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Dietary advanced glycation end-products elicit toxicological effects by disrupting gut microbiome and immune homeostasis

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ABSTRACT

The aging immune system is characterized by a low-grade chronic systemic inflammatory state ("inflammaging") marked by elevated serum levels of inflammatory molecules such as interleukin (IL)-6 and C-reactive protein (CRP). These inflammatory markers were also reported to be strong predictors for the development/severity of Type 2 diabetes, obesity, and COVID-19. The levels of these markers have been positively associated with those of advanced glycation end-products (AGEs) generated via non-enzymatic glycation and oxidation of proteins and lipids during normal aging and metabolism. Based on the above observations, it is clinically important to elucidate how dietary AGEs modulate inflammation and might thus increase the risk for aging-exacerbated diseases. The present narrative review discusses the potential pro-inflammatory properties of dietary AGEs with a focus on the inflammatory mediators CRP, IL-6 and ferritin, and their relations to aging in general and Type 2 diabetes in particular. In addition, underlying mechanisms – including those related to gut microbiota and the receptors for AGEs, and the roles AGEs might play in affecting physiologies of the healthy elderly, obese individuals, and diabetics are discussed in regard to any greater susceptibility to COVID-19.

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Introduction and methods

Advanced glycation end-products (AGEs) are a class of heterogenous irreversible products primarily generated during the late stage of Maillard reactions, non-enzymatic glycation reactions between reducing sugars and amino acids/lipids/nucleic acids (Hodge 1953; Namiki and Hayashi 1983). AGE precursors can also be produced from the oxidation of sugars (Dyer et al. 1991), lipids (Fu et al. 1996), and via polyol pathways, mainly following the formation of intermediary highly reactive dicarbonyls. Among frequently-reported AGEs (Figure 1) are N^{ε}-carboxymethyl lysine (CML) (Ahmed et al. 1986), N^{ε}-carboxymethyl lysine (CEL) (Ahmed et al. 1997), pentosidine (Miyata et al. 1996), argpyrimidine (Gomes et al. 2005), GOLD, MOLD or DOLD (lysine dimers crosslinked by two dicarbonyl molecules [glyoxal {GO}, methylglyoxal {MG} or 3DG, respectively]) (Nagaraj et al. 1996; Wells-Knecht et al. 1996), as well as GODIC, MODIC, and DODIC (arginine and lysine crosslinks) (Lederer and Klaiber 1999; Biemel et al. 2001). All these AGEs are referenced by their core structures. As free amino acids, peptides, and proteins are involved in the crosslinking, the actual molecular weights (MWs) of AGEs are highly diverse, and there is no clear separation between high and low MW AGEs (Poulsen et al. 2013).

AGEs are known for imparting detrimental effects on human health, in part because they accumulate in the extracellular matrix of various tissues; ultimately, such effects contribute to aging and chronic diseases (Kellow and Coughlan 2015). The modes of action by which AGEs act *in situ* include: (1) crosslinking of proteins, lipids, and nucleic acids, leading to alterations in cell structures and functions; (2) activation of receptors for AGEs, resulting in cell proliferation, autophagy, inflammation, and/or apoptosis; (3) generation of reactive oxygen species (ROS) that contribute to oxidative stress; and, (4) impairing mitochondrial function. Furthermore, some AGEs can be recognized as antigens to induce immune responses. Dietary AGEs are also known to possess allergenicity and immunogenicity properties that may play a role in food allergy (Gupta et al. 2018).

In this review, the immunotoxic characteristics of dietary AGEs are reviewed in terms of pro-inflammatory potentials, with a focus on relationships with biomarkers of aging and Type 2 diabetes, that is, C-reactive protein (CRP), interleukin (IL)-6, ferritin, and overall lymphopenia. Cross-disciplinary approaches, including those in food science, toxicology, physiology, and immunology, have been used to critically assess the contributions of dietary AGEs to disease progression through immune disruption. Potential underlying mechanisms of action for these AGEs in a host, including changes induced in gut microbiota and their receptors for AGEs that lead to aging-exacerbated diseases, are discussed here as well (Figure 2).

For this review, various databases including Google Scholar and PubMed were searched using terms such as aging, Type 2 diabetes, COVID-19, inflammation, advanced glycation end-products, and microbiome.

AGEs in food

AGEs can be generated both endogenously and exogenously. Food is a major exogenous source of AGEs, especially those

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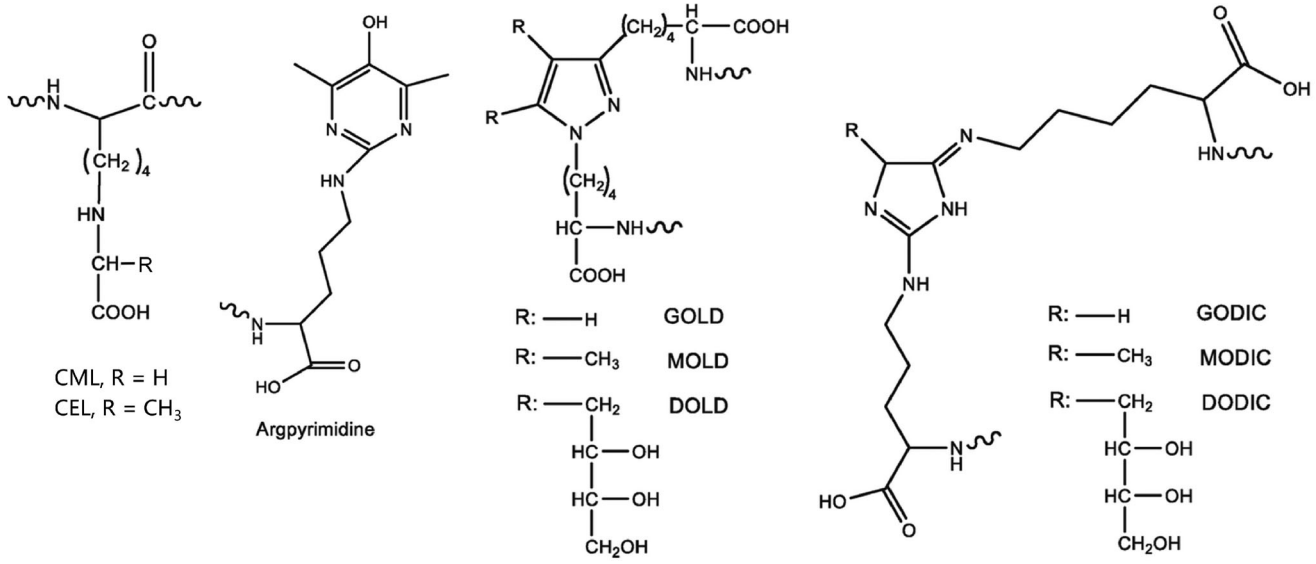


Figure 1. Structures of common AGEs. Modified from Akıllıoğlu and Gökmen (2019).

