such as active dicarbonyl groups, free radicals, and nitrogen species. This mechanism effectively hinders sugar attachment to proteins, thereby reducing sugar oxidation and oxidative stress. Additionally, AGEs inhibitors can also

decompose the formed AGE crosslinks (Aldini et al., 2013). The collective effects of these actions highlight the potential of AGEs inhibitors in combating diabetes and related complications.

For synthetic AGEs inhibitors, only a limited number of compounds have been identified to effectively disrupt the initial connection between reducing sugars and amino groups, exerting their effects in the early stages of glycation. This inhibition prevents the formation of Schiff bases and subsequent generation of AGEs (Peng, Ma, Chen, & Wang, 2011; Sarmah & Roy, 2022). As an example, aspirin, also known as acetylsalicylic acid, acts as a glycation inhibitor by acetylating the free amino groups of proteins, thereby impeding the attachment of reducing sugars. Through this mechanism, aspirin minimizes the occurrence of late complications associated with diabetes, such as sugar-induced cataracts, and reduces glucose concentration (Peng, Ma, Chen, & Wang, 2011; Sarmah & Roy, 2022).

Most synthetic inhibitors are known to impede the formation of AGEs during the late glycation stage. This primarily occurs through their ability to eliminate active carbonyl and free radicals that are generated during the glycation process or by hindering the formation of intermediate Amadori products. Aminoguanidine (AG) and pyridoxamine are two widely studied and considered typical AGEs inhibitors (Lee, 2008). AG, a nucleophilic hydrazine derivative, exhibits a high reaction capacity with β-glycation-induced dicarbonyl intermediates, which is closely associated with its potential in preventing diabetes-related complications (Aldini et al., 2013). Pyridoxamine, on the other hand, demonstrates greater efficiency in inhibiting the formation of antigen AGEs in a model composed of bovine serum albumin. This efficacy is largely attributed to its ability to capture dicarbonyl compounds (Li, Zheng, Sang, & Lv, 2014; Peng et al., 2008; Peng, Ma, Chen, & Wang, 2011).

Although the aforementioned synthetic compounds have demonstrated significant effectiveness in impeding the formation or disruption of AGEs cross-linking, it is crucial to acknowledge that they may also give rise to serious adverse reactions (Sharma, Kaur, Thind, Singh, & Raina, 2015). For instance, the initial inhibitor, AG, encountered safety concerns and exhibited inadequate efficacy during clinical trials, which ultimately led to the termination of the ACTION II trial (Peng, Ma, Chen, & Wang, 2011). Clinical trials involving aminoguanidine revealed adverse reactions including gastrointestinal disorders, anemia, and flu-like symptoms. Therefore, it is imperative to take into account these potential adverse effects when considering the use of aminoguanidine (Peng, Ma, Chen, & Wang, 2011).

4.3 Anti-AGEs compounds

Over the past three decades, there has been a significant surge in the utilization of natural sources for formulating anti-AGEs compounds. This shift can be attributed to the recognition of the toxicity and adverse effects associated with synthetic molecules observed during clinical trials. Natural products present themselves as promising contenders, offering effective inhibition of AGEs along with a more encouraging profile (Awasthi, Singh, Pandey, & Dwivedi, 2016). Plant chemicals, for instance, demonstrate a range of anti-glycation mechanisms, encompassing alterations in glucose metabolism, attenuation of oxidative stress, clearance of dicarbonyl species, and modulation of gene expression (Khangholi et al., 2016). Numerous

studies have investigated the effects of plant extracts and their phenolic components on AGEs formation and their anti-oxidant activity (Dedvisitsakul & Watla-lad, 2022). Hence, natural products exhibiting robust inhibition of AGEs hold promise as potential therapeutics for preventing AGEs-related diseases and disorders, warranting further exploration (Freund, Chen, & Decker, 2018). Nevertheless, it remains unclear whether plant chemicals provide protection against damage inflicted by glycotoxins (Wu, Huang, Lin, & Yen, 2011).

