Studies in Natural Products Chemistry

Atta-ur-Rahman, FRS
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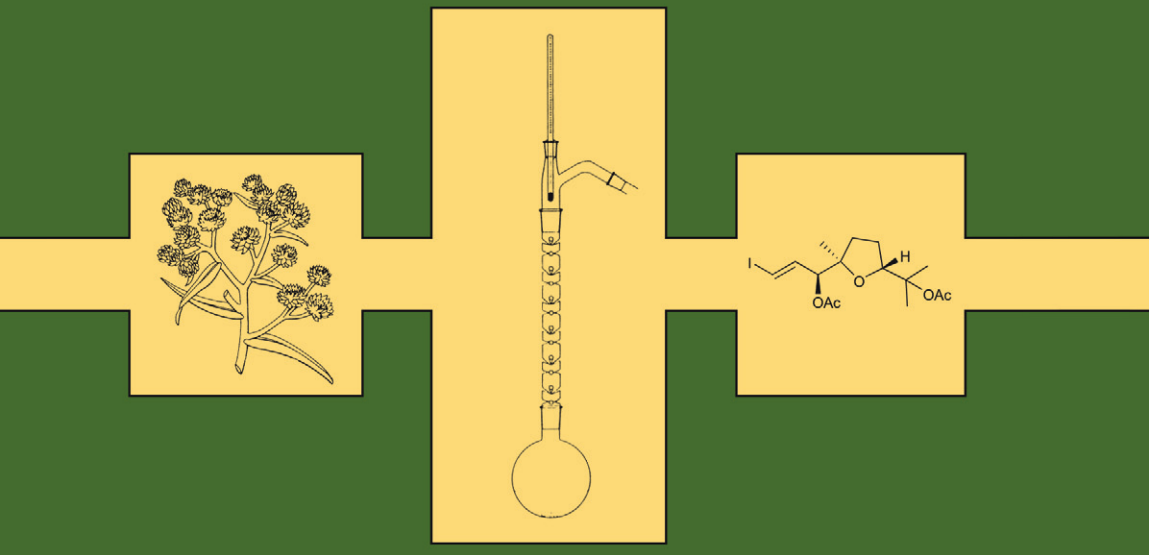

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Chapter 9

Natural inhibitory compounds of advanced glycation end products (AGEs) from the Maillard reaction

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Introduction

In 1912, the French biochemist Louis-Camille Maillard published an article in which the reaction between glycine and glucose was described, which produced a discoloration or browning during heating. This reaction has been recognized as the Maillard reaction (MR) and has become an important member of the nonenzymatic browning reactions that occur in foods and beverages, as well as in the paper, textile, and biopharmaceutical industries [1,2]. During MR, different low molecular weight products such as aldehydes, ketones, dicarbonyls, acrylamides, heterocyclic amines, advanced glycation end products (AGEs), and high molecular weight products such as melanoidin's can be formed. Recently, there is an increased concern and interest in

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MRPs, specifically AGEs, and their effects on the consumer since these are abundantly contained in foods [2,3].

AGEs were identified from MR between reducing sugars and cooked food proteins; however, this reaction also occurs in vivo, and AGEs have been reported to play an important role in the pathophysiology of many chronic diseases [4]. Therefore, it is believed that protein glycation in humans generates intermediates derived from carbohydrates and lipids that produce changes in the functional properties of proteins, lipids, and DNA, thus generating long-term complications in diabetes mellitus, atherosclerosis, kidney failure, and Alzheimer's disease [5]. These same changes may be linked to the production of reactive oxygen species (ROS) that are formed from the glycation of proteins and the formation of AGEs, which are very harmful to cells and their metabolism [6]. There are receptors for AGEs in the cells of the human body, and one of the main ones is the receptor for AGEs (RAGE). The interaction between AGEs and RAGE causes the activation of this receptor and the release of ROS and proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL) 1, and 6, leading to oxidative stress and cellular inflammation [7].