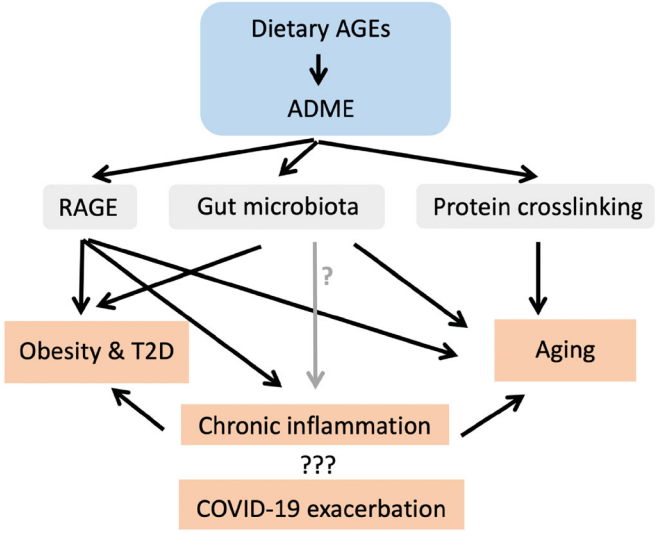


Figure 2. Dietary advanced glycation end-products (AGEs) induce toxicological effects by activating RAGE, modulating gut microbiota and inducing collagen crosslinking – potential roles in severity of COVID-19, aging, obesity and Type 2 diabetes. ADME: Absorption, distribution, metabolism, and excretion.

prepared under high-temperature conditions and stored for long periods or with food additives (Luevano-Contreras and Chapman-Novakofski 2010). AGEs are naturally present in animal-derived foods, and cooking processes result in additional AGE formation (Uribarri et al. 2010). The absorption rate for dietary AGEs is ≈10% in the human gastrointestinal (GI) tract; this correlates with AGE levels in circulation and tissues (Koschinsky et al. 1997). Due to heterogeneity in composition, various markers are used to quantify AGEs in various specimens. The most commonly used marker for AGEs is the non-fluorescent CML, because of their high abundance/wide distribution in biological (Reddy et al. 1995) and non-biological (Uribarri et al. 2010) samples. Fluorescence of AGEs is another marker; however, not all AGEs fluoresce and any fluorescence characteristics are specific to each individual AGE. Thus, any analytical readouts are highly dependent on the composition of the AGEs present and a combination of excitation/emission wavelengths applied (Schmitt et al. 2005).

Several studies have been conducted in attempts to establish a database for AGEs. Most of the large-scale studies quantified CML levels using ELISA (Goldberg et al. 2004; Uribarri et al. 2010; Takeuchi et al. 2015) or LC-MS/MS (Hull et al. 2012; Scheijen et al. 2016). One study used ELISA to compare CML to glyceraldehyde, glucose, or fructose-derived AGEs in a total of 1650 beverages/foods commonly consumed in Japan (Takeuchi et al. 2015). Another study compared CML to two other markers of AGEs, CEL and N^{δ}-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine (MG-H1), in 190 foods using LC-MS/MS (Scheijen et al. 2016). In general, foods with high AGE content include nuts, biscuits, and cooked meat (Uribarri et al. 2010; Hull et al. 2012; Scheijen et al. 2016). Heating steps, such as occur in cooking and industrial processing, dramatically increase AGE levels in food. For example, the AGE level in beef was >10-times higher after 4 min of grilling (Uribarri et al. 2010) and 5- to 10-times higher in evaporated semi-skimmed milk than in semi-skimmed milk (Scheijen et al. 2016). Kinetically, the Maillard reaction rate can be increased by 4- to 8-fold/10 °C (Kaanane and Labuza 1989). In comparison, fruits and vegetables are low in AGEs (Uribarri et al. 2010). Lastly, most beverages are low in CML, CEL, or MG-H1 (Uribarri et al. 2010; Takeuchi et al. 2015; Scheijen et al. 2016), but high in fructose- and glucose-derived AGEs (especially the latter).

Large discrepancies have been found regarding AGE content in high-fat foods and cereals when using different quantifying methodologies. For example, higher AGE levels were detected in fatty foods by ELISA, and in cereals by LC-MS/MS (Uribarri et al. 2010; Hull et al. 2012; Scheijen et al. 2016). One study compared GC-MS and ELISA approach in the quantitation of CML levels in three types of milk samples: (1) powdered infant formula, (2) milk consisting of whey protein isolate (WPI), lactose and ascorbate, and (3) hydrolyzed liquid infant formula. The two methods correlated well for powdered infant formula (r^2 = 0.966) and milk consisting of WPI, lactose, and ascorbate (r^2 = 0.996), although a higher CML level was detected in the powdered formula with the ELISA. In contrast, no satisfactory correlation was obtained for hydrolyzed liquid infant formula, with a much higher CML detection when ELISA was used (Charissou et al. 2007). This might be explained by an unspecific interference of ELISA by the lipid matrix, which could account

for the overestimation of AGEs in fatty foods by ELISA in general. Another study quantitated CML levels in gruel samples by ELISA and ESI-LC-MS/MS: average CML levels measured by ELISA was 54% of that measured by ESI-LC-MS/MS (Tareke et al. 2013), suggesting under-estimation of AGE levels in cereal by quantitating CML using ELISA. Using UPLC-MS, CML levels in cereals were identified as low; however, the intake of cold breakfast cereals could lead to elevated serum and urinary CML levels in adults (Semba et al. 2012). A "fructositis" hypothesis has been proposed to explain this phenomenon: high fructose-to-glucose ratios promote the intestinal *in situ* formation of fructose-associated AGEs (de Christopher 2017).

