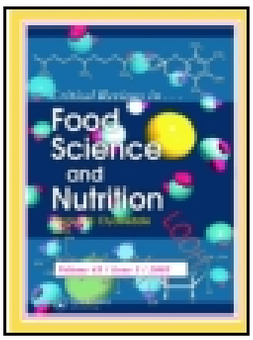

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REVIEW

Advanced glycation end products in food and their effects on intestinal tract

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ABSTRACT

With the development of living standards, harmful substances in diet and food safety have seriously endangered people health and life. Advanced glycation end products (AGEs), which formed by Maillard reactions in processed food, have been shown a significantly associated with many chronic diseases, such as nephropathy, atherosclerosis, Alzheimer's disease, and tumors. In recent years, the research about diet advanced glycation end products (dAGEs) have widespread controversy in academia. The main arguments include the production mechanism of dAGEs, metabolic pathways, and relationships with chronic diseases, especially related to the intestines, gut microbiota, and intestinal disorders. So this review attempts to briefly summarize the dAGE in following aspects, including the influencing factors, metabolism, absorption, and so forth. In addition, the effects of dAGEs on intestinal health and gut microbes were discussed, which can offer a goal for boff in to design low dAGEs products and provided some perspectives for further study with AGEs in the future.

KEYWORDS

AGEs; diet; food safety; gut microbiota; intestinal

Introduction

More than a 100 years ago, the Maillard reaction was defined by Louis Camille Maillard, who described the reaction between carbohydrates and amino acids during heating. Since then, many scientists and research groups have continued to study the Maillard reaction. In 1953, Hodge presented the coherent scheme of the Maillard reaction (Wedzicha 1992), which can be divided into three stages: early, advanced, and final. All these stages are interrelated and can occur simultaneously, and they are affected by reaction conditions (de Oliveira et al. 2016). In brief terms, labile *N*-substituted amino sugar generated Schiff base, Then, rearrangement of the Schiff base occurs via 1,2-eneaminol resulting in Amadori rearrangement products, which is significant nonvolatile flavor precursors (Cui et al. 2019; Harohally, Srinivas, and Umesh 2014). Consequently, the Maillard products play a vital role in food flavor; however, not all of them are beneficial.

Advanced glycation end products (AGEs) are generated in the Maillard-reactions, which cannot only be formed in thermal processed foods but also are endogenously formed as a consequence of a high dietary sugar intake (Aragno and Mastrocola 2017) The endogenous AGEs are produced by glycosylation of carbohydrates and proteins, which according to a series of complex enzymatic metabolic reactions occur in the body. The conditions of endogenous AGEs producing are relatively mild, but the formation period is long. The harm of endogenous AGEs has been clearly confirmed by the medical community, as it is considered a potent toxic molecule that promotes cell death and thus contributes to damage to the organs (Byun et al. 2017). Exogenous AGEs are mostly brought into the human body through the diet, so named dietary advanced glycation end products (dAGEs). The dAGEs are derived from the Maillard reaction of reducing sugars and nitrogen-containing groups in food components. The formation process of dAEGs is a non-enzymatic reaction, the conditions are relatively intense, and the formation time is short. Now, there are approximately 40 kinds of AGEs have been discovered, such as N^{ε}-(carboxyethyl)-lysine (CEL), N^{ε}-(carboxymethyl)-lysine (CML), fructosyl-lysine (FL), and pyrraline (Delgado-Andrade and Fogliano 2018; Hohmann et al. 2017). Assuredly, more AGEs will be discovered in the future.

Nowadays, it is widely accepted in the academic community that the intake of dAGEs increases the amount of AGEs in the blood. The levels of AGEs in the blood of healthy people have a significantly correlation with the intake of dAGEs (Delgado-Andrade and Fogliano 2018) In addition, western diet is one of the main sources of dAGEs and reasons for the accumulation of AGEs in vivo. Therefore, dAGEs have a significant value to be researched in the future. We have summarized the study about dAGEs in this review and explore the production, inhibition, gastrointestinal absorption, role in gut microbiota reshaping, and association with intestinal disorders.

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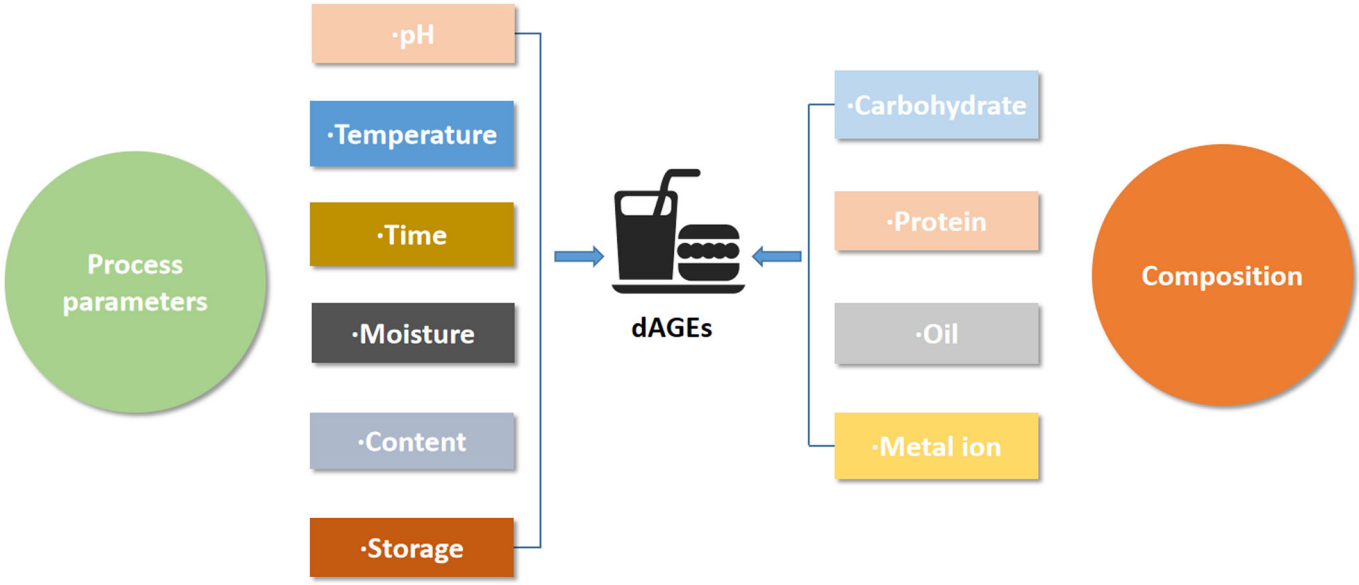

Figure 1. Factors affecting the formation of dAGE.

dAGEs in heat processed food

More recently, the mounting interest toward the health effects of food promoted the research of dAGEs (Delgado-Andrade and Fogliano 2018). However, the formation process of dAGEs is complicated and the content of different kinds of food is different. Among them, baking food is rich in Maillard product. This chapter mainly focus on the formation of dAGEs in heat processed food.

The effect of food processing technology

Maillard reaction is an important source of hot processing food flavor that can increase palatability, improve texture, and luster, which is according to an extremely complicated reaction between a carbonyl compound, often a reduced saccharide, and an amino compound, usually an amino acid, a peptide or a protein (Liang et al. 2016) Its various changes in food have both nutritional and toxicological effects. During the advanced stage of the Maillard reaction, various adducts with medical implications are formed on the side chains of amino acid residues, such as melanoidins and AGEs. Therefore, as one of the products of Maillard reaction, the factors affecting the formation mechanism of dAGE depend on the Maillard reaction factors, including temperature, moisture content, reaction time, and pH in storage time (Figure 1).

Almost hot processing foods undergo the Maillard reaction and producing AGEs during thermal processing and period, especially long-term or high-temperature cooking methods such as roasting, grilling, and frying (Lin et al. 2019). Some studies reported that AGEs are formed spontaneously in living organisms and in stored or heat-processed foods (Csongová et al. 2019; Leonova et al. 2020). Therefore, the nutritional content of foods is highly correlated with producing of AGEs, among which high protein foods like meat, eggs, and milk rich in AGEs, followed by foods with high amounts of fat such as oil and nuts. On the other hand, fruits and vegetables are considered to have the lowest levels of AGEs. In the heat processing method, temperature and heating time also have a great influence on the formation of new AGEs. Dry heat processing seems to generate AGEs more readily than wet heat processing. High temperature frying or grilling generates higher amounts of AGEs than other ways of cooking (Chao, Hsu, and Yin 2009; Uribarri et al. 2010). Hull et al. (2012) studied how different processing ways to the changes in content of CML. The results showed that the content of dAGE was related to the type of meat, processing conditions, and the final center temperature of the sample.

The dAGEs are not only derived from the food but also from the seasoning and minor ingredient which were used in food processing. Chao, Hsu, and Yin (2009) found that the levels of AGEs in several common seasonings and effect on the product of dAGEs. The results showed that a majority of seasonings contain different concentration of AGEs. In addition, heating and frying oils significantly increased the levels of dAGEs. Zhang et al. (2011) used the LC-MS/MS method to detect the changes of free state and binding state AGEs contents in unprocessed and roasted large almonds, which usually be used in baking food. The results showed that the free AGEs accounted for 1.3–26.8% of the total AGEs, indicating that the combined AGEs had a higher content in large almonds. The baking process significantly promoted the formation of AGEs. After that, the CML content in the free state increased by 50%, CEL content in the free state increased by 120%, and the total CML and CEL content increased by 186% and 413%, respectively.

The effect of food components

Water activity and pH also had great effects of the formation rate of Maillard reaction products. In 1989, a research proposed that, as the higher the water content is, the more active the reactants are, and the rate of the Maillard reaction

Table 1. The amount of AGE in different kinds of food.