Cinnamon (*Cinnamomum verum* J. Presl, Lauraceae) is a traditional spice renowned for its potential to alleviate symptoms associated with metabolic syndrome, such as insulin resistance, elevated blood sugar, protein glycation, and inflammation (Qin, Panickar, & Anderson, 2010). Previous studies have demonstrated that ethyl acetate extracts of the tree bark, containing proanthocyanidins B2, catechins, and epicatechin, possess the ability to inhibit the formation of CML and pentose (Bottone et al., 2019). Furthermore, it has been established that the presence of catechins can effectively reduce graphene oxide to physiological levels (Lo et al., 2006). Allium sativum L., an Amaryllidaceae extract, contains s-ethylcysteine and s-propylcysteine, which act as potent antioxidants and free radical scavengers. These compounds demonstrate inhibitory effects on the formation of CML and plasma glycated hemoglobin (HbA1c) (Wu, Huang, Lin, & Yen, 2011). Resveratrol, a natural antioxidant found in grapes, has also been identified as an inhibitor of advanced glycation end product-induced proliferation and collagen synthesis in vascular smooth muscle cells (Mizutani, Ikeda, & Yamori, 2000). In summary, to mitigate the intake of AGEs, individuals ought to embrace a healthier lifestyle, curtail the consumption of fried or grilled foods, and prioritize the advancement of natural inhibitors targeting AGEs.

In summary, the main mitigation strategies to reduce dietary AGE intake and accumulation in the body include: (1) Processing methods: processing cooking methods that produce fewer AGEs, for example, steaming, boiling, stewing, and poaching are preferable to frying, grilling, or roasting at high temperatures; (2) Processing temperature control: Avoid processing at high temperatures and for prolonged periods, as this can increase the formation of AGEs, using lower processing temperatures and shorter cooking times whenever possible; (3) Moist heat cooking: Using moist heat cooking methods such as steaming, boiling, or stewing, as these methods produce fewer AGEs compared to dry heat cooking methods like grilling or frying; (4) Marinating: Marinating foods in acidic ingredients like lemon juice, vinegar, or yogurt before cooking can help reduce AGE formation; (5) Antioxidant-rich foods: Include antioxidant-rich foods in diet, such as fruits, vegetables, and green tea, to help counteract the oxidative stress associated with AGE accumulation; (5) High-fiber Foods: Consuming a diet high in fiber may help mitigate the effects of AGEs by reducing their absorption in the intestines; (6) Supplements: Some supplements, such as carnosine and pyridoxamine, have been shown to inhibit the formation of AGEs and may be beneficial in reducing AGEs-related damage; (7) Limit processed foods: Processed foods tend to be higher in AGEs due to the cooking processes involved in their production, limiting processed and packaged foods can help reduce dietary AGE intake; (7) Choose lean proteins: Opt for lean proteins such as poultry, fish, and legumes instead of red meat, which tends to contain higher levels of AGEs, especially when cooked at high temperatures; (8) Herbs and spices: Incorporate herbs

and spices like turmeric, cinnamon, and ginger into cooking, as they contain compounds that may help mitigate the effects of AGEs. By adopting these dietary AGEs mitigation strategies, individuals can help reduce their intake and accumulation of AGEs, potentially lowering their risk of AGEs-related diseases and promoting overall health and longevity.

5. Conclusions and future outlook

This review provides a comprehensive overview of diseases associated with dietary AGEs and strategies for mitigating AGEs. The formation of AGEs initiates with the generation of Schiff base and Amadori products. Subsequently, during the Amadori rearrangement, α-dicarbonyl groups can react with lysine and arginine functional groups on proteins, leading to the formation of stable AGEs compounds. Accumulating evidence has established a strong link between dietary AGEs accumulation and various diseases. Consequently, enhancing food processing techniques, optimizing food formulations and ingredients, and incorporating natural AGEs inhibitors emerge as effective approaches for alleviating dietary AGEs.

As a conventional method for food processing, thermal processing is generally perceived as safe and dependable. While it enhances the flavor and appearance of food, it also brings certain chemical risks, which including AGEs. In recent years, previously unidentified inherent hazards associated with food processing have garnered worldwide concern. Studies have elucidated that prolonged exposure to heat-related hazards can detrimentally impact human health and contribute to the development of chronic diseases. Therefore, a comprehensive exploration into the realm of dietary AGEs is imperative.