Absorption, distribution, metabolism, and excretion (ADME) of dietary AGEs

Exposure to dietary AGEs is dependent on eating habits and age since AGE content varies in different foods. A Western diet (WD) high in processed and red meats, high-fat dairy, refined grains, sweets, and desserts, contains much higher AGE levels than a prudent diet high in fruits, vegetables, fish, legumes, whole grains) (Lopez-Garcia et al. 2004). A 70-kg adult fed a WD is estimated to take in 1 mg CML/kg body weight (BW) daily, while a 6-kg infant takes in $>$ 2.5 mg CML/kg BW/day through consumption of 1 L infant formula (Delgado-Andrade et al. 2007; Hull et al. 2012; van Rooijen et al. 2014). Breastfeeding significantly reduces levels of AGEs in infants compared to those who are formula-fed (Federico et al. 2016).

It was estimated $\approx$ 10% of dietary AGEs can be absorbed after oral ingestion and then transported into circulation, with two-thirds of these AGEs remaining in the body (Koschinsky et al. 1997). Due to this low absorption rate, pathological effects of dietary AGEs have been mostly neglected, even though both human and animal studies have shown dietary AGEs can contribute to the pool of AGEs in a body. In a cohort of 450 participants, uptake of high-dietary AGEs resulted in an elevation of free CML, CEL, and MG-H1 levels in plasma and urine, but not in the protein-bound forms (Scheijen et al. 2018), suggesting protein-bound AGEs likely arise endogenously. Another study of 90 healthy people showed a reduction of dietary intake of AGEs was associated with an average 30–40% decrease in serum AGE levels (Uribarri et al. 2005). Exposure to heat-treated (200 °C, 10 min) high-fat diet by male ApoE$^{-/-}$ mice for 8 weeks produced increases in plasma CML and CEL levels and in spleen weight when compared to values in mice fed a control high-fat diet (Marungruang et al. 2016).

Interestingly, there seemed to be a threshold for dietary AGEs to have an effect on AGE levels in the body. It was seen that dietary consumption of AGEs at levels $< 0.5 \times 10^6$ U would not result in increases in serum AGE levels. Once the threshold was reached, a significant correlation ($r^2 = 0.8$, $p < 0.05$) was found between the amounts of AGEs ingested and resultant elevations in serum AGE kinetics (Koschinsky et al. 1997). This plateau phenomenon for serum AGEs has also been observed in mice. C57BL/6 male mice fed chow containing 323 ng CML/g had no detectable CML in their sera. However, further oral administration of WPI-glucose-derived AGEs at a dose equivalent to the amount of CML the mouse received in the diet produced an average serum CML level of 150 ng/ml (Chen and Guo 2019). In another mouse study, serum CML levels almost doubled when dietary CML intake increased from 16.0×10^4 to 24.4×10^4 U/day, and remained at that level even when dietary CML intake was 30×10^4 U/day (Cai et al. 2012).

It was reported in animal studies that oral AGE exposure was associated with increased AGE levels in the kidney, liver, lung, heart, tendons (Roncero-Ramos et al. 2013, 2014; Li et al. 2015), and GI tract (Yuan et al. 2018). A limitation with those studies was that they were unable to differentiate if increases in tissue AGE levels were directly a result of deposition of exogenous AGEs or indirectly from the boosted accumulation of endogenous AGEs. One study used dietary protein-bound [^{13}C]-labeled CML that directly traced the distribution of dietary AGEs to discriminate it from endogenous AGEs. After chronic oral exposure, the [^{13}C]-CML was directly deposited in organs, with high levels found in the kidney, ileum, colon, and lung; the material was found at $>$ 10-times lower levels in the brain, testis, heart, skeletal muscle, liver, and fat. Moreover, an intake of CML that was $\approx$ 10 times higher than the dietary level increased endogenous CML levels in the colon (almost doubled) and muscles, but not in other organs (Tessier et al. 2016).

The fate of ingested AGEs is under extensive investigation; there are many reports available on AGE deposition and distribution in organs and tissues (Figure 2). A human study showed that 1/3 of absorbed AGEs was secreted into the urine within 48 h (Koschinsky et al. 1997). Another study found urinary CML secretion was related to the forms and complexity of CML, that is, high MW and insoluble fractions from bread crust extractions decreased urinary secretion rates compared to whole bread crust extraction (Roncero-Ramos et al. 2013); this was due to the anti-digestive properties of insoluble protein-bound CML. Fecal excretion is another major route for AGE disposition, that is, $\approx$1/3 of dietary AGEs eliminated based on CML quantitation (Roncero-Ramos et al. 2013). This quantity might be under-estimated because part of the dietary AGEs was likely degraded to low MW compounds by gut microbiota (Tuohy et al. 2006). Also, a small portion of serum CML can be passed into breast milk (Dittrich et al. 2006).

In terms of metabolism, AGEs are not typical substrates for detoxifying Phase 1 and 2 enzymes (Poulsen et al. 2013). Small endogenously-formed glycated and misfolded proteins are targets for intracellular degradation by the ubiquitin-proteasome-system 20S proteasome (Jung et al. 2009). Large bulky glycated proteins can also form after oxidation and cross-linking. If not eliminated by the lysosomal system, they can accumulate in cells and tissues (Teodorowicz et al. 2018).

Mechanisms of immunotoxicity following dietary exposure to AGEs

AGEs are considered immunotoxicants as part of their overall toxicologic profile (Kellow and Coughlan 2015). The main effects of AGEs on immunity are to induce pro-inflammatory responses. In the current review, two mechanisms, including regulation of receptor for AGEs (RAGE) and gut microbiota, are discussed to illustrate how dietary AGE induces immunotoxicity (Figure 2). Other mechanisms have also been reported. For example, the AGE receptor 1 (AGER1, responsible for endocytic uptake and degradation of AGEs) can suppress RAGE expression and negatively regulate any oxidative stress and inflammation induced by AGEs (Lu et al. 2004; Ott et al. 2014). Consumption of dietary AGEs can deplete AGER1 in adipocytes, resulting in increases in inflammation, oxidative stress, and insulin resistance (Cai et al. 2012).