Food stuff	CML mg/kg protein	The amount of AGE (kU/100g)	CML μg/g of protein	Detection method	References
Dairy products	< LOD-181937.52	–	–	UPLC-MS/MS	(Hull et al. 2012)
UHT milk	29–46	–	–	LC-ESIMS/MS	(Fenaille et al. 2006)
UHT milk	259	–	–	GLC (gas-liquid chromatographic)	(Büser et al. 1987)
condensed milk	390	–	–	HPLC	(Hartkopf and Erbersdobler 1994)
Breastmilk (fresh)	–	6.67	–	ELISA	(Kutlu 2016)
Infant formula (Cow)	–	–	95	ELISA	(Prosser, Carpenter, and Hodgkinson 2019)
Infant formula (Goat)	–	–	13	ELISA	(Prosser, Carpenter, and Hodgkinson 2019)
Infant formula (Cow whey hydrolysate)	–	–	233	ELISA	(Prosser, Carpenter, and Hodgkinson 2019)
Infant formula	–	486.64	–	ELISA	(Kutlu 2016)
Cereal	69.45–489.99	–	–	UPLC-MS/MS	(Hull et al. 2012)
Breads and savory biscuits	21.34–909.50	–	–	UPLC-MS/MS	(Hull et al. 2012)
white bread	204.51–234.26	–	–	LC-MS/MS	(He et al. 2014)
Whole meal bread	946.86–1098.92	–	–	LC-MS/MS	(He et al. 2014)
Whole meal bread	–	53	–	ELISA	(Kutlu 2016)
Pasta	–	242	–	ELISA	(Kutlu 2016)
Fruit and vegetables	< LOD-76.69	–	–	UPLC-MS/MS	(Hull et al. 2012)

would increase in a positive correlation to the water content within limits, until the water activity is between 0.4 and 0.7, the rate of the reaction reaches its highest limit (O'Brien and Morrissey 1989). Tauer et al. (1999) studied the composition of infant formula and found that samples with different moisture content also had different levels of CML. When the moisture content is 4%, the CML concentration in the milk powder samples were 673 ng/mg protein, and in a water content of 8%, the CML concentration in the samples were 818 ng/mg protein. These results showed that the elevated CML levels correlate with the increasing water within a certain range of water content. However, this conclusion does not apply to all systems. In another report, it was pointed out that the levels of AGEs in food after low-temperature and high-water heating treatment were much lower than those at high-temperature and low-water heating treatment (Lieuw-A-Fa et al. 2004). Hot and dry processing, such as baking can speed up the formation of AGEs in foods. In most of the foods studies, the AGEs content in the dry and hot processed foods was 100 times higher than untreated foods (Uribarri et al. 2010). However, in the presence of high moisture, shorter heating times led to a lower heating temperature, or acidic components such as lemon juice or vinegar there seems to be less generation of AGEs in the food. In a study simulating the change of CML concentration in muffin making process, the influence of several components in muffin making formula were studied (Mildner-Szkudlarz et al. 2015). Several ingredients, including flour, baking powder, salt, sugar, and vegetable oil, have a significant impact on CML concentration. The results showed that the level of CML in muffins made with glucose was significantly higher than that of a muffin made with beet sugar and sucrose, while the content of CML in muffins made with beet sugar was the lowest. Compared with refined sucrose, raw sucrose can produce more CML, because it contains a certain amount of metal ions, which can catalyze the degradation of fructose lysine. The saturation of vegetable oils used also affects the CML content of muffins. Muffins made with grape seed oil had a CML concentration of 11.42 mg/kg, while muffins made with olive oil had the lowest CML concentration of 1.82 mg/kg. According to the degree of unsaturation, the order of CML concentration of various vegetable oils was: olive oil < rice bran oil- < rapeseed oil < grape seed oil. The polyphenols contained in vegetable oil can effectively reduce the formation of CML.

The effect of storage period

In the long-term storage process of food, AGEs will continuously be generated and the formation rate is affected by storage time, temperature and other conditions (Birlouez-Aragon et al. 2005; Bosch, Alegría, et al. 2007; Bosch, Sanz, et al. 2007). Bosch et al. (2008) studied three kinds of milk and cereal baby food, which were stored at 37 °C for 25 d, 30 d, and 9 months to observe changes in AGE concentrations. In this experiment, the concentrations of AGEs in the samples were 310–340 mg/100g protein, while after storage for 9 months the levels reached 426–603 mg/100g protein. Storage temperature significantly affected the concentration of AGEs in samples. The higher temperature, the greater increase in AGEs level, and the concentration of AGEs in honey-containing samples was higher than in samples without honey. The effect of storage time on the concentration of AGEs in food cannot be ignored, so it is very important for manufacturers and sellers to control the temperature and the storage time of food. Another research has reported the changes of AGEs level in two kinds of wheat seeds during storage for 3 and 6 months. The results showed that the CML content of wheat seeds significantly increased during the storage period, while the CML content of seeds to be germinated was relatively low, indicating a high correlation between seed aging and accumulation of AGEs (Bosch et al. 2008; Delgado-Andrade et al. 2010). Currently, research on how food storage affects AGEs levels is mainly focused on foods such as infant formula and milk powder. There are no

reports about foods that need to be stored. Therefore, it is important to study the changes in AGEs content during food refrigeration and freezing to guide people to better choose food storage conditions in daily life.

Food rich in AGEs

The composition of the dAGEs formed by the Maillard reaction is complicated. Currently, researchers measure the levels of dAGEs mainly by evaluating the concentration of representative substances such as CML, CEL, and Pyraline.

As shown in Table 1, dAGEs are widely distributed in different kinds of food in our daily life. Among them, milk and whey protein powder contain high levels of AGEs, and whey protein powder can be further introduced into the deep processed foods used as raw materials. Several studies have reported that CML levels between different types of milk-based formulas for infants can vary by a factor of 10 or more (Birlouez-Aragon et al. 2004; Šebeková et al. 2008). Prosser, Carpenter, and Hodgkinson (2019) found that goat milk contained 7- to 12-fold less CML than cow milk, compared to whey hydrolysates the intact proteins contain lower levels of CML, which means that whey additions contribute significantly to CML levels in food. Not only dairy products but also a lot of plant oils contain abundant amounts of AGEs, because they are rich in protein and fat (Goldberg et al. 2004). In addition, using different processing techniques on the same ingredients will result in significant changes in AGEs concentration (Uribarri et al. 2005).

In western food, CML is the main AGEs in daily food, but not in the east. For instance, according to competitive enzyme-linked immunosorbent assays involving immunoaffinity-purified specific antibodies, Takeuchi et al. have measured the concentration of four kinds of AGEs (Glu-AGEs, fructose-derived AGEs [Fru-AGEs], CML, and Glycer-AGEs) in a total of 1650 beverages and foods that are commonly consumed in Japan. The result showed that Glu-AGEs and Fru-AGEs (especially Glu-AGEs), but not CML or Glycer-AGEs, are quiet high in beverages and foods that are commonly consumed by Japanese (Takeuchi et al. 2015). Moreover, previous studies have found that cereal, fruit, and vegetable categories have the highest and lowest mean level of CML respectively, when expressed in food. This result is against the long-standing advice that foods rich in carbohydrates contain less AGEs, although the result of vegetable categories is in accord with previous research. Furthermore, the some researchers found that Uribarri's results could not be replicated, although they use the same detecting techniques and even more advanced technology (DeChristopher 2017; Scheijen et al. 2016; Trevisan et al. 2016). This is the reason why a lot of research about dAGEs contribution to chronic diseases has been debated (Kellow and Coughlan 2015). So, the research about the concentration of AGEs needs to be studied with more scientific, accurate, and easily reproducible standard methods for their quantification in both foods and biological samples.

Potential health hazards of AGEs

A large number of studies have shown that the accumulation of excessive AGEs in the body is closely related to the pathogenesis of some chronic diseases, such as nephropathy (El-Nashar et al. 2020), atherosclerosis (Korca et al. 2020), Alzheimer's disease (Hipkiss 2018; Lovestone and Smith 2014), tumors (Ahmad et al. 2018), diabetes (Lee and Hwang 2020), and its complications. The AGE can bind with protein in vivo, and long-lived proteins are more easily modified by AGEs. In addition, collagen and low-density lipoprotein (LDL) are also prone to cross-linking with AGE, leading to increased arteriosclerosis and decreased LDL uptake by LDL receptors (Zieman and Kass 2004), cross-linking between AGE and crystal proteins has been shown to alter their functions (Rowan et al. 2017), and AGE cross-links with kidney tissue proteins increase renal basement membrane thickness (Schwenger et al. 2001). Thus, the accumulation of AGEs in various organs appears to be associated with diabetic complications in the retina, kidney, nerves, and atherosclerotic plaques (Vlassara and Striker 2010). In addition, some studies have shown that AGEs have a potential role for protein aggregation, which is associated with amyloidosis and Alzheimer's disease (Cai et al. 2014). Therefore, an important cause of toxicity and disease in AGEs in vivo is the high affinity of some AGEs with proteins in the body and their ability to cause aggregation of certain protein structures. The binding receptors of AGEs include AGEs receptor (RAGE), oligosaccharyl transferase-48 (OST-48; also known as AGER1), and 80 K-H phosphoprotein (80 K-H phosphoprotein; Also known as AGER2), galectin-3 (also known as AGER3), type I scavenger receptor, and type II scavenger receptor (Thornalley 1998). Since RAGE and AGER1 are the most characteristic and important receptors, they are also the most studied in recent years (Ahmad et al. 2018; Dehnad et al. 2020; Sharma et al. 2020).

Epidemiological studies have shown that serum AGEs levels and the severity of type 1 and type 2 diabetes, development of diabetes and its complications such as microvascular complications (Hwang, Shin, and Yang 2005) and macrovascular complications (Kilhovd et al. 2007), and inflammatory markers and the level of endothelial cell dysfunction index was positively correlated. Studies have also shown that AGEs in food can increase the burden of AGEs in the body, and the intake of AGE is related to the concentration of AGEs in serum (Chao et al. 2010; Uribarri et al. 2003), and is also associated with oxidative stress and inflammatory markers, both of which are the risk factors for diabetic patients. The negative effect of AGEs on type 1 and type 2 diabetes increase the level of inflammatory markers, glucose oxidation in LDL, and vascular toxicity to human endothelial cells by activating the redox-dependent MAPK signaling pathway (Chao et al. 2010). The mechanism of AGEs effects on human health can be summarized as follows: (1) The modification of protein structure by AGEs may cause abnormal function of the protein; (2) The intramolecular or intermolecular crosslinks of AGEs may lead to changes in the structure of tissues; (3) AGEs promote the formation of free radicals in the body and aggravate the

oxidative damage of tissues; (4) AGEs bind to receptor RAGEs or cell surface receptors, which may cause proinflammatory reactions, and proinflammatory responses may also cause further rising levels of AGEs. The interaction between AGEs and receptor RAGE can regulate the proinflammatory pathway through transcriptional activation and can also change the expression of proinflammatory mediators such as cytokines, which can trigger the occurrence of proinflammatory responses (Ramasamy, Yan, and Schmidt 2011). However, most of researches about the health hazards of AGEs were not in contact with food. So the relationship between health hazards of AGEs and food are worth to investigate deeply.