On the other hand, drugs capable of inhibiting the formation of AGEs such as aminoguanidine, carnosine, metformin, and pyridoxamine have been implemented. However, aminoguanidine administered to diabetic patients has been seen to cause side effects such as vitamin B6 deficiency [8]. For this reason, the search for natural compounds that can inhibit the formation of AGEs as plant antioxidants and active ingredients has recently increased [9]. Examples of this are polyphenols [10], flavonoids [11], fatty acids [12], and plant extracts [13]. In addition to those compounds or extracts that are capable of blocking or suppressing the AGE-RAGE interaction [14,15]. Based on the above, this chapter aims to show the main recent studies on natural compounds obtained from plants and other natural products where their ability to inhibit AGEs in vitro in protein-carbohydrate model systems and in vivo has been demonstrated, as well as the RAGE receptor inhibition.

Maillard reaction and AGEs (description, formation, and quantification)

MR is a nonenzymatic type of reaction that is catalyzed by heat. This leads to the generation of dark pigments, flavors, and odors related to the cooking, storage, and nutritional value of foods, especially those with high protein content [16]. After the investigation published by Maillard in 1912, a more detailed description of this phenomenon emerged by Hodge in 1953 [17], which is widely accepted in the literature and is displayed in Fig. 9.1. The reaction has been generally divided into three stages: initial, intermediate, and advanced. In the initial stage, the carbonyl group of a reducing sugar such as glucose is covalently bonded to a free amino group from an amino acid or

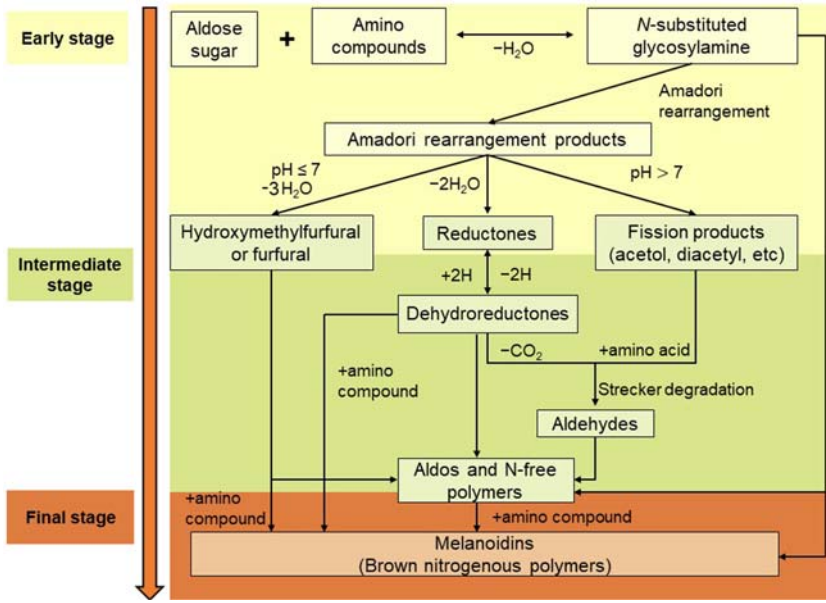

FIGURE 9.1 General scheme of the Maillard reaction. The stages of the MR is divided by colored boxes. *Illustration adapted from J.E. Hodge, J. Agric. Food Chem. 1 (1953) 928–943.*

protein to form an imine or Schiff base bond (*N*-substituted glycosylamine), which undergoes a conformational change to form the Amadori rearrangement product (ARP). In the intermediate stage, the ARP is transformed depending on some factors, such as pH and temperature. At pH $\leq$ 7, 1, 2-enolization predominates, transforming into furfural or hydroxymethylfurfural. At pH $>$ 7, 2, 3-enolization predominates, giving rise to the Strecker degradation, where fission products such as acetol, pyruvaldehyde, and diacetyl are formed, which are highly reactive carbonyls and condense with free amino groups, giving rise to aldehydes and α-aminoacetones. In the final stage, complex reactions such as condensations, cyclizations, rearrangements, isomerizations, and dehydrations occur that bring about the formation of brown nitrogenous polymers known as melanoidins [18,19].

It can be noted that during the MR the aforementioned MRPs originate, which are usually used to describe the nonenzymatic browning reaction in foods or model systems, while the AGEs are also described from the MR and are used to refer to those produced in living organisms, where the origin of the reaction is known as glycation. Although there is confusion because some authors use the terms MR and glycation and MRPs and AGEs as synonyms [20]; however, in general terms, AGEs are part of all MRPs starting from MR.