Receptor for AGEs

RAGE (a 35 kD transmembrane receptor of immunoglobulin superfamily; Neeper et al. 1992) is expressed on a range of cell

types, including immune cells (Ott et al. 2014). RAGE plays an important role in inflammatory processes and endothelial activation. *In vitro* application of AGEs induces inflammatory responses in macrophages (van der Lugt et al. 1975; Jin et al. 2015) and promotes differentiation of native $CD4^+$ T-cells toward a pro-inflammatory status by its binding to RAGE (Han et al. 2014). Up-regulation of RAGE expression in different organs and tissues has been observed in rodents on diets/drinking water containing AGE/MG (Cai et al. 2012; Sena et al. 2012). Activation of RAGE results in intracellular ROS production (Coughlan et al., 2009) and activation of p21(ras)-dependent mitogen-activated protein kinase (MAPK) pathways (Lander et al. 1997), which eventually lead to up-regulation of NF-κB and inflammation (Figure 3). The consequent elevations in circulating levels of cytokines such as IL-1, IL-6, and tumor necrosis factor (TNF)-α ultimately will support a persistent state of inflammation. In a study that investigated the effects of various AGEs (BSA + *D*-glyceraldehyde, BSA + *D*-glycolaldehyde, BSA + MG, BSA + GO) on monocyte expression of adhesion molecules, interferon (IFN)-γ and TNF-α production, and T-cell proliferation, it was found that the effect of AGEs on immune cells depended on the AGE subtype present (Ohashi et al. 2010).

In contrast, it was reported that mixed and purified Maillard reaction products (MRPs) containing AGEs imparted antioxidative and anti-inflammatory effects when applied to human Caco-2 epithelial colorectal adenocarcinoma cells (Chen and Kitts 2011; Kitts et al. 2012). It was also shown that ribose-tryptophan MRPs had anti-inflammatory effects in the lipopolysaccharide (LPS)-treated murine macrophage RAW 264.7 cell line (Qin et al. 2018). Those investigators identified one anti-inflammatory ribose-tryptophan MRP as 532.24 Da 3-((1H-indol-3-yl)-methyl)-8-(5-((1H-indol-3-yl)methyl)-6-oxomorpholin-2-yl)-9-hydroxy-1,7,4-dioxazecan-2-one (Qin et al. 2018). In another study, Huang et al. (2015) found that AGEs attenuated nitric oxide effects on human renal tubular cells via RAGE-JAK2-STAT1/STAT3 activation and consequent SOCS-3 suppression. These apparently contradictory findings to the main literature reflect the fact that binding of RAGE ligands may not only lead to pro- but to anti-inflammation as well (Figure 3). Treatment of THP-1 macrophage cells with 1 μg/ml high mobility group box (HMGB) 1 (RAGE ligand) polarized the cells to an anti-inflammatory M2 state; this too was via impact on RAGE-SHIP/SOCS1 (Rojas et al. 2016). The dual roles of RAGE in a pro-\anti-inflammatory balance seem dose-related; however, this needs further study. Interestingly, anti-inflammatory "functions" of AGEs can be RAGE-independent. For example, BSA-glucose-derived AGEs suppressed LPS-induced M1 polarization of bone marrow-derived macrophages, and the effect was due to a dampening of NLRP3 inflammasome assembly (Son et al. 2017).

Another possibility could be some MRPs (other than AGEs) in the above-tested mixtures imparted anti-inflammatory effects. Studies have shown WPI-glucose-derived early glycation products (MRPs; Figure 4(A)) and AGEs differentially-modulated host macrophage cytokine/chemokine profiles (Chen et al. 2018; Chen and Guo 2019). AGEs induced inflammation (consistent with a majority of reports) and EGPs were anti-inflammatory (Chen et al. 2018). The latter effect was further evidenced by a dramatic elevation in serum IL-10 levels (Figure 4(B)) and enhanced M2 polarization in C57BL/6 male mice with prostate tumors orally administered EGPs (Chen and Guo 2019). Though the inflammatory responses induced by WPI-glucose-derived AGEs were conceivable via RAGE, anti-inflammatory responses induced by EGPs could be using a different mechanism. One study found that EGPs at levels up to 10 mg/ml were unable to induce RAGE expression in human macrophages (unpublished observation). In addition to RAGE, AGEs can also interact with scavenger receptors predominantly involved in the capture, removal, and degradation of AGEs. This group includes Type I and Type II macrophage scavenger receptors, CD36, FEEL-1 and FEEL-2, SR-BI and SR-BII, and Lox-1 (Byun et al. 2017). Thus, EGPs might bind one of these receptors to initiate effects.

Gut microbiota

The microbiota plays a major role in inflammation because of its tight relationship with immune system development and

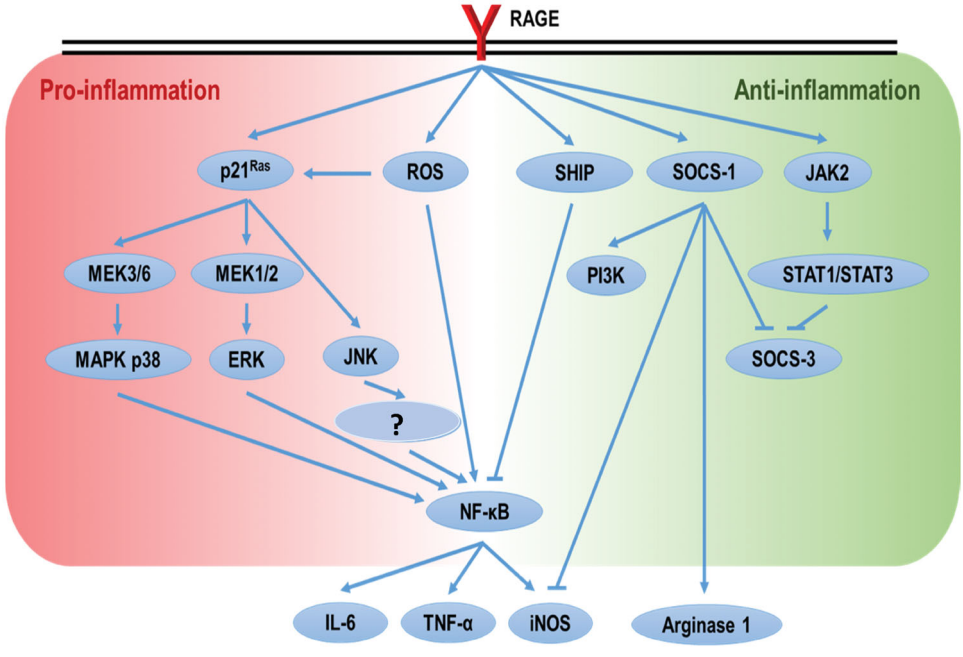
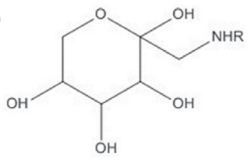