The methods of reducing the health hazards of AGEs

Because of many, researches about the potential health hazards of AGEs have been reported. How to inhibit the production of AGEs have become an orientation for many scientists. In sum, the methods of inhibiting the production of AGEs can be summarized into two categories. The first category is to inhibit the formation of AGEs. The second is to inhibit the activity of receptor of AGE (RAGE) in vivo.

Aminoguanidine (AG), as a nucleophilic hydrazide, which could effectively inhibit the formation of AGEs in vivo. The main mechanism is that the binding of Amadori, an intermediate product in the process of AG and AGEs formation, blocks the continued generation of carbonyl compounds in Amadori and ultimately inhibits the generation of AGEs (Delgado-Andrade et al. 2012). Studies have found that AG can inhibit the formation of non-enzymatic saccharification products. The main function of AG is to react with carbonyl group on glucose to form an aldehyde, which reduces the concentration of free glucose and blocks the generation of AGEs (Poulsen et al. 2013). The non-enzymatic glycosylation system was established to screen the anti-AGEs drugs. After AG was added into the reaction system, the fluorescence value significantly decreased. The inhibitory rate of AG on CML was 44.3% (Wang et al. 2019). However, more researchers found that AG is not only inhibit the generation of AGEs but also cause a series of side-effect such as causing gastrointestinal disorders, vasculitis and damage to lung function, even been demonstrated to exacerbate brain injury in rats (Potipiranun et al. 2018; Schiavone et al. 2017). Another AGEs inhibitor studied more is pyridoxine. Pyridoxine is a nucleophilic reagent that reacts with the active carbonyl compounds produced in the generation process of AGEs and ultimately reduces the conversion of glycosylated intermediates to AGEs (Cunnane 2005). After 12 weeks of treatment with pyridoxine in diabetic rats, the results showed that compared with the control group untreated diabetic rats, pyridoxine significantly reduced the accumulation of AGEs in the cerebral visual cortex, thereby inhibiting the body injury induced by activation of the AGE-RAGE signaling pathway (Uribarri et al. 2005). In addition to AG and pyridoxine, some clinical drugs and natural products, such as polyphenol, acarbose, and Vc, have been found to have certain inhibitory effects on the formation of AGEs. The thiobarbituric (thiopyrimidine trione) enamine derivatives and its analogues barbituric acid derivatives was found to inhibit α-glucosidase activity in a reversible mixed-type manner, thus inhibited the generation of AGEs (Ali et al. 2020). Resveratrol and 4-hexylresorcinol were reported inhibiting the production of AGEs according to against α-glucosidase (Gowd et al. 2020; Song et al. 2020).

Unlike inhibitors, decomposition agents can reduce or even reverse the AGEs which have already formed in the body. For example, *N*-phenylacetylthiazole (PTB) was used to decompose AGEs according to bovine serum-glucose system. The results showed that PTB could significantly decompose AGEs (Uribarri et al. 2007). ALT711 is developed by Alteon company in the United States to decompose AGEs and their cross-linked structures. ALT711 has been studied in clinical stage 2 and has achieved good results in the trial. No adverse reactions have been reported (Tessier and Birlouez-Aragon 2012). In addition, binding to the receptor for advanced glycation end-products (RAGE) is an important way for AGEs to participate in the development and progression of a variety of diseases in vivo. The RAGE is a transmembrane receptor composed of 400 amino acids and another target for the treatment of diseases. Current researches mainly include soluble RAGE (sRAGE) and anti-RAGE antibodies. RAGE is a transmembrane receptor composed of 400 amino acids. The mechanism of action of s-RAGE is mainly through binding to ligand AGEs in tissues and organs, blocking the intracellular signaling pathway induced by AGEs binding to RAGE, thereby reducing the damage induced by AGEs. After treatment with s-RAGE in diabetic mice, incidence of glomerulonephritis and atherosclerosis in mice was significantly reduced, as was the occurrence of proteinuria (Lin et al. 2003). After the anti-RAGE antibody was used to treat diabetic model mice, ultrasound was used to measure the blood flow in the hind limbs of the mice. The results showed that compared with the mice treated with normal saline, the angiographic signal of the mice treated with anti-RAGE antibody was significantly increased, indicating that RAGE antibodies had therapeutic effect on peripheral arterial disease in mice (Zheng et al. 2002). Blocking the effects of oxidative stress, indirectly inhibiting AGEs by reducing oxidative stress response and restoring the dynamic balance of oxygen free radicals in the body is an effective therapeutic strategy for the treatment of diabetes complications caused by AGEs. MET guanidine was found to inhibit oxidative stress response and apoptosis in osteoblasts in a concentration-dependent manner, significantly reducing the damage of AGEs to osteoblasts (Feng et al. 2007). Temopril and omethartan were used to treat rabbits with aortic vascular smooth muscle cells away with this, and it was found that both of them could reduce the production of reactive oxygen species (ROS), thereby reducing apoptosis (Šebeková et al. 2003). In addition, pyridoxine has also been shown to effectively inhibit AGEs induced injury of nephridium, and one of the important ways it plays a role is to reduce oxidative stress reaction by reducing oxygen free radicals produced in the process of non-

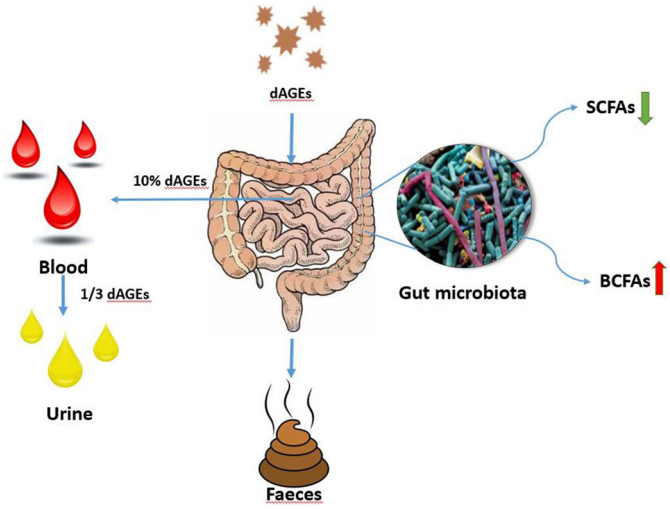

Figure 2. The absorption and metabolism of dAGEs.

enzymatic glycosylation (ŠebekovÁ et al. 2005). Currently, the effects of natural products on AGEs have been increasingly explored. The effects of natural products on AGEs are mainly through inhibition of AGEs formation and activities. For example, flavonoids have been shown to have antioxidant, anti-inflammatory, and anti-cardiovascular and cerebrovascular effects, and have an inhibitory effect on the formation of AGEs (Harcourt et al. 2011). Moreover, quercetin has been shown to significantly inhibit accumulation of AGEs in diabetic mice, and quercetin also showed stronger AGEs inhibition than AG in in vitro experiments (Hwang, Shin, and Yang 2005). Polysaccharide extracts from many natural plants, such as green tea and aloe vera, also have an inhibitory effect on the formation of AGEs (Kilhovd et al. 2007). These drugs and natural products may be used to treat diseases caused by AGEs in the future, thereby improving human health.

The absorption and metabolism of dAGEs

The dAGEs have significantly contribute to the total endogenous AGEs (Almajwal et al. 2020). Higher levels of AGEs have been found in healthy individuals with high dietary AGEs intakes than in individuals who eat foods containing fewer AGEs (Chen et al. 2018). It is noteworthy that because of the difficulty to separate AGEs from MRPs, some researchers often chose the digestion and absorption mechanism of MRPs to replace the digestion and absorption mechanism of AGEs when studying the above mechanism of AGEs in the past many years. However, in recent years, with the development of detection technology, more and more reports about the absorption and metabolism of AGEs have been reported metabolism of dAGEs in the body is a complex process. As shown in Figure 2, nearly about 10% of dAGEs are absorbed by the small intestine and enter the blood circulation, of which about 1/3 are excreted through urine and the remainder remain in the body (He et al. 1999; Koschinsky et al. 1997; Salazar-Villanea et al. 2018). In many, research about AGEs showed that the digestion and absorption characteristics of various AGEs are different. The digestion and absorption characteristics of pyrrole, pentosidine, and CML are the hotspots of current research. The research reported that the vast majority of food-borne pyrrole can be digested and absorbed by the gastrointestinal tract and enter the body's metabolic cycle, but after metabolism most of the pyrrole is excreted quickly through the urine, only a small fraction of pyrrole may accumulate in the body (Foerster and Henle 2003). However, the same research group reached different conclusions in short-term clinical trials: only 50% of the gastrointestinal digestive pyrrole and 60% of the free pentose is excreted in the urine (Förster, Kühne, and Henle 2005). They demonstrated that pentosidine in free form in coffee drinks has a higher absorption rate than pentosidine in bound form in baked foods (Förster, Kühne, and Henle 2005). The studies of CML absorption and excretion have shown that in healthy adolescents aged 11–14 years, CML absorption and fecal excretion are highly dependent on dietary CML intake levels, although CML urine excretion also depends on diet and the level of CML intake, but there is a certain saturation limit for CML urine excretion (Delgado-Andrade et al. 2012). The absorption and response of AGEs in the intestines is extremely complicated, and different types of AGEs absorb differently. The absorption rates of low molecular weight (LMW) AGEs and high molecular weight (HMW) AGEs are in different. LMW AGEs include free AGEs and peptide binding AGEs. The previous are most likely to be absorbed by intestinal endothelial cells through simple diffusion rather than transport (Grunwald et al. 2006). However, the latter are mainly absorbed by intestinal endothelial cells through peptide transporters such as PEPT1 (Hellwig et al. 2011). In addition, a part of HMW AGEs needs to be degraded into small molecules by gastrointestinal proteases which is another reason why it have a slower absorption rate. In general, food type, gastrointestinal environment, and HMW AGEs' residence time in the intestine determine the degradation degree of HMW AGEs. For example, thermal processing leads to protein denaturation in food, thus reducing the sensitivity of HMW AGEs to gastrointestinal enzyme degradation, which leads to reduce the absorbed of AGEs by intestinal endothelial cells (Poulsen et al. 2013). Moreover, it is reported that renal excretion of AGEs in patients with kidney disease is significantly inhibited (Stinghen et al. 2016). Free AGEs (glycated amino acids) and protein-bound AGEs (protein glycation adducts) have different bioavailability and physiological effects (Miao et al. 2019). Compared with the increase in plasma protein binding age (2–5 fold), the free AGEs of patients undergoing hemodialysis increases much faster (4–40 fold; Zhao et al. 2019). The free AGEs could be excreted through the urine, however the protein-bound AGEs could be reabsorbed actively in the proximal tubules, and the clearance rate of peptide-bound AGEs in humans was lower than that of creatinine (Asano et al. 2002; Zhao et al. 2019). The result showed that the clearance rates of AGEs with diverse binding methods are different in kidney. Except a little part of AGEs absorbed in the small intestine and into the blood, most of the AGEs become the potential nutrients of the intestinal flora.