A particular interest in glycation and AGEs was initiated when the glycation of human hemoglobin (HbA1c) was described. This is elevated in the blood when there are hyperglycemic conditions, and its measurement is used to control diabetes mellitus [21]. The glycation of proteins in the human organism gives them changes in their structure and functionality. In addition to hemoglobin, other glycation target proteins include immunoglobulin G (IgG), human serum albumin (HSA), and collagen. The main consequences of their glycation are complications in rheumatoid arthritis in the case of IgG, while HSA, which is considered to be very susceptible to glycation, is also used as an indicator of hyperglycemia, and collagen suffers deterioration, stiffness, and the formation of cross-linking of protein chains [22]. Due to protein glycation, AGEs are produced in the human body, generating oxidative stress and inflammation, as well as other damages [23].

Exogenously, AGEs can be obtained through the diet, with the preparation of baked, cooked, or fried foods at high temperatures and long cooking times. While the endogenous form is also produced with protein glycation, but in a slower way [24]. More than 20 AGEs have been identified in blood and tissue samples, as well as food. These have been classified into different groups due to their chemical structures and the ability to fluoresce and cross-link [25]. The classification mainly consists of three groups: (1) Fluorescent and cross-linked AGEs; (2) nonfluorescent and cross-linked AGEs; and (3) nonfluorescent and noncross-linked AGEs [26].

Pentosidine is one of these types of AGE integrating group 1, this is found in skin collagen, and its concentration increases with age. It is formed by the glycation of lysine and arginine residues in proteins [27]. Similarly, the glyceraldehyde-derived pyridinium compound is formed by glyceraldehyde with lysine, which causes the generation of ROS and increased concentrations have been reported in plasma, tail collagen, and brain of diabetic rats compared to nondiabetic rats [28,29]. Other examples of fluorescent and cross-linked AGEs are pentodilysine, crossline, AGE-XI, vesperlysine A, and vesperlysine C [25], which can be seen in Fig. 9.2. In group 2, some AGEs can be mentioned, such as those that contain in their chemical structure the imidazolium dilysine group and are cross-linked. These are known as glyoxal-lysine dimers, formed by the reaction between glyoxal (GO) and two lysine molecules, as well as methylglyoxal-lysine dimer formed by the reaction of methylglyoxal (MGO) and two lysine molecules. Other AGEs within this group are imidazolium cross-link derived from glyoxal and lysine-arginine (GODIC) and imidazolium cross-links derived from methylglyoxal and lysine-arginine (MODIC). GODIC is formed by the reaction of GO, and two lysine molecules, and MODIC is formed by the reaction of MG and protein residues of lysine and arginine [19,25,26,30]. Another compound within this group is alkyl formyl glycosyl pyrroles, which are formed by the reaction between two sugar molecules and lysine molecule [26]. Also, glucosepane is nonoxidatively originated from glycated lysine residues and is the most