When considering toxicity, AGEs can be categorized into dietary AGEs and biological AGEs, both could exert toxicological effects via multiple pathways. Therefore, it is imperative to discern the toxicity disparities between dietary AGEs and biological AGEs. In the human body, dietary AGEs undergo digestion, absorption within the gastrointestine, and subsequent excretion through the kidneys. Consequently, AGEs present in the diet might adversely influence kidney and intestinal health, thereby potentially contributing to related renal and intestinal ailments. Furthermore, understanding the renal-brain cascade and the gut-brain axis becomes crucial. Moreover, although limited evidence exists concerning the physiological toxicity of AGEs, current research utilizing metabolomics, transcriptomics, and proteomics to investigate AGEs as therapeutic targets has garnered significant attention.

In relation to the inhibition of AGEs, there are three key factors implicated in impeding the formation of dietary AGEs: (1) food constituents; (2) food processing techniques; and (3) internal interventions. Currently, the majority of strategies employed to inhibit dietary AGEs revolve around the antioxidant theory. However, it is worth noting that certain substances with potent anti-oxidant properties may paradoxically foster the generation of AGEs. Furthermore, interventions of this nature might potentially impact the flavor and palatability of food. Consequently, it becomes imperative to explore more efficacious and scientifically sound control measures for AGEs.

Due to the ambiguous correlation between the physicochemical properties and biological activity of AGEs, there exists a plethora of controversies surrounding their physiological effects. Furthermore, most

research pertaining to AGEs neglects to examine or compare the biochemical and structural attributes of unbound AGEs and AGEs protein adducts, as well as their impact on AGEs metabolic absorption and physiological consequences. Instead, these studies primarily concentrate on evaluating the influence of carbohydrate-modified proteins (e.g. AGEs-BSA, AGEs-HSA, AGEs-casein, and fructose-modified egg whites) or foods rich in MR products (e.g. foreskin and heat-treated foods) on diseases via *in vitro* and *in vivo* experiments. Given the incomplete understanding of the physiological role of AGEs in existing literature, it is advisable for researchers in this area to focus on devising more comprehensive experimental frameworks to investigate the association between AGEs and various diseases.

Different scholars hold different views on the types of compounds contained in AGEs, which implies that different findings may not be attributed to the same AGEs substances. In order to address this issue, future AGEs researchers should strive to establish a unified definition of AGEs and develop standardized experimental platforms to evaluate their physicochemical properties and biological activities. These efforts will help overcome current research obstacles and elucidate the physiological role of AGEs. When designing an experimental platform, it is crucial to consider the standardized preparation and precise analysis of AGEs, as well as the impact of digestion on gut microbiota and the influence of non-AGEs generated through thermal processing in test samples on nutritional loss. Furthermore, recent studies have begun exploring the relationship between dietary AGEs, gut microbiota, immune regulation, circulating AGEs, and the spectrum of AGEs-related diseases. These investigations can provide further insights into the impacts of AGEs on health and potentially pave the way for new avenues of AGEs investigations.

However, what is the current limitation to control the harmful impacts of dietary AGEs? Currently, several limitations still exist in controlling the harmful impacts of dietary AGEs: (1) Lack of Comprehensive Guidelines: There are currently no universally accepted dietary guidelines specifically targeting AGE intake. While research is ongoing, the dietary recommendations for AGEs are not as well-established as those for other nutrients; (2) Variability in Food Composition: The AGE content in foods can vary widely based on factors like cooking methods, temperature, and duration. This variability makes it challenging to provide precise recommendations for reducing AGE intake; (3) Complexity of Food Processing: Many processed foods, which often have high AGE levels, are staples in modern diets. Reducing AGE intake requires not just individual dietary changes but broader shifts in food processing and consumption patterns; (4) Limited Public Awareness: There is relatively low public awareness about AGEs and their potential health impacts. Without widespread knowledge, it's difficult for individuals to make informed dietary choices to limit AGEs; (5) Challenges in Measuring Intake: Accurately measuring AGE intake and exposure is challenging, as it requires detailed food diaries and sophisticated laboratory analysis, which can be impractical for most people; (6) Nutrient Trade-offs: Some methods for reducing AGEs, like boiling instead of frying, might affect the flavor or nutritional quality of food. This trade-off can make it harder for people to adopt these methods consistently; (7) Individual Variability: People have different metabolic responses to AGEs, which can affect how significantly AGEs impact their health. This variability complicates the development of one-size-fits-all

recommendations. Addressing these limitations involves ongoing research, improved food labeling, public education, and possibly policy changes to encourage healthier food preparation and consumption practices.

Declaration of competing interest

The authors declare no conflicts of interest.

Data availability

Data will be made available on request.

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