The effect of AGEs on gut microbes

In recent year, more research about the relation between microbiota and health have been reported, and this is presently one of the hottest areas of scientific and medical research. It exerts a marked influence on the host during homeostasis and disease (Bell et al. 2018), affects the development and function of essentially all organ systems and contributes to adaptation and evolution, while protecting against pathogenic microorganisms and toxins (Flandroy et al. 2018). However, the composition of the gut microbiota could be affected by diet, nature environment, antibiotics, and so on (Shang and Liu 2018). Especially, diets play an important role in involvement of the microbiota in inflammatory diseases, which contributes to obesity, depression, diabetes, and so on (Bell et al. 2018). It has been confirmed that gut microbiota is closely tied to immune health, because the major immune system resides in the tonsils and gut, so when the gut microbiota is subjected to imbalance, the function of immune health will be destroyed (Rubio and Schmidt 2018). Battson et al. (2018) feed C57BL/6J mice Western diet and the mice randomized to receive either unsupplemented drinking water or water containing a broad-spectrum antibiotic cocktail. Seven months of Western diet caused gut dysbiosis, increased arterial stiffness, and endothelial dysfunction et al. In Antibiotic treatment group, the gut microbiota was abrogated and arterial stiffness and endothelial dysfunction was reversed, which means the gut microbiota play an important role in vascular dysfunction. As an important source of AGE, the influence of Western diet on intestinal microbes can be regarded as an indirect intervention of AGEs on the intestinal tract. Previous research has shown that most of the HMW dAGEs directly enter the colon for colonic bacterial fermentation or are excreted with the feces (Somoza 2005; Tuohy et al. 2006). Moreover, Delgado-andrade et al. (2012) found that there was a positive correlation between AGEs in feces and AGEs in urine, but not with AGEs in urine. Note that although most of dAGES, such as CML, pyrraline, and maltosine, can be degraded by gut microbiota, it affords energy, carbon, and nitrogen for microbial growth (Hellwig et al. 2015; Son et al. 2017). The result showed that dAGEs reduced α-diversity and altered microbiota composition. Elevated Helicobacter levels were found in the High-AGE group, and among the 57 perturbed metabolites, protein-fermentation products (i.e., p-cresol and putrescine) were increase, which means dAGEs own the capacity for perturbing the gut microbiome and microbial metabolites. Additionally, the research by Yacoub et al. also showed that dAGEs restriction may thus result in gut microbiota changes forperitoneal dialysis patients (Yacoub et al. 2017). In addition, the research of Qu et al. support this view that dAGEs can modify gut microbial composition in rats (Qu et al. 2017). They found that dAGEs resistance to digestive enzymes, adversely altering gut microbiota abundance, diversity, and composition. Moreover, dietary AGEs increased protein fermentation but weakened the fermentation of carbohydrates, as evidenced by increased levels of the putrefactive toxic metabolites ammonia and BCFAs at the expense of beneficial metabolites like SCFAs. Furthermore, dietary AGEs damaged the colonic epithelial barrier, enabling more endotoxins to enter the systemic circulation. At present, research on AGEs for the gut and microbes is just beginning, among them have controversial even completely different experimental results (Snelson and Coughlan, 2019). Mr. DeChristopher proposed a new perspective that the source of the serum and urinary AGEs is the intestines, not the food (DeChristopher 2017). He found that many experimental results about dAGEs was conflicted, sometimes even with opposite results. Some healthy foods containing higher dAGEs, while some traditional junk foods have lower AGE levels. However, foods contain low level AGEs can increase the levels of AGE in serum and urine. The authors analyzed that the AGEs in serum and urine are produced by the intestines. Recent in vitro research found that fructose and reactive amino acids and peptides (but not with glucose) at a pH consistent with the intestines within 1 h of exposure, a time frame well within the time window of digestion (Bains and Gugliucci 2017). This discovery provided indirect support and plausibility of enteral fructose-associated advanced glycation end product (FruAGE) formation, an overlooked source of proinflammatory AGEs. Notably, recent epidemiologic research with nationally representative survey data has provided evidence that intake of beverages with high fructose-to-glucose ratios, including fruit drinks and apple juice, are associated with higher odds and prevalence of asthma, chronic bronchitis, non–age-associated arthritis, and coronary heart disease, possibly due to underlying fructose malabsorption and enteral FruAGE formation.

The effect of AGEs on intestinal disorders

It was reported that the majority of the dietary protein-bound AGE accumulate in the ileum and colon (Tessier et al. 2016). These AGEs could attenuate the first-line antioxidant defenses and stimulate the inflammatory response in gastrointestinal tract by downregulating enzymatic antioxidative pathways and increasing inflammatory cytokine levels (Lingelbach et al. 2000). There are many reports on the association of AGEs with inflammatory response and increasing of oxidative stress (Son et al. 2017; Widjaja, Rusdiana, and Savira 2018). The interaction begins with the recognition of AGEs conformational epitopes by the pattern recognition receptors (PRRs), then a downstream signaling to the nucleus, following to NF-κB activation and consequent cellular responses (Muscat et al. 2007). Several PRRs have the potential recognition ability and binding affinity for AGEs but their interaction may lead to various responses. As a result of the interaction between AGE and RAGE receptors, increased production of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 occurs in endothelial cells and monocytes are increased. An increase in free radicals and oxidative stress aggravates the inflammatory state, eventually affect long-lived proteins and further lead to a series of related diseases (Cai et al. 2007). In 2018, Teodorowicz et al. (2018) discussed the relationship between

Table 2. The effect of AGE in IBD, CRC, and IBS.

Disease	Research object	AGEs	Influence	References
Inflammatory bowel diseases (IBD)	Mice	CML	Repeated oral exposure to CML limits dysbiosis in experimental colitis	(Aljahdali et al. 2017)
Colorectal cancer (CRC)	Human	Glucose-derived AGEs	AGEs promoted invasion and migration of colorectal cancer	(Deng et al. 2017)
		Glyceraldehyde-derived AGEs	Promote colorectal cancer development.	(Kong et al. 2015)
Irritable bowel syndrome (IBS)	Mice	Lactose and Fructo-oligosaccharides derived AGEs	Increases abdominal sensitivity	(Kamphuis et al. 2020)

metabolism of feed derived AGEs and animal's immunomodulation. In their study, these AGEs can be released in the intestinal tract as a consequence of the interaction with digestive enzymes and also intestinal microbiota. When these dAGEs were absorbed, it will bind to some receptors such as CD36, SR-A1, RAGE, which was expressed on immune cells. Then, these activities produce ROS and cytokines, it will cause a series of body damage and disease. As shown in Table 2, the Glyceraldehyde-derived AGEs, glyceraldehyde contributes to the production of a group of compounds, was reported have significant association with colorectal cancer (CRC; Kong et al. 2015). The researchers collected 1055 CRC cases (colon $n = 659$; rectal $n = 396$) and determined the content of circulating glycer-AGEs. The result showed that circulating glycer-AGEs showed a positive association with the risk of ectal cancer but not associated with risk of colon cancer. Other studied showed that AGEs could promote the invasion and metastasis of CRC partially through the RAGE/ERK/SP1/MMP2 cascade (Deng et al. 2017). As the RAGEs, heightened RAGE expression was reported for many cancers in recent year, including CRC (Bedoui et al. 2020). Researchers found that AGER rs2853807 and rs77170610 are positively correlated with CRC, indicating that these AGER polymorphisms contribute to the systemic inflammation that accompanies CRC and other cancers. Contrarily, Chen et al. measured the blood levels of CML-AGE and sRAGE in 93,676 postmenopausal women (50–79 years; Chen et al. 2016). They found that circulating CML-AGE and sRAGE are positively correlated with adiponectin, and negatively correlated with obesity and hyperinsulinemia. However, there was no significant interaction between CML-AGE and BMI on the risk of CRC was found. Interestingly, in another research, compared with type 2 diabetic patients without CRC, patients with type 2 diabetes with CRC have higher levels of triglycerides, total cholesterol, IL-6 and circulating sRAGE, and lower drug use rates. Which means circulating sRAGE is independently risk factor for CRC, and also closely related to inflammation, dyslipidemia in type 2 diabetes patients (Zhou et al. 2020). Furthermore, AGEs and RAGE indicate close associations with inflammatory bowel diseases (IBD; Luceri et al. 2019; Moura et al. 2020). AGE/RAGE is related to the inflammatory process and oxidative stress, which could activate two cellular pathways, proinflammatory based on NF-κB and p53M, nuclear expression of pro-oxidant and cancer-promoting genes, related to NF-κB activation, deoxyribonucleic acid damage, and oncogenes expression. In addition, RAGE polymorphisms and increased RAGE levels are found in IBD patients. The research about differential expression of soluble receptors for AGEs in mice susceptible or resistant to chronic colitis showed that RAGE pathway is clinically relevant in the onset of chronic colitis (Bramhall et al. 2020). They found that RAGE was highly dysregulated between resistant and susceptible mice before the pathological signs. The increase of sRAGE in serum and feces of drug-resistant mice was correlated with the decrease of colitis score. It was reported that mice gavage with lactose or fed fructo-oligosaccharides had increased abdominal sensitivity, associated with increased numbers of mast cells in colon and expression of the receptor for AGER in proximal colon epithelium (Kamphuis et al. 2020). Those signs seems indicated that dAGEs and RAGE can act directly on the intestines and takes part in intestinal diseases. However, this conclusion remains controversial. Aljahdali et al. (2017) found daily oral administration of CML did not induce intestinal inflammation and had limited impact on gut microbiota composition. Furthermore, the CML could limit the severity of weight loss and the gut microbiota dysbiosis in enteritis mice, that was treated with dextran sulfate sodium salt. Oh et al. (2017) synthesized sugar-amino acid Maillard reaction products from three different sugars (glucose, fructose, and galactose) and amino acids (lysine, arginine, and glycine). They studied the anti-inflammatory effect of sugar-amino acid Maillard reaction products on intestinal inflammation model in vitro and in vivo according to coculture system consisting of Caco-2 and RAW264.7. The results suggested that the oral administration of composite from lysine and galactose could have anti-inflammatory effects in the intestine by suppressing TNF-α expression of macrophages followed by decreased secretion of inflammatory cytokines including IL-8 and IL-1b of intestinal immune cells. However, the in vivo inflammatory activity of the characterized compounds in composite from lysine and galactose and their inflammatory mechanism require further study. Therefore, the effects of AGEs on the intestines need more systematic and scientific research.