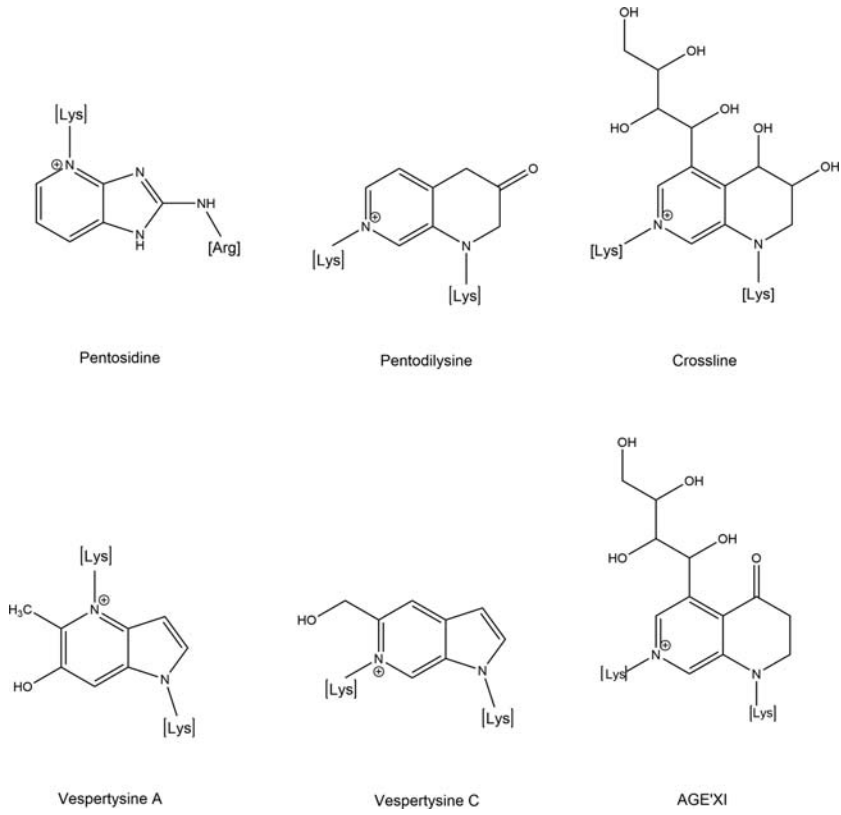

FIGURE 9.2 Examples of AGEs fluorescents and cross-linked.

abundant cross-linking AGE in the extracellular matrix, giving structural changes to tissues in aging and diabetes [31,32]. The AGEs mentioned in this group can be visualized in Fig. 9.3.

Within group 3, the main nonfluorescent and noncrosslinked AGEs are *N*-carboxymethyl-lysine (CML), *N*-carboxyethyl-lysine (CEL), and pyrraline [25]. CML is one of the main AGEs found in vivo and in food. It is formed by the reaction of the epsilon amino group of lysine with GO. It is also caused by the oxidative disintegration of ARP and is found in high concentrations in the collagen and serum of diabetic patients. CEL is formed by the reaction of MGO and lysine, while pyrraline is formed by the reaction of 3-deoxyglucosone (3-DG) and lysine [26,30]. AGEs mentioned in this group can be visualized in Fig. 9.4.

Something important to note is that reducing sugars are not the only molecules that contribute to the formation of AGEs via protein glycation.