Figure 3. Schematic representation of paradoxical control of pro- and anti-inflammation by RAGE activation.

(A)



(B)

	EGPs	AGEs
IL-3	No	↑
IL-4	No	↑[a]
IL-10	↑	No
IL-12p70	No	↑[a]
IL-17	No	↑
RANTES	No	↑

Figure 4. Differential immunomodulating capabilities of EGPs and AGEs. (A) Structure of glucose-derived Amadori compounds (early glycation products). R = protein/peptide/amino acid. (B) Comparison of EGPs and AGEs in modulating cytokine/chemokine production. Modified from Chen and Guo (2019). No: no significant change when compared to non-reacted control. [a]Value significantly different from EGPs but not from non-reacted control.

maturation. Much dietary AGEs has high MW and are not absorbed in the intestine; instead, they pass through the GI to the colon and are potentially metabolized by gut microbiota (GMB). Thus, it is not surprising to see an increasing body of literature that shows that dietary AGEs can induce gut dysbiosis, for example, a GMB imbalance (Table 1).

In male BALB/c mice orally exposed to CML, *Bacteroidaceae* levels were increased while those of *Lachnospraceae* decreased (Al Jahdali et al. 2017). In male ApoE$^{-/-}$ mice, there were increases in plasma CML and CEL levels after host exposures to heat-treated high-fat diets; this was accompanied by a decreased α diversity (increases in *Allobaculum* and unclassified genus of *Clostridiales* and decreases in *Bacteroides*, unclassified genera of *Lachnospiraceae*, *Rikenellaceae* and *Ruminococcaceae* at genus level) (Marungruang et al. 2016). Decreased α diversity was also seen in male C57BL/6 mice exposed to an AIN-93G diet enriched with AGEs; these hosts manifest increased gut levels of *Alloprevotella*, *Helicobacter*, *Parabacteroides*, *Ruminococcaceae_UCG-014*, and unclassified genus of *Rhodospirillaceae*, and decreased *Alistipes*, *Desulfovibrio*, *Lachnospiraceae_NK4A136_group*, and *Rikenellaceae_RC9_ gut* group levels. The diet with high AGE levels also altered fecal short-chain fatty acid (SCFA) levels in the hosts, for example, increasing isobutyrate and isovalerate while decreasing acetate and butyrate levels (Qu et al. 2018). The same high-AGE diet also decreased α diversity (i.e. decreased *Alloprevotella* and *Ruminococcaceae*, while increased *Allobaculum* and *Bacteroides*) in male Sprague-Dawley rats (Qu et al. 2017). The ammonia concentration in the rat cecal contents was increased, while that of acetate concentration was decreased. In addition, increased epithelial damage and lymphocyte infiltration, and decreased tight junction in the colon were noted.

One conclusion reached based on all the above data is that AGE consumption decreases GMB species richness – based on consistent patterns of decreased α diversity. As for individual bacteria, no broad conclusions can yet be drawn due to inconsistencies among the animal studies. However, *Alistipes* (decreased in mice by a diet containing high levels of AGEs [Qu et al. 2018]), was found at a lower abundance in the gut of peritoneal dialysis patients (Yacoub et al. 2017) who had higher serum AGE levels (Table 1) and in patients with nonalcoholic fatty liver disease (Jiang et al. 2015). In addition, gut levels of some strains of *Helicobacter* were augmented by increases in AGEs (Qu et al. 2018).

In contrast, some GMB changes induced by AGEs seem to be beneficial. For example, colonization/prevalence of several gut inflammation-inducing strains from the *Desulfovibrio* genus was decreased by consumption of diets containing high AGE levels (Loubinoux et al. 2002; Figliuolo et al., 2017; Qu et al. 2018). Increasing levels of *Allobaculum* due to consumption of an AGE-rich diet by ApoE$^{-/-}$ mice (Marungruang et al. 2016) and Sprague-Dawley rats (Qu et al. 2017) were suggested to be beneficial to maintaining a healthy colon mucus layer and a reduced overall inflammatory status (Jakobsson et al. 2015). Interestingly, there is one report to show that oral CML exposure alleviated gut dysbiosis induced by dextran sulfate sodium salt, but not by trinitro-benzenesulfonic acid, in colitic mice (Al Jahdali et al. 2017).

As discussed above, the disagreement between AGE-induced beneficial and detrimental changes in GMB could partially be due to the composition and abundance of MRP in the test diet or samples (Snelson and Coughlan 2019). Two experiments were conducted in which adolescent male humans consumed diets that were either high or low in hydroxymethylfurfural (HMF, an MRP generated in intermediate stage) and CML, and male weanling Wister rats fed diets with or without a glucose-lysine mixture high in Amadori compounds, HMF and CML (Seiquer et al. 2014). No significant differences were detected for plasma biochemical\anthropometric parameters in either experiment; however, discrepancies between the two studies occurred in trying to correlate GMB and MRP markers as further discussed below. In the human study, negative correlations were found between *Lactobacilli* numbers and dietary advanced MRPs (e.g. AGEs), whereas *Bifidobacteria* counts were negatively correlated with Amadori compound intake (e.g. EGPs). In the rats, total bacteria and *Lactobacilli* levels negatively correlated with MRP intake, and no correlations were found for *Bifidobacteria* (Table 1). The authors concluded specific effects of dietary MRPs were likely due to dietary amounts of the different browning compounds with distinct chemical structures. This notion was verified in a study using different fractions isolated from bread crust to feed weanling rats (Delgado-Andrade et al. 2017). Low and high MW fractions rich in Amadori compounds were found to up-regulate total levels of gut SCFAs, formic, and propionic acid, while the same agents down-regulated gut *Lactobacillus* spp. levels. It was also seen that the insoluble fraction abundant in HMF and CML up-regulated gut formic and acetic acid levels, while down-regulating gut *Eubacterium rectale/Colletotrichum coccoides* and *Clostridium leptum* levels.