Conclusion

dAGEs square measure fashioned from external sources in food, particularly food parched at warm temperature for semipermanent use of dry heat. These dAGE-rich foods can cause inflammation and increase the level of oxidative stress,

which will affect health and cause a series of diseases. Some drugs, polyphenol, flavonoids, and nature products can effectively inhibit the production of dAGEs and endogenous AGEs. Absorption of dAGEs is limited, there is evidence that most of the protein from the gastrointestinal tract by binding to the AGEs in the colon, which can be used as a substrate of the intestinal microflora. However, the characterization and bioactivities of dAGEs are complex and varied, although we have already found a series of them such as CML, CEL, MGO and analyzed their structural. In addition, there is widespread debate about the relationship between dAGEs and endogenous AGEs. So the relationship between dose-response of dAGEs and contain of endogenous AGEs need further research in the future. To sum up, the effects of dAGEs on the intestine can be summarized in two approaches, the first is the direct effect after absorption by the intestinal tract, the other way is to perturb the gut microbiome and microbial metabolites. However, the origin and composition of dAGEs are complex, so the role of either approach is controversial and need more research to verify it in the future. Moreover, the specific mechanism of the association between AGEs and intestinal diseases also need further study. To our belief, several important questions need to be resolved, including whether diet-bound AGEs have higher bioavailability, whether combined AGEs play a more important role in the RAGE-dependent pathway than free AGEs, and how absorbed AGEs covalently bind to protein tissues in the body, and so forth.

Disclosure statement

No potential conflict of interest was reported by the authors.

Author contributions

C.N., Y.L., and L.W. designed research; H.Q. and H.Y. contributed to information collection; C.N., Y.L., and L.W. wrote the manuscript. All authors read and approved the final manuscript.

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References

Ahmad, S., H. Khan, Z. Siddiqui, M. Y. Khan, S. Rehman, U. Shahab, T. Godovikova, V. Silnikov, and Moinuddin. 2018. AGEs, RAGEs and s-RAGE; friend or foe for cancer. *Seminars in Cancer Biology*, 49:44–55.

Ali, M., A. Barakat, A. El-Faham, H. H. Al-Rasheed, K. Dahlous, A. M. Al-Majid, A. Sharma, S. Yousuf, M. Sanam, Z. Ul-Haq, M. I. Choudhary, et al. 2020. Synthesis and characterisation of thiobarbituric acid enamine derivatives, and evaluation of their α-glucosidase inhibitory and anti-glycation activity. *Journal of Enzyme Inhibition and Medicinal Chemistry* 35 (1):692–701. doi: 10.1080/14756366.2020.1737045.

Aljahdali, N., P. Gadonna-Widehem, C. Delayre-Orthez, D. Marier, B. Garnier, F. Carbonero, and P. M. Anton. 2017. Repeated oral exposure to N ε-carboxymethyllysine, a Maillard reaction product, alleviates gut microbiota dysbiosis in colitic mice. *Digestive Diseases and Sciences* 62 (12):3370–84. doi: 10.1007/s10620-017-4767-8.

Almajwal, A. M., I. Alam, M. Abulmeaty, S. Razak, G. Pawelec, and W. Alam. 2020. Intake of dietary advanced glycation end products influences inflammatory markers, immune phenotypes, and antiradical capacity of healthy elderly in a little-studied population. *Food Science & Nutrition* 8 (2):1046–57. doi: 10.1002/fsn3.1389.

Aragno, M., and R. Mastrocola. 2017. Dietary sugars and endogenous formation of advanced glycation endproducts: Emerging mechanisms of disease. *Nutrients* 9 (4):385. doi: 10.3390/nu9040385.

Asano, M., Y. Fujita, Y. Ueda, D. Suzuki, T. Miyata, H. Sakai, and A. Saito. 2002. Renal proximal tubular metabolism of protein-linked pentosidine, an advanced glycation end product. *Nephron* 91 (4): 688–694. doi: 10.1159/000065032.

Bains, Y., and A. Gugliucci. 2017. Ilex paraguariensis and its main component chlorogenic acid inhibit fructose formation of advanced glycation endproducts with amino acids at conditions compatible with those in the digestive system. *Fitoterapia* 117:6–10. doi: 10.1016/j.fitote.2016.12.006.

Battson, M. L., D. M. Lee, D. K. Jarrell, S. Hou, K. E. Ecton, T. L. Weir, and C. L. Gentile. 2018. Suppression of gut dysbiosis reverses Western diet-induced vascular dysfunction. *American Journal of Physiology-Endocrinology and Metabolism* 314 (5):E468–477. doi: 10.1152/ajpendo.00187.2017.

Bedoui, S. A., M. Barbirou, M. Stayoussef, M. Dallel, A. Mokrani, L. Makni, A. Mezlini, B. Bouhaouala-Zahar, B. Yacoubi-Loueslati, and W. Y. Almawi. 2020. Identification of novel advanced glycation end products receptor gene variants associated with colorectal cancer in Tunisians: A case-control study. *Gene* 754:144893. doi: 10.1016/j.gene.2020.144893.

Bell, V., J. Ferrao, L. Pimentel, M. Pintado, and T. Fernandes. 2018. One health, fermented foods, and gut microbiota. *Foods* 7 (12):195. doi: 10.3390/foods7120195.

Birlouez-Aragon, I., N. Locquet, E. De St Louvent, D. J.-R. Bouveresse, and P. Stahl. 2005. Evaluation of the Maillard reaction in infant formulas by means of front-face fluorescence. *Annals of the New York Academy of Sciences* 1043 (1):308–318. doi: 10.1196/annals.1333.038.

Birlouez-Aragon, I., M. Pischetsrieder, J. Leclère, F. J. Morales, K. Hasenkopf, R. Kientsch-Engel, C. J. Ducauze, and D. Rutledge. 2004. Assessment of protein glycation markers in infant formulas. *Food Chemistry* 87 (2):253–9. doi: 10.1016/j.foodchem.2003.11.019.

Bosch, L., A. AlegríA, R. Farré, and G. Clemente. 2008. Effect of storage conditions on furosine formation in milk–cereal based baby foods. *Food Chemistry* 107 (4):1681–6. doi: 10.1016/j.foodchem.2007.09.051.

Bosch, L., A. Alegría, R. Farré, and G. Clemente. 2007. Fluorescence and color as markers for the Maillard reaction in milk–cereal based infant foods during storage. *Food Chemistry* 105 (3):1135–1143. doi: 10.1016/j.foodchem.2007.02.016.

Bosch, L., M. L. Sanz, A. Montilla, A. Alegría, R. Farré, and M. D. del Castillo. 2007. Simultaneous analysis of lysine, Nε-carboxymethyllysine and lysinoalanine from proteins. *Journal of Chromatography B* 860 (1):69–77. doi: 10.1016/j.jchromb.2007.10.011.

Bramhall, M., K. Rich, A. Chakraborty, L. Logunova, N. Han, J. Wilson, J. McLaughlin, A. Brass, and S. M. Cruickshank. 2020. Differential expression of soluble receptor for advanced glycation end-products in mice susceptible or resistant to chronic colitis. *Inflammatory Bowel Disease* 26 (3):360–368. doi: 10.1093/ibd/izz311.

Büser, W., H. F. Erbersdobler, and R. Liardon. 1987. Identification and determination of N-ε-carboxymethyllysine by gas-liquid chromatography. *Journal of Chromatography A* 387:515–9. doi:10.1016/S0021-9673(01)94562-5.

Byun, K., Y. Yoo, M. Son, J. Lee, G.-B. Jeong, Y. M. Park, G. H. Salekdeh, and B. Lee. 2017. Advanced glycation end-products

produced systemically and by macrophages: A common contributor to inflammation and degenerative diseases. *Pharmacology & Therapeutics* 177:44–55. doi: 10.1016/j.pharmthera.2017.02.030.

Cai, W., J. C. He, L. Zhu, X. Chen, S. Wallenstein, G. E. Striker, and H. Vlassara. 2007. Reduced oxidant stress and extended lifespan in mice exposed to a low glycotoxin diet: Association with increased AGER1 expression. *The American Journal of Pathology* 170 (6): 1893–902. doi: 10.2353/ajpath.2007.061281.

Cai, W., J. Uribarri, L. Zhu, X. Chen, S. Swamy, Z. Zhao, F. Grosjean, C. Simonaro, G. A. Kuchel, M. Schnaider-Beeri, et al. 2014. Oral glycotoxins are a modifiable cause of dementia and the metabolic syndrome in mice and humans. *Proceedings of the National Academy of Sciences of the United States of America* 111 (13): 4940–5. doi: 10.1073/pnas.1316013111.

Chao, P.-C., C.-N. Huang, C.-C. Hsu, M.-C. Yin, and Y.-R. Guo. 2010. Association of dietary AGEs with circulating AGEs, glycated LDL, IL-1α and MCP-1 levels in type 2 diabetic patients. *European Journal of Nutrition* 49 (7):429–34. doi: 10.1007/s00394-010-0101-3.

Chao, P. C., C. C. Hsu, and M. C. Yin. 2009. Analysis of glycative products in sauces and sauce-treated foods. *Food Chemistry* 113 (1): 262–6. doi: 10.1016/j.foodchem.2008.06.076.

Chen, J. H., X. Lin, C. H. Bu, and X. G. Zhang. 2018. Role of advanced glycation end products in mobility and considerations in possible dietary and nutritional intervention strategies. *Nutrition & Metabolism* 15:72. doi: 10.1186/s12986-018-0306-7.

Chen, L., Z. Duan, L. Tinker, H. Sangi-Haghpeykar, H. Strickler, G. Y. F. Ho, M. J. Gunter, T. Rohan, C. Logsdon, D. L. White, et al. 2016. A prospective study of soluble receptor for advanced glycation end-products and colorectal cancer risk in postmenopausal women. *Cancer Epidemiology* 42:115–23. doi: 10.1016/j.canep.2016.04.004.