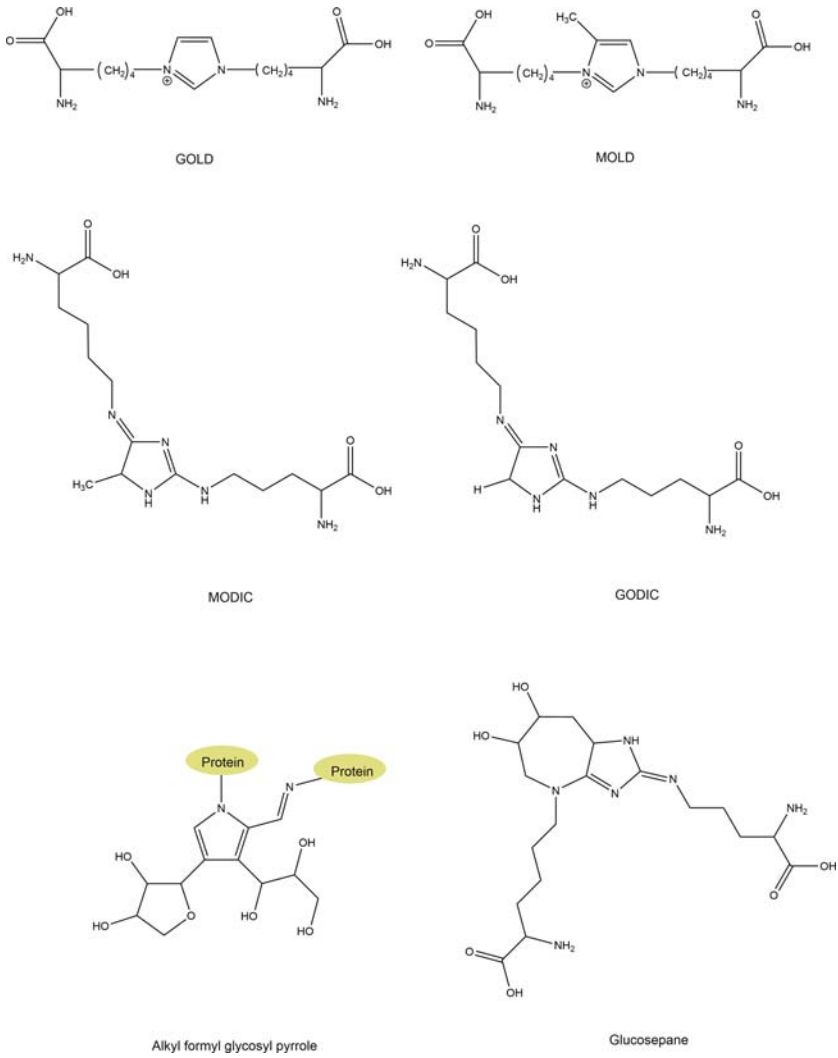

FIGURE 9.3 Examples of AGEs fluorescents and noncrosslinked.

Other molecules, such as α-dicarbonyls, that are highly reactive can react with ARP and proteins.These molecules can be referred as intermediate glycation products (IGPs). These are GO, MGO and 3-DG, as mentioned above. Other IGPs are free glycolaldehyde, 1-deoxyglucosone (1-DG), 4,5-dioxopentose, and 5,6-dioxohexose [33,34]. One of the most studied IGPs is MGO, which can be formed in cells by various mechanisms, mainly as a byproduct of glycolysis through the spontaneous degradation of glyceraldehyde-

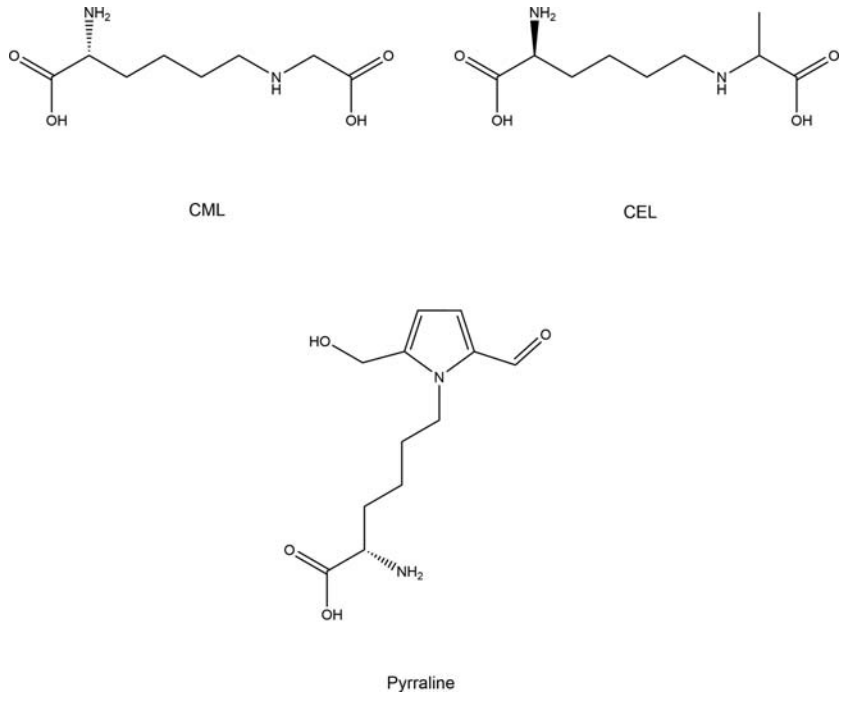

FIGURE 9.4 Examples of AGEs nonfluorescents and noncrosslinked.

3-phosphate and dihydroxyacetone phosphate. In addition, it can be formed by the catabolism of threonine, the oxidation of ketone bodies (acetone), lipid peroxidation, and the degradation of glycosylated proteins [33]. These mentioned IGPs can be visualized in Fig. 9.5.