The effects of Amadori compounds on GMB have been explored. When exposed to a diet high in furosine (Amadori compound-derived marker for the initial stage of Maillard reaction), CML and CEL, Sprague–Dawley rats (when compared to counterparts fed a heated-control diet) had decreased colonic levels of inflammatory TNFα and IL-6, and altered GMB (increased *Akkermansia*, *Allobaculum*, and *Lachnospiraceae_UCG-006*, and decreased *Erysipelatoclostridium* at genus level). In addition, these rats displayed normal colons with only some decreases in crypt depth (Han et al. 2018). These likely beneficial effects on gut health suggested a regulatory effect for Amadori compounds on GMB and anti-inflammatory responses.

In recent studies, aged male non-obese diabetic (NOD) mice were treated by gavage with EGPs that contained only Amadori compounds generated from a WPI-glucose system (Chen et al.

Table 1. Summary of human and lab animal microbiome studies on Maillard reaction products (AGE and EGP).

Disease model	Population/ animal model	Exposure windows	MRP/dose/ concentration	Routes of administration	Diet	Effects	Reference
Autoimmune prostatitis	Male NOD mice	Feeding (6 months) starting at ≈4-months-of-age	600 mg EGPs/kg	Gavage	Diet 5053, PicoLab	Increased *Anaerostipes*, *Parabacteroides*, *Prevotella*, *Allobaculum* and *Bacteroides* and decreased *Adlercreutzia* and *Roseburia* in terms of relative abundance.	Chen, et al. 2019
Not specified	Weanling Wistar rats	Feeding for 88 days	Diets containing bread crust or its soluble high molecular weight, soluble low molecular weight or insoluble fractions	In food	AIN-93G purified diet	Low and high MW fractions rich in Amadori compounds down-regulated *Lactobacillus spp.*; the insoluble fraction abundant in HMF and CML down-regulated *E. rectale/C. coccoides* and *C. leptum*	Delgado-Andrade et al. 2017
Not Specified	Sprague–Dawley rats	Feeding for 2 weeks	High in furosine (Amadori compound-derived marker for initial stage of Maillard reaction), CML, and CEL	In food		Increases in *Akkermansia*, *Allobaculum* and *Lachnospiraceae_UCG-006*, and a decrease in *Erysipelatoclostridium* at genus level compared to in hosts fed heated control	Han et al. 2018
Atherosclerosis	Male ApoE$^{-/-}$ mice	Feeding (8 weeks) starting at 8-weeks-of-age	Plasma CML and CEL increased 1.7- and 2.5-fold, respectively	In food	Heat-treated high-fat diet	Decreased α diversity accompanied by increases in *Allobaculum* and unclassified genus of *Clostridiales* and decreases in *Bacteroides*, unclassified genera of *Lachnospiraceae*, *Rikenellaceae* and *Ruminococcaceae* at genus level	Marungruang et al. 2016
Inflammatory bowel diseases	Male BALB/c mice	Feeding (3 weeks) starting at 7-weeks-of-age	N$^{\varepsilon}$-Carboxymethyllysine; 1.6 mg/kg/day	*Per os*	Standard chow	*Bacteroidaceae* increased, *Lachnospraceae* decreased	Al Jahdali et al. 2017
Not specified	Male Sprague–Dawley rats	Fed for 6, 12, or 18 weeks	Fluorescent AGE (968 v. 2148 AU/g), CML (272 v. 143 μg/g), CEL (6.26 v. 0.97 μg/g), GO (49.1 v. 12.1 mg/kg), and MGO (28.7 v. 1.1 mg/kg) were higher in the H-AGE diet	In food	AIN-93G diet enriched with AGEs	Decreased α diversity, *Alloprevotella* and *Ruminococcaceae*, while increasing *Allobaculum* and *Bacteroides*	Qu et al. 2017
Not specified	Male C57BL/6 mice	Feeding (8 months) starting at 6-weeks-of-age	Same as above	In food	Same as above	Decreased α diversity, increased *Alloprevotella*, *Helicobacter*, *Parabacteroides*, *Ruminococcaceae_UCG-014* and unclassified genus of *Rhodospirillaceae*, and decreased *Alistipes*, *Desulfovibrio*, *Lachnospiraceae_NK4A136_group* and *Rikenellaceae_RC9_gut* group.	Qu et al. 2018
Not specified	Adolescent men	2-weeks randomized two-period crossover trial	Diets high or low in hydroxy-methylfurfural (HMF; 5-fold) and CML (2-fold)	In food	Prepared by a local catering firm	Negative correlations between *Lactobacilli* numbers and dietary advanced MRP (e.g. AGEs); *Bifidobacteria* counts negatively correlated with Amadori compound intake (e.g. EGPs).	Seiquer et al. 2014
Not specified	Male weanling Wister rats	Feeding (87 days) starting at weanling	High in Amadori compounds, HMF and CML	In food	AIN 93 G diet	Total bacteria and *Lactobacilli* were negatively-correlated with MRP intake; no correlations were found with *Bifidobacteria*.	Seiquer et al. 2014

(*continued*)

Table 1. Continued.