Csongová, M., E. Renczés, V. Šarayová, L. Mihalovičová, J. Janko, R. Gurecká, A. D. Troise, P. Vitaglione, and K. Šebeková. 2019. Maternal consumption of a diet rich in Maillard reaction products accelerates neurodevelopment in F1 and sex-dependently affects behavioral phenotype in F2 rat offspring. *Foods* 8 (5):168. doi: 10.3390/foods8050168.

Cui, H. P., J. Y. Yu, S. Q. Xia, E. Duhoranimana, Q. R. Huang, and X. M. Zhang. 2019. Improved controlled flavor formation during heat-treatment with a stable Maillard reaction intermediate derived from xylose-phenylalanine. *Food Chemistry* 271:47–53. doi: 10.1016/j.foodchem.2018.07.161.

Cunnane, S. C. 2005. Origins and evolution of the Western diet: Implications of iodine and seafood intakes for the human brain. *The American Journal of Clinical Nutrition* 82 (2):483. doi: 10.1093/ajcn.82.2.483.

de Oliveira, F. C., J. S. D. Coimbra, E. B. de Oliveira, A. D. G. Zuniga, and E. E. G. Rojas. 2016. Food protein-polysaccharide conjugates obtained via the Maillard reaction: A review. *Critical Reviews in Food Science and Nutrition* 56 (7):1108–25. doi: 10.1080/10408398.2012.755669.

DeChristopher, L. R. 2017. Perspective: The paradox in dietary advanced glycation end products research-the source of the serum and urinary advanced glycation end products is the intestines, not the food. *Advances in Nutrition (Bethesda, MD)* 8 (5):679–83. doi: 10.3945/an.117.016154.

Dehnad, A., W. Fan, J. X. Jiang, S. R. Fish, Y. Li, S. Das, G. Mozes, K. A. Wong, K. A. Olson, G. W. Charville, et al. 2020. AGER1 downregulation associates with fibrosis in nonalcoholic steatohepatitis and type 2 diabetes. *The Journal of Clinical Investigation* 130 (8): 4320–30. doi: 10.1172/Jci133051.

Delgado-Andrade, C., and V. Fogliano. 2018. Dietary advanced glycosylation end-products (dAGEs) and melanoidins formed through the Maillard reaction: Physiological consequences of their intake. *Annual Review of Food Science and Technology* 9:271–91. doi: 10.1146/annurev-food-030117-012441.

Delgado-Andrade, C., I. Seiquer, A. Haro, R. Castellano, and M. P. Navarro. 2010. Development of the Maillard reaction in foods cooked by different techniques. Intake of Maillard-derived compounds. *Food Chemistry* 122 (1):145–53. doi: 10.1016/j.foodchem.2010.02.031.

Delgado-Andrade, C., F. J. Tessier, C. Niquet-Leridon, I. Seiquer, and M. Pilar Navarro. 2012. Study of the urinary and faecal excretion of Nε-carboxymethyllysine in young human volunteers. *Amino Acids.* 43 (2):595–602. doi: 10.1007/s00726-011-1107-8.

Deng, R., H. Wu, H. Ran, X. Kong, L. Hu, X. Wang, and Q. Su. 2017. Glucose-derived AGEs promote migration and invasion of colorectal cancer by up-regulating Sp1 expression. *Biochimica et Biophysica Acta: General Subjects* 1861 (5 Pt A):1065–74. doi: 10.1016/j.bbagen.2017.02.024.

El-Nashar, H. A. S., N. M. Mostafa, M. El-Shazly, and O. A. Eldahshan. 2020. The role of plant-derived compounds in managing diabetes mellitus: A review of literature from 2014 to 2019. *Current Medicinal Chemistry*. doi: 10.2174/0929867328999201123194510.

Fenaille, F., V. Parisod, P. Visani, S. Populaire, J.-C. Tabet, and P. A. Guy. 2006. Modifications of milk constituents during processing: A preliminary benchmarking study. *International Dairy Journal* 16 (7): 728–39. doi:10.1016/j.idairyj.2005.08.003.

Feng, J. X., F. F. Hou, M. Liang, G. B. Wang, X. Zhang, H. Y. Li, D. Xie, J. W. Tian, and Z. Q. Liu. 2007. Restricted intake of dietary advanced glycation end products retards renal progression in the remnant kidney model. *Kidney International* 71 (9):901–11. doi: 10.1038/sj.ki.5002162.

Flandroy, L., T. Poutahidis, G. Berg, G. Clarke, M.-C. Dao, E. Decaestecker, E. Furman, T. Haahtela, S. Massart, H. Plovier, et al. 2018. The impact of human activities and lifestyles on the interlinked microbiota and health of humans and of ecosystems. *The Science of the Total Environment* 627:1018–38. doi: 10.1016/j.scitotenv.2018.01.288.

Foerster, A., and T. Henle. 2003. Glycation in food and metabolic transit of dietary AGEs (advanced glycation end-products): Studies on the urinary excretion of pyrraline. *Biochemical Society Transactions* 31 (Pt 6):1383–5. doi: 10.1042/bst0311383.

Förster, A., Y. Kühne, and T. O. Henle. 2005. Studies on absorption and elimination of dietary Maillard reaction products. *Annals of the New York Academy of Sciences* 1043 (1):474–81. doi: 10.1196/annals.1333.054.

Goldberg, T., W. Cai, M. Peppa, V. Dardaine, B. S. Baliga, J. Uribarri, and H. Vlassara. 2004. Advanced glycoxidation end products in commonly consumed foods. *Journal of the American Dietetic Association* 104 (8):1287–91. doi: 10.1016/j.jada.2004.05.214.

Gowd, V., Q. Kang, Q. Wang, Q. Wang, F. Chen, and K.-W. Cheng. 2020. Resveratrol: Evidence for its nephroprotective effect in diabetic nephropathy. *Advances in Nutrition (Bethesda, MD)* 11 (6):1555–68. doi: 10.1093/advances/nmaa075.

Grunwald, S., R. Krause, M. Bruch, T. Henle, and M. Brandsch. 2006. Transepithelial flux of early and advanced glycation compounds across Caco-2 cell monolayers and their interaction with intestinal amino acid and peptide transport systems. *The British Journal of Nutrition* 95 (6):1221–8. doi: 10.1079/BJN20061793.

Harcourt, B. E., K. C. Sourris, M. T. Coughlan, K. Z. Walker, S. L. Dougherty, S. Andrikopoulos, A. L. Morley, V. Thallas-Bonke, V. Chand, S. A. Penfold, et al. 2011. Targeted reduction of advanced glycation improves renal function in obesity. *Kidney International* 80 (2):190–8. doi: 10.1038/ki.2011.57.

Harohally, N. V., S. M. Srinivas, and S. Umesh. 2014. ZnCl2-mediated practical protocol for the synthesis of Amadori ketoses. *Food Chemistry* 158:340–4. doi: 10.1016/j.foodchem.2014.02.094.

Hartkopf, J, and H. F. Erbersdobler. 1994. Modelluntersuchungen zu Bedingungen der Bildung vonNε-Carboxymethyllysin in Lebensmitteln. *Zeitschrift für Lebensmittel-Untersuchung Und-Forschung* 198 (1):15–9. doi:10.1007/BF01195275.

He, J., M. Zeng, Z. Zheng, Z. He, and J. Chen. 2014. Simultaneous determination of N ε-(carboxymethyl) lysine and N ε-(carboxyethyl) lysine in cereal foods by LC–MS/MS. *European Food Research and Technology* 238 (3):367–74. doi:10.1007/s00217-013-2085-8.

He, C., J. Sabol, T. Mitsuhashi, and H. Vlassara. 1999. Dietary glycotoxins: Inhibition of reactive products by aminoguanidine facilitates renal clearance and reduces tissue sequestration. *Diabetes* 48 (6): 1308–15. doi: 10.2337/diabetes.48.6.1308.

Hellwig, M., D. Bunzel, M. Huch, C. M. A. P. Franz, S. E. Kulling, and T. Henle. 2015. Stability of individual Maillard reaction products in the presence of the human colonic microbiota. *Journal of Agricultural and Food Chemistry* 63 (30):6723–30. doi: 10.1021/acs.jafc.5b01391.

Hellwig, M., S. Geissler, R. Matthes, A. Peto, C. Silow, M. Brandsch, and T. Henle. 2011. Transport of free and peptide-bound glycated amino acids: Synthesis, transepithelial flux at caco-2 cell monolayers, and interaction with apical membrane transport proteins. *Chembiochem: A European Journal of Chemical Biology* 12 (8): 1270–9. doi: 10.1002/cbic.201000759.

Hipkiss, A. R. 2018. Glycotoxins: Dietary and metabolic origins; possible amelioration of neurotoxicity by carnosine, with special reference to Parkinson's disease. *Neurotoxicity Research* 34 (1):164–72. doi: 10.1007/s12640-018-9867-5.

Hohmann, C., K. Liehr, C. Henning, R. Fiedler, M. Girndt, M. Gebert, M. Hulko, M. Storr, and M. A. Glomb. 2017. Detection of free advanced glycation end products in vivo during hemodialysis. *Journal of Agricultural and Food Chemistry* 65 (4):930–7. doi: 10.1021/acs.jafc.6b05013.

Hull, G. L. J., J. V. Woodside, J. M. Ames, and G. J. Cuskelly. 2012. N-epsilon-(carboxymethyl)lysine content of foods commonly consumed in a Western style diet. *Food Chemistry* 131 (1):170–4. doi: 10.1016/j.foodchem.2011.08.055.

Hwang, J. S., C. H. Shin, and S. W. Yang. 2005. Clinical implications of Nε-(carboxymethyl)lysine, advanced glycation end product, in children and adolescents with type 1 diabetes. *Diabetes, Obesity and Metabolism* 7 (3):263–7. doi: 10.1111/j.1463-1326.2004.00398.x.

Kamphuis, J. B. J., B. Guiard, M. Leveque, M. Olier, I. Jouanin, S. Yvon, V. Tondereau, P. Rivière, F. Guéraud, S. Chevolleau, et al. 2020. Lactose and fructo-oligosaccharides increase visceral sensitivity in mice via glycation processes, increasing mast cell density in colonic mucosa. *Gastroenterology* 158 (3):652–63.e6. doi: 10.1053/j.gastro.2019.10.037.

Kellow, N. J., and M. T. Coughlan. 2015. Effect of diet-derived advanced glycation end products on inflammation. *Nutrition Reviews* 73 (11):737–759. doi: 10.1093/nutrit/nuv030.