In addition to AGEs, other advanced MR products called advanced lipoxidation end products (ALEs) can be formed. These are generated when the products of lipid peroxidation react with proteins. The group of ALEs can include some covalent adducts generated by the nonenzymatic reaction of carbonyl species such as IGPs, which, being produced by lipid peroxidation and metabolism, can react with the nucleophilic residues of proteins, DNA, and aminophospholipids. Some AGEs and ALEs have the same chemical structure since they arise from common precursors but from different pathways, such as the formation of CML, generated by GO, which in turn is formed by the oxidative degradation of lipids and sugars [32]. AGEs and ALEs contribute to the aging and dysfunction of tissue and plasma proteins. The levels of these compounds are increased in chronic diseases such as diabetes, atherosclerosis, liver disease, and neurodegenerative diseases [35]. Therefore,

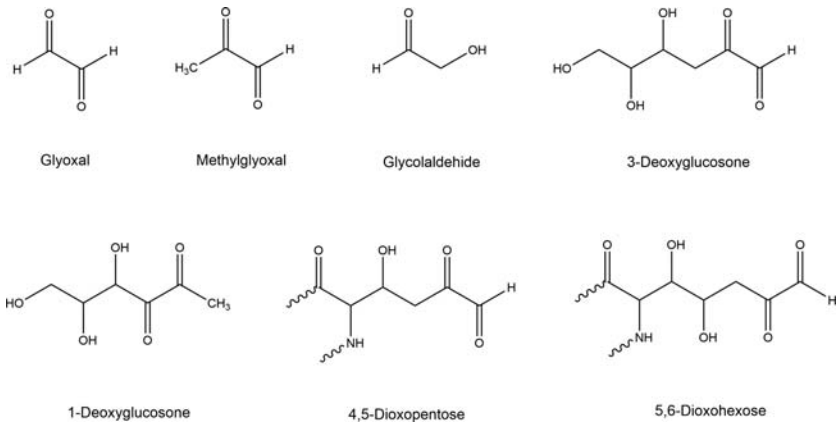

FIGURE 9.5 Examples of intermediate glycation products.

the study of ALEs and their inhibition is also interesting; however, in this chapter, only the inhibition of AGEs is described.

On the other hand, it should be noted that CML is one of the most studied and referenced AGEs in the literature. CML is considered a marker to assess a diet rich in MRPs/AGEs, or conditions of oxidative stress and/or inflammation. However, such effects can be attributed to it, but it is not as reactive as other unstable AGEs [20]. CML has also been used as a biomarker to measure microvascular complications in type 2 diabetes mellitus [36], as well as a biomarker of AGEs from processed food products [37]. In addition, there has been an increased interest on the study of other types of AGEs such as toxic AGEs (TAGE), which are formed between the reaction of glyceraldehyde and intracellular proteins. The generation and accumulation of intracellular TAGE leads to cell damage in neurons, hepatocytes, cardiomyocytes, myoblasts, pancreatic, and endothelial cells. Also, TAGE increases the risk of chronic diseases such as diabetes mellitus, Alzheimer's, and cardiovascular diseases; in addition, TAGE has also been used as a biomarker for these diseases [38,39]. In this sense, it is important to highlight the synergy that can occur with dietary and endogenous AGEs and TAGE, which can promote cell activation, tissue disorders, and therefore damage to health [39,40].

Instrumental methods or immunochemical assays have been highlighted to identify AGEs as well as measure their concentrations in different samples of food, serum, and plasma from patients with some chronic diseases linked to AGEs. Those that identify and quantify CML in different matrices are also highlighted. Instrumental analytical methods include high-performance liquid chromatography (HPLC), gas chromatography coupled with mass spectrometry (GC-MS), liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS), and ultrahigh-pressure liquid chromatography. The HPLC

method is reverse-phase and can include detectors such as diode array detectors (DAD), fluorescence, and tandem mass spectrometers (MS/MS). For the identification of CML by HPLC or GC, derivatization is necessary. Therefore, the most suitable method is LC-MS/MS since it gives greater sensitivity and does not require derivatization of the sample. On the other hand, the competitive enzyme-linked immunosorbent assay (ELISA) is also used to identify CML. This technique is widely used and uses an antiCML monoclonal antibody. Results are expressed as kunits/100 g of food, while LC-MS/MS results are usually expressed as mg/kg protein or food. Therefore, it is difficult to compare both methods [41,42].

AGEs receptors and action mechanism

The main receptor for AGEs and the one most extensively studied is RAGE. This belongs to the group of pattern recognition receptors, which, apart from AGEs, can also recognize other ligands such as S100 proteins, high mobility group box-1 protein, β2-integrin, macrophage 1 antigen, CD11b, amphoterins, β-amyloids, among others. RAGE is made up of three domains and belongs to the immunoglobulin family. It contains two constant domains (C1 and C2 regions) and one variable domain (V region), in addition to a transmembrane domain and a cytoplasmic domain. When AGEs or other ligands bind to RAGE, it triggers inflammation and pathogenesis in various diseases [43,44].