Disease model	Population/ animal model	Exposure windows	MRP/dose/ concentration	Routes of administration	Diet	Effects	Reference
End stage renal disease (ESRD) patients	Undergoing peritoneal dialysis	One-month dietary AGEs restriction	Dietary AGEs restriction resulted in decreases in serum CML (29.6 vs. 23.3 u/ml) and methylglyoxal-derivatives (5.6 vs. 4.0)	In food	Habitually consuming a high AGE diet	Dietary AGE restriction significantly decreased *Prevotella copri* and *Bifidobacterium animalis* relative Abundance, and increased *Alistipes indistinctus, Clostridium citroniae, Clostridium hathewayi* and *Ruminococcus gauvreauii* relative abundance	Yacoub et al. 2017

2019). These EGP-treated mice had an increased survival rate and decreased inflammation and immune infiltration into their prostatic lobes (Chen, Guo, et al. 2020). When the microbial taxa at the genus level were compared, EGP treatment led to increases in gut levels of *Anaerostipes*, *Parabacteroides*, *Prevotella*, *Allobaculum*, and *Bacteroides*, but decreases in *Adlercreutzia* and *Roseburia* (in terms of relative abundance; Table 1). The up-regulated *Bacteroides acidifaciens* was correlated with most of the immune parameters measured in the rats. *Anaerostipes* spp. express enzymes required for the production of butyrate that protects NOD mice against diabetes (Mariño et al. 2017), and it is associated with a reduction of plasma glucose, insulin resistance, and body weight in diabetic mice fed with a high-fat diet (Xu et al. 2018). *Bacteroides acidifaciens* is important for promoting IgA production in the large intestine, and it is a potential treatment for metabolic diseases like obesity (Yanagibashi et al. 2013). Overall, EGP-treated mice exhibited a healthier GMB than that of the controls.

Toxicological effects of dietary AGEs on diseases through immune disruption

Formation of AGEs takes place as a part of normal aging and metabolism and occurs at an accelerated rate in hyperglycemic, inflammatory, and oxidative stress conditions. In this section, the toxicological effects of dietary AGEs on aging and Type 2 diabetes in relation to RAGE and gut dysbiosis are discussed (Figure 2).

Aging

A substantial body of evidence shows that AGEs and their functionally-compromised adducts are linked to, and perhaps responsible for, changes seen in the function of cells and tissues during aging, and then in the development of many age-related morbidities, for example, atherosclerosis, nephropathies, retinopathy, osteoarthritis, neurodegenerative diseases, diabetes mellitus (Ott et al. 2014; Spauwen et al. 2015; Drenth et al. 2018). High levels of circulating AGEs can be used to predict cardiovascular disease mortality among older community-dwelling women (Semba et al. 2009). Administration of aminoguanidine (inhibitor of AGE formation) for 24–30 weeks in normotensive WAG/Rij rats prevented age-related cardiac hypertrophy and arterial stiffness (Corman et al. 1998). Similarly, a presence of AGEs was also associated with motor function decline in aging, and it was speculated that high levels of AGEs may be a biomarker for low physical activity (Drenth et al. 2018). In a study of 559 moderate-to-severely disabled women (age 65 and older), women with higher CML concentrations had less grip strength than those with lower CML; from this, it was concluded that women with higher AGEs have more muscle weakness (Dalal et al. 2009). Interestingly, brain tissues of Alzheimer's disease patients were found to contain higher AGE levels than brains of age-matched controls (Cruz-Sánchez et al. 2010).

It is likely that increases in endogenous production and exogenous intake, and lower clearance and detoxification, lead to the accumulation of AGEs in older populations. However, higher AGE levels occur in both healthy older adults and those with chronic diseases. Studies have/are being tried to identify mechanisms to explain why some human tissues are damaged while others are not in those states. One mechanism involves increased crosslinking within collagen and the extracellular matrix with age-related increases in AGE levels (Sims et al. 1996). Glycated low-density lipoproteins can crosslink with collagen to prevent

uptake by cell receptors. These modified low-density lipoproteins are instead more likely phagocytosed by macrophages to form foam cells and, ultimately, the development of atheroma (Bucala et al. 1994). Tissue accumulation of AGEs can be further enhanced by some cardiovascular changes associated with aging, such as vascular stiffening, diastolic dysfunction, and endothelial dysfunction (Fishman et al. 2018).

The aging immune system is characterized by a low-grade chronic systemic inflammatory state ("inflammaging") marked by elevated inflammatory molecules, such as IL-6, CRP, ferritin, and lymphopenia (Dennis et al. 1998; Li et al. 2011; Cankurtaran et al. 2012). In hemodialysis patients, tissue levels of AGEs are an independent determinant of CRP levels (Nagano et al. 2011). Though CRP is an acute-phase protein of hepatic origin, AGEs cannot directly stimulate hepatocytes to produce CRP, but they enhance its expression by stimulating monocytes/macrophages to produce cytokines like IL-6 (Li et al. 2007). Circulating AGE levels correlate with those for IL-6 and other inflammatory markers in rheumatoid arthritis (Hein et al. 2005). In gingival fibroblasts, AGEs also increase IL-6 expression (Nonaka et al. 2018). In a group of elderly patients with mild cognitive impairment, serum RAGE levels were positively correlated with both AGE and CRP levels (Gorska-Ciebiada et al. 2015). Further, CRP can up-regulate RAGE expression in endothelial cells (Zhong et al. 2006) and in THP-1 cells (Mahajan et al. 2010). Thus, AGEs may contribute to the aging processes through exacerbating "inflammaging".

Ferritin is a major tissue iron-storage protein that exhibits a variety of activities relevant to the immune system, including binding to T-cells, suppressing delayed-type hypersensitivity reactions (to induce anergy), suppressing B-cell antibody production, reducing phagocytosis by granulocytes, and regulating granulo-monocytopoietic processes (Zandman-Goddard and Shoenfeld 2008). Ferritin level increases with aging as a part of "inflammaging" (Cankurtaran et al. 2012). Macrophages accumulate ferritin during inflammation and polarization to pro-inflammatory M1. In β-thalassemia patients, circulating ferritin levels were seen to positively correlate with levels of pentosidine, a fluorescent protein crosslink used as a biomarker for AGEs (Mirlohi et al. 2018).