Kilhovd, B. K., A. Juutilainen, S. Lehto, T. Rönnemaa, P. A. Torjesen, K. F. Hanssen, and M. Laakso. 2007. Increased serum levels of advanced glycation endproducts predict total, cardiovascular and coronary mortality in women with type 2 diabetes: A population-based 18 year follow-up study. *Diabetologia* 50 (7):1409–17. doi: 10.1007/s00125-007-0687-z.

Kong, S. Y., M. Takeuchi, H. Hyogo, G. McKeown-Eyssen, S.-I. Yamagishi, K. Chayama, P. J. O'Brien, P. Ferrari, K. Overvad, A. Olsen, et al. 2015. The association between glyceraldehyde-derived advanced glycation end-products and colorectal cancer risk. *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 24 (12):1855–1863. doi: 10.1158/1055-9965.Epi-15-0422.

Korca, E., V. Piskovatska, J. Borgermann, A. Navarrete Santos, and A. Simm. 2020. Circulating antibodies against age-modified proteins in patients with coronary atherosclerosis. *Scientific Reports* 10 (1): 17105. doi: 10.1038/s41598-020-73877-5.

Koschinsky, T., C.-J. He, T. Mitsuhashi, R. Bucala, C. Liu, C. Buenting, K. Heitmann, and H. Vlassara. 1997. Orally absorbed reactive glycation products (glycotoxins): An environmental risk factor in diabetic nephropathy. *Proceedings of the National Academy of Sciences* 94 (12):6474–9. doi: 10.1073/pnas.94.12.6474.

Kutlu, T. 2016. Dietary glycotoxins and infant formulas. *Türk Pediatri Arşivi* 51 (4):179–85. doi:10.5152/TurkPediatriArs.2016.2543.

Lee, H. S., and J. S. Hwang. 2020. Impact of type 2 diabetes mellitus and antidiabetic medications on bone metabolism. *Current Diabetes Report* 20 (12):78. doi: 10.1007/s11892-020-01361-5.

Leonova, T., V. Popova, A. Tsarev, C. Henning, K. Antonova, N. Rogovskaya, M. Vikhnina, T. Baldensperger, A. Soboleva, E. Dinastia, et al. 2020. Does Protein Glycation Impact on the Drought-Related Changes in Metabolism and Nutritional Properties of Mature Pea (Pisum sativum L.) Seeds?. *International Journal of Molecular Sciences* 21 (2):567 doi:10.3390/ijms21020567.

Liang, Z. L., L. Li, Q. Y. Fu, X. Zhang, Z. B. Xu, and B. Li. 2016. Formation and elimination of pyrraline in the Maillard reaction in a saccharide-lysine model system. *Journal of the Science of Food and Agriculture* 96 (7):2555–64. doi: 10.1002/jsfa.7376.

Lieuw-A-Fa, M. L. M., V. W. M. van Hinsbergh, T. Teerlink, R. Barto, J. Twisk, C. D. A. Stehouwer, and C. G. Schalkwijk. 2004. Increased levels of Nϵ-(carboxymethyl)lysine and Nϵ-(carboxyethyl)lysine in type 1 diabetic patients with impaired renal function: Correlation with markers of endothelial dysfunction. *Nephrology Dialysis Transplantation* 19 (3):631–6. doi: 10.1093/ndt/gfg619.

Lin, P. H., C. C. Chang, K. H. Wu, C. K. Shih, W. Chiang, H. Y. Chen, Y.-H. Shih, K.-L. Wang, Y.-H. Hong, T.-M. Shieh, et al. 2019. Dietary glycotoxins, advanced glycation end products, inhibit cell proliferation and progesterone secretion in ovarian granulosa cells and mimic PCOS-like symptoms. *Biomolecules* 9 (8):327. doi: 10.3390/biom9080327.

Lin, R.-Y., R. P. Choudhury, W. Cai, M. Lu, J. T. Fallon, E. A. Fisher, and H. Vlassara. 2003. Dietary glycotoxins promote diabetic atherosclerosis in apolipoprotein E-deficient mice. *Atherosclerosis* 168 (2): 213–220. doi: 10.1016/S0021-9150(03)00050-9.

Lingelbach, L. B., A. E. Mitchell, R. B. Rucker, and R. B. McDonald. 2000. Accumulation of advanced glycation endproducts in aging male Fischer 344 rats during long-term feeding of various dietary carbohydrates. *The Journal of Nutrition* 130 (5):1247–55. doi: 10.1093/jn/130.5.1247.

Lovestone, S., and U. Smith. 2014. Advanced glycation end products, dementia, and diabetes. *Proceedings of the National Academy of Sciences of the United States of America* 111 (13):4743–4. doi: 10.1073/pnas.1402277111.

Luceri, C., E. Bigagli, S. Agostiniani, F. Giudici, D. Zambonin, S. Scaringi, F. Ficari, M. Lodovici, and C. Malentacchi. 2019. Analysis of oxidative stress-related markers in Crohn's disease patients at surgery and correlations with clinical findings. *Antioxidants* 8 (9):378. doi: 10.3390/antiox8090378.[Mismatch] 10.

Miao, J., S. Lin, T. Soteyome, B. M. Peters, Y. Li, H. Chen, J. Su, L. Li, B. Li, Z. Xu, et al. 2019. Biofilm formation of staphylococcus aureus under food heat processing conditions: First report on CML production within biofilm. *Scientific Reports* 9 (1):1312. doi: 10.1038/s41598-018-35558-2. 10.1038/s41598-018-35558-2

Mildner-Szkudlarz, S., A. Siger, A. Szwengiel, and J. Bajerska. 2015. Natural compounds from grape by-products enhance nutritive value and reduce formation of CML in model muffins. *Food Chemistry* 172:78–85. doi: 10.1016/j.foodchem.2014.09.036.

Moura, F. A., M. O. F. Goulart, S. B. G. Campos, and A. S. da Paz Martins. 2020. The close interplay of nitro-oxidative stress, advanced glycation end products and inflammation in inflammatory bowel diseases. *Current Medicinal Chemistry* 27 (13):2059–76. doi: 10.2174/0929867325666180904115633.

Muscat, S., J. Pelka, J. Hegele, B. Weigle, G. Münch, and M. Pischetsrieder. 2007. Coffee and Maillard products activate NF-kappaB in macrophages via H2O2 production. *Molecular Nutrition & Food Research* 51 (5):525–35. doi: 10.1002/mnfr.200600254.

O'Brien, J., and P. A. Morrissey. 1989. Nutritional and toxicological aspects of the Maillard browning reaction in foods. *Critical Reviews in Food Science and Nutrition* 28 (3):211–48. doi: 10.1080/10408398909527499.

Oh, J.-G., S.-H. Chun, D. H. Kim, J. H. Kim, H. S. Shin, Y. S. Cho, Y. K. Kim, H.-D. Choi, and K.-W. Lee. 2017. Anti-inflammatory effect of sugar-amino acid Maillard reaction products on intestinal inflammation model in vitro and in vivo. *Carbohydrate Research* 449:47–58. doi: 10.1016/j.carres.2017.07.003.

Potipiranun, T., S. Adisakwattana, W. Worawalai, R. Ramadhan, and P. Phuwapraisirisan. 2018. Identification of Pinocembrin as an Anti-Glycation Agent and α-Glucosidase Inhibitor from Fingerroot (Boesenbergia rotunda): The Tentative Structure–Activity Relationship towards MG-Trapping Activity. *Molecules* 23 (12):3365 doi:10.3390/molecules23123365.

Poulsen, M. W., R. V. Hedegaard, J. M. Andersen, B. de Courten, S. Bügel, J. Nielsen, L. H. Skibsted, and L. O. Dragsted. 2013. Advanced glycation endproducts in food and their effects on health. *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 60:10–37. doi: 10.1016/j.fct.2013.06.052.

Prosser, C. G., E. A. Carpenter, and A. J. Hodgkinson. 2019. Nε-carboxymethyllysine in nutritional milk formulas for infants. *Food Chemistry* 274:886–90. doi: 10.1016/j.foodchem.2018.09.069.

Qu, W., X. Yuan, J. Zhao, Y. Zhang, J. Hu, J. Wang, and J. Li. 2017. Dietary advanced glycation end products modify gut microbial composition and partially increase colon permeability in rats. *Molecular Nutrition & Food Research* 61 (10):1700118. doi: 10.1002/mnfr.201700118.

Ramasamy, R., S. F. Yan, and A. M. Schmidt. 2011. Receptor for AGE (RAGE): Signaling mechanisms in the pathogenesis of diabetes and its complications. *Annals of the New York Academy of Sciences* 1243 (1):88–102. doi: 10.1111/j.1749-6632.2011.06320.x.

Rowan, S., S. Jiang, T. Korem, J. Szymanski, M.-L. Chang, J. Szelog, C. Cassalman, K. Dasuri, C. McGuire, R. Nagai, et al. 2017. Involvement of a gut-retina axis in protection against dietary glycemia-induced age-related macular degeneration. *Proceedings of the National Academy of Sciences of the United States of America* 114 (22):E4472–81. doi: 10.1073/pnas.1702302114.

Rubio, C. A., and P. T. Schmidt. 2018. Severe defects in the macrophage barrier to gut microflora in inflammatory bowel disease and colon cancer. *Anticancer Research* 38 (7):3811–5. doi: 10.21873/anticanres.12664.

Salazar-Villanea, S., C. I. Butre, P. A. Wierenga, E. M. A. M. Bruininx, H. Gruppen, W. H. Hendriks, and A. F. B. van der Poel. 2018. Apparent ileal digestibility of Maillard reaction products in growing pigs. *PLoS One* 13 (7):e0199499. doi: 10.1371/journal.pone.e0199499. 10.pone.0199499

Scheijen, J. L. J. M., E. Clevers, L. Engelen, P. C. Dagnelie, F. Brouns, C. D. A. Stehouwer, and C. G. Schalkwijk. 2016. Analysis of advanced glycation endproducts in selected food items by ultra-performance liquid chromatography tandem mass spectrometry: Presentation of a dietary AGE database. *Food Chemistry* 190: 1145–50. doi: 10.1016/j.foodchem.2015.06.049.

Schiavone, S., M. Neri, L. Trabace, and E. Turillazzi. 2017. The NADPH oxidase NOX2 mediates loss of parvalbumin interneurons in traumatic brain injury: Human autoptic immunohistochemical evidence. *Scientific Reports* 7 (1):8752. doi: 10.1038/s41598-017-09202-4.