Studies in animals have suggested GMB alterations might cause aging. The GMB from old mice contributes to "inflammaging" after fecal microbiota transplantation to young germ-free mice (Fransen et al. 2017). Work with African turquoise killifish has shown that acute transfer of GMB from young donors to antibiotic-treated middle-age recipients extends lifespan and delays behavioral aging (Smith et al. 2017). The elderly have a different GMB profile when compared to healthy adults. Generally, the diversity of GMB and abundance of commensals that maintain immune tolerance in the gut are reduced, while that of opportunistic pathogens that stimulate gut inflammation is increased (Nagpal et al. 2018) – this is somewhat consistent with gut dysbiosis induced by AGEs [discussed earlier]. Aging generally leads to chronic systemic inflammatory states with hyperactive innate immune responses, particularly in the form of elevated neutrophil (PMN) accumulation following respiratory infection (Chen, Kelley, et al. 2020). Depletion of GMB using antibiotics significantly reduces levels of circulating aged neutrophils (Zhang et al. 2015).

It is of note that older people have greater susceptibility to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2; COVID-19), and that COVID-19 patients have increased circulating PMN-to-lymphocyte ratios (Liu, Liu, et al. 2020). Adverse effects of AGEs on PMN are well-known, including inhibited bacterial killing (Collison et al. 2002), suppressed migration (Touré et al. 2008), and induction of both oxidative stress and respiratory burst (Wong et al. 2003; Bansal et al. 2012). AGEs also impact promotion of $CD4^+$ T-cell differentiation to pro-inflammatory states (Lu et al. 2019). Thus, it is likely modulation of innate immunity induced by AGEs contributes to the observed "age-enhanced" mortality to SARS-CoV-2 infection. It is possible these outcomes are mediated in part through AGE-induced alterations in the host GMB.

Type 2 diabetes (T2D)

T2D, which accounts for ≈ 90% of all diabetes cases, is characterized by insufficient secretion of insulin from pancreatic β-islet cells, coupled with impaired insulin actions in target tissues such as muscle, liver, and fat (termed insulin resistance). Approximately one-third of U.S. adults > 65 year-of-age have T2D, and an additional one-third of older adults have pre-diabetes (Cowie et al. 2009). Serum or plasma AGE levels are generally elevated in T2D patients due to hyperglycemia (Vlassara et al. 2002). RAGE was also dramatically up-regulated in T2D patients (Yan et al. 2009). Hyperglycemia increases glycation processes in insulin-independent tissues and cells (like red blood cells, peripheral nerves, endothelial cells, eye lenses, and kidneys) (Tessier 2010). *In vitro,* pancreatic β-cells exposed to AGEs displayed insulin secretory defects; *in vivo*, islets were damaged in Sprague-Dawley rats after chronic intraperitoneal injections of AGEs in the form of modified rat serum albumin (Coughlan et al. 2011).

The immune system plays an important role in controlling whole-body metabolism and contributes significantly to the pathogenesis of T2D (Tsalamandris et al. 2019). Intake of AGEs in the diet increases levels of inflammatory mediators (i.e. CRP, TNF-α, VCAM-1) found in the sera of T2D patients (Vlassara et al. 2002), and the increased serum AGE level is related to the rapid development of diabetic complications (Zheng et al. 2002; Rhee and Kim, 2018). For example, AGEs have also been implicated in a delayed wound healing in T2D patients (Peppa et al. 2009). In elderly T2D patients with mild cognitive impairment, serum AGE, RAGE, and CRP levels were increased (Gorska-Ciebiada et al. 2015). On the other hand, Vlassara et al. (2002) noted that reduced intake of AGEs in T2D patients contributed to decreased levels of circulating AGEs and inflammatory markers like TNFα and CRP. Another study suggested blood IL-6 and AGE levels were significant independent determinants of CRP in diabetics (Tan et al. 2004).

T2D is frequently associated with elevated levels of serum ferritin (Lecube et al. 2004). T2D is also associated with intestinal dysbiosis. Among the commonly reported findings, the genera of *Bifidobacterium*, *Bacteroides*, *Faecalibacterium*, *Akkermansia*, and *Roseburia* were negatively associated with T2D, while the genera of *Ruminococcus*, *Fusobacterium*, and *Blautia* were positively associated with T2D (Gurung et al. 2020).

COVID-19

While this review was in preparation, various investigators have hypothesized a role for the RAGE axis in COVID-19 pathogenesis (Kerkeni and Gharbi 2020; Stilhano et al. 2020), as well as in diabetes (de Francesco et al. 2020) and lung inflammation (Andersson et al. 2020; Rojas et al. 2020). Unfortunately, at present, there do not appear to be any studies specifically tackling

the topic of dietary AGEs and any potential contribution to COVID-19 morbidity. It is worth noting a recent spike in studies surrounding soluble RAGE measures in COVID patients (see Dozio et al. 1975; Lim et al. 2021). AGEs may contribute to organ damage by promoting host cell death (Mao et al. 2018). Importantly, the levels of soluble RAGE in bronchoalveolar lavage fluid – which reflect tissue RAGE expression (Nakamura et al. 2007) – were found to correlate with the severity of various inflammatory lung diseases (Uchida et al. 2006; Kamo et al. 2015; Stockley et al. 2019). Thus, it seems it would be clinically important to elucidate if AGEs help to exacerbate inflammation, and by doing so increase the risk for COVID-19 development and severity in susceptible populations.

Conclusions

In this review, dietary sources, ADME, immunotoxic effects, and underlying mechanisms of action by AGEs were discussed. Dietary AGEs are an important exogenous source of AGEs and may contribute to an AGE pool in a body. Some studies indicated effects of AGEs are subtype-dependent. Most studied AGEs were mixtures generated in reactions between BSA and glucoses. Even with the same reactants, the composition/abundance of each component of AGEs can vary; these are often primarily determined by the incubation conditions (e.g. time, pH, temperature, reactant ratio). A complete reaction leads to the production of melanoidins, while an incomplete reaction results in the generation of EGPs in the initial or intermediate stages. Mixture impurity could also affect assay outcomes. Therefore, further identification and purification of functional AGE(s) would be a strategy to permit stronger conclusions to be reached. Nonetheless, elevated serum and organ levels of AGEs can induce chronic inflammation and contribute to the progression of various diseases, including aging, Type 2 diabetes, and possibly COVID-19.

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