Schwenger, V., M. Zeier, T. Henle, and E. Ritz. 2001. Advanced glycation endproducts (AGEs) as uremic toxins. *Nahrung/Food* 45 (3): 172–6. doi: 10.1002/1521-3803(20010601)45:3 < 172::AID-FOOD172 > 3.0.CO;2-U.

Šebeková, K., V. Faist, T. Hofmann, R. Schinzel, and A. Heidland. 2003. Effects of a diet rich in advanced glycation end products in the rat remnant kidney model. *American Journal of Kidney Diseases* 41 (3):S48–S51. doi: 10.1053/ajkd.2003.50084.

Šebeková, K., T. Hofmann, P. Boor, K. Šebeková, O. Ulicná, H. F. Erbersdobler, J. W. Baynes, S. R. Thorpe, A. Heidland, and V. Somoza. 2005. Renal effects of oral Maillard reaction product load in the form of bread crusts in healthy and subtotally nephrectomized rats. *Annals of the New York Academy of Sciences* 1043 (1): 482–91. doi: 10.1196/annals.1333.055.

Šebeková, K., G. Saavedra, C. Zumpe, V. Somoza, K. Klenovicsová, and I. Birlouez-Aragon. 2008. Plasma concentration and urinary excretion of Nε-(carboxymethyl)lysine in breast milk– and formula-fed infants. *Annals of the New York Academy of Sciences* 1126 (1): 177–80. doi: 10.1196/annals.1433.049.

Shang, F.-M., and H.-L. Liu. 2018. Fusobacterium nucleatum and colorectal cancer: A review. *World Journal of Gastrointestinal Oncology* 10 (3):71–81. doi: 10.4251/wjgo.v10.i3.71.

Sharma, A., S. Kaur, M. Sarkar, B. C. Sarin, and H. Changotra. 2020. The AGE-RAGE axis and RAGE genetics in chronic obstructive pulmonary disease. *Clinical Reviews in Allergy & Immunology*. Advance online publication. doi: 10.1007/s12016-020-08815-4.

Snelson, M, and M. Coughlan. 2019. Dietary Advanced Glycation End Products: Digestion, Metabolism and Modulation of Gut Microbial Ecology. *Nutrients* 11 (2):215–230 doi:10.3390/nu11020215.

Somoza, V. 2005. Five years of research on health risks and benefits of Maillard reaction products: An update. *Molecular Nutrition & Food Research* 49 (7):663–72. doi: 10.1002/mnfr.200500034.

Son, S., I. Hwang, S. H. Han, J.-S. Shin, O. S. Shin, and J.-W. Yu. 2017. Advanced glycation end products impair NLRP3 inflammasome-mediated innate immune responses in macrophages. *The Journal of Biological Chemistry* 292 (50):20437–48. doi: 10.1074/jbc.M117.806307.

Song, S., Q. Liu, W.-M. Chai, S.-S. Xia, Z.-Y. Yu, and Q.-M. Wei. 2020. Inhibitory potential of 4-hexylresorcinol against α-glucosidase and non-enzymatic glycation: Activity and mechanism. *Journal of Bioscience and Bioengineering*. doi: 10.1016/j.jbiosc.2020.10.011.

Stinghen, A. E., Z. A. Massy, H. Vlassara, G. E. Striker, and A. Boullier. 2016. Uremic toxicity of advanced glycation end products in CKD. *Journal of the American Society of Nephrology: JASN* 27 (2): 354–70. doi: 10.1681/ASN.2014101047.

Takeuchi, M., J.-I. Takino, S. Furuno, H. Shirai, M. Kawakami, M. Muramatsu, Y. Kobayashi, and S.-I. Yamagishi. 2015. Assessment of the concentrations of various advanced glycation end-products in beverages and foods that are commonly consumed in Japan. *PLoS One* 10 (3):e0118652. doi: 10.1371/journal.pone.0118652.

Tauer, A., K. Hasenkopf, T. Kislinger, I. Frey, and M. Pischetsrieder. 1999. Determination of Nε-carboxymethyllysine in heated milk products by immunochemical methods. *European Food Research and Technology* 209 (1):72–6. doi: 10.1007/s002170050460.

Teodorowicz, M., W. H. Hendriks, H. J. Wichers, and H. F. J. Savelkoul. 2018. Immunomodulation by processed animal feed: The role of Maillard reaction products and advanced glycation end-products (AGEs). *Frontiers in Immunology* 9:2088. doi: 10.3389/fimmu.2018.02088.

Tessier, F. J., and I. Birlouez-Aragon. 2012. Health effects of dietary Maillard reaction products: The results of ICARE and other studies. *Amino Acids* 42 (4):1119–31. doi: 10.1007/s00726-010-0776-z.

Tessier, F. J., C. Niquet-Léridon, P. Jacolot, C. Jouquand, M. Genin, A.-M. Schmidt, N. Grossin, and E. Boulanger. 2016. Quantitative assessment of organ distribution of dietary protein-bound 13C-labeled Nε-carboxymethyllysine after a chronic oral exposure in mice. *Molecular Nutrition & Food Research* 60 (11):2446–56. doi: 10.1002/mnfr.201600140.

Thornalley, P. J. 1998. Cell activation by glycated proteins. AGE receptors, receptor recognition factors and functional classification of AGEs. *Cellular and Molecular Biology (Noisy-le-Grand, France)* 44 (7):1013–23. doi: 10.1038/sj.cdd.4400448.

Trevisan, A. J. B., D. de Almeida Lima, G. R. Sampaio, R. A. M. Soares, and D. H. Markowicz Bastos. 2016. Influence of home cooking conditions on Maillard reaction products in beef. *Food Chemistry* 196:161–9. doi: 10.1016/j.foodchem.2015.09.008.

Tuohy, K. M., D. J. S. Hinton, S. J. Davies, M. J. C. Crabbe, G. R. Gibson, and J. M. Ames. 2006. Metabolism of Maillard reaction products by the human gut microbiota-implications for health. *Molecular Nutrition & Food Research* 50 (9):847–57. doi: 10.1002/mnfr.200500126.

Uribarri, J., W. Cai, M. Peppa, S. Goodman, L. Ferrucci, G. Striker, and H. Vlassara. 2007. Circulating glycotoxins and dietary advanced glycation endproducts: Two links to inflammatory response, oxidative stress, and aging. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 62 (4):427–33. doi: 10.1093/gerona/62.4.427.

Uribarri, J., W. Cai, O. Sandu, M. Peppa, T. Goldberg, and H. Vlassara. 2005. Diet-derived advanced glycation end products are major contributors to the body's AGE pool and induce inflammation in healthy subjects. *Annals of the New York Academy of Sciences* 1043 (1):461–6. doi: 10.1196/annals.1333.052.

Uribarri, J., M. Peppa, W. Cai, T. Goldberg, M. Lu, S. Baliga, J. A. Vassalotti, and H. Vlassara. 2003. Dietary glycotoxins correlate with circulating advanced glycation end product levels in renal failure patients. *American Journal of Kidney Diseases: The Official Journal*

of the National Kidney Foundation 42 (3):532–8. doi: 10.1016/S0272-6386(03)00779-0.

Uribarri, J., S. Woodruff, S. Goodman, W. Cai, X. Chen, R. Pyzik, A. Yong, G. E. Striker, and H. Vlassara. 2010. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *Journal of the American Dietetic Association* 110 (6):911–6.e2. doi: 10.1016/j.jada.2010.03.018.

Vlassara, H., and G. E. Striker. 2010. Intake of advanced glycation end-products: Role in the development of diabetic complications. In *Principles of diabetes mellitus*, ed. L. Poretsky, 313–30. Boston, MA: Springer US.

Wang, Y., H. Liu, D. Zhang, J. Liu, J. Wang, S. Wang, and B. Sun. 2019. Baijiu vinasse extract scavenges glyoxal and inhibits the formation of N(epsilon)-carboxymethyllysine in dairy food. *Molecules* 24 (8):1526. doi: 10.3390/molecules24081526.

Wedzicha, B. L. 1992. Chemistry of sulphiting agents in food. *Food Additives and Contaminants* 9 (5):449–59. doi: 10.1080/02652039209374097.

Widjaja, S. S., Rusdiana, and M. Savira. 2018. CD4 and its relevance to advanced glycation end products in tuberculosis patients with co-morbidity diabetes. *Open Access Macedonian Journal of Medical Sciences* 6 (11):2115–8. doi: 10.3889/oamjms.2018.347.

Yacoub, R., M. Nugent, W. Cai, G. N. Nadkarni, L. D. Chaves, S. Abyad, A. M. Honan, S. A. Thomas, W. Zheng, S. A. Valiyaparambil, et al. 2017. Advanced glycation end products dietary restriction effects on bacterial gut microbiota in peritoneal dialysis patients; a randomized open label controlled trial. *PLoS One* 12 (9): e0184789. doi: 10.1371/journal.pone.0184789.

Zhang, G., G. Huang, L. Xiao, and A. E. Mitchell. 2011. Determination of advanced glycation endproducts by LC-MS/MS in raw and roasted almonds (*Prunus dulcis*). *Journal of Agriculture Food Chemistry* 59 (22):12037–46. doi: 10.1021/jf202515k.

Zhao, D., B. Sheng, Y. Wu, H. Li, D. Xu, Y. Nian, S. Mao, C. Li, X. Xu, and G. Zhou. 2019. Comparison of free and bound advanced glycation end products in food: A review on the possible influence on human health. *Journal of Agricultural and Food Chemistry* 67 (51):14007–18. doi: 10.1021/acs.jafc.9b05891.

Zheng, F., C. He, W. Cai, M. Hattori, M. Steffes, and H. Vlassara. 2002. Prevention of diabetic nephropathy in mice by a diet low in glycoxidation products. *Diabetes/Metabolism Research and Reviews* 18 (3):224–37. doi: 10.1002/dmrr.283.

Zhou, X., N. Lin, M. Zhang, X. Wang, Y. An, Q. Su, P. Du, B. Li, and H. Chen. 2020. Circulating soluble receptor for advanced glycation end products and other factors in type 2 diabetes patients with colorectal cancer. *BMC Endocrine Disorders* 20 (1):170. doi: 10.1186/s12902-020-00647-9.

Zieman, S. J., and D. A. Kass. 2004. Advanced glycation end product cross-linking: Pathophysiologic role and therapeutic target in cardiovascular disease. *Congestive Heart Failure (Greenwich, Conn.)* 10 (3): 144–51. doi: 10.1111/j.1527-5299.2004.03223.x.