When the AGE-RAGE interaction occurs, ROS are produced through the NADPH oxidase pathway and start the activation of intracellular signaling cascades such as those of extracellular signal-regulated kinase (ERK) 1,2/mitogen-activated protein kinase (MAPK), Janus kinase (JAK)/signal transducer and activators of transcription (STAT), stress-activated protein kinases/c-Jun *N*-terminal kinase (JNK)/MAPK, protein kinase B, phosphoinositide 3-kinase, caspase-3/7, transforming growth factor beta (TGF-β)-Smad, p21-ras, and cdc42/rac [44]. In addition, this interaction can activate the p21 protein, also causing intracellular signaling with the stimulation of the same ERK, JNK, MAPK, and JAK/STAT pathways. This finally leads to the activation of transcription factors such as NF-κB and therefore to the synthesis of proinflammatory cytokines such as TNF-α, IL-1, 6, and 17, as well as vascular cell adhesion molecule-1. This AGE-RAGE activation mechanism can be visualized in Fig. 9.6 [45].

AGE receptors, including RAGE, are expressed on numerous cell types, including monocytes, macrophages, podocytes, tubular epithelial cells, endothelial cells, mesangial cells, astrocytes, microglia, and smooth muscle cells [46]. RAGE is composed of 404 amino acids and has a molecular mass of ∼55 kDa. It is expressed by the human RAGE gene (or referred to as advanced glycation end products receptor (AGER)) and is located at 6p21.3 in the region of the major histocompatibility complex class III, which contains 11 exons intertwined by 10 introns. Nineteen RAGE splicing variants have been

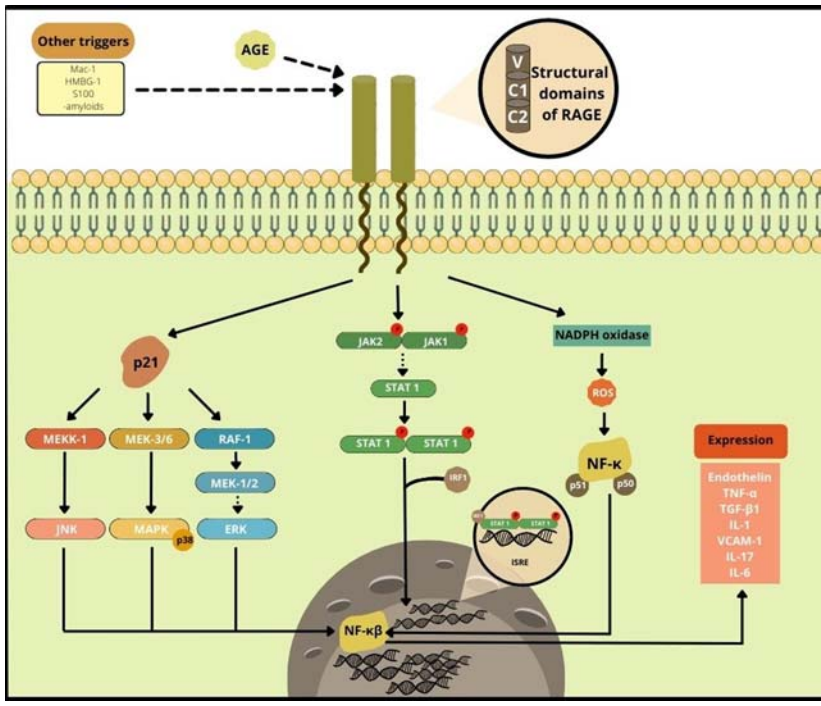

FIGURE 9.6 Cellular signaling pathways derived from the activation of RAGE through AGEs and other triggers. *Illustration adapted from J. Salazar et al., Int. J. Environ. Res. Public Health 18 (2021) 1−24.*

identified that also produce RAGE proteins (sRAGE1, sRAGE2, and sRAGE3, among others). RAGE can undergo proteolytic cleavage and circulate as soluble RAGE (sRAGE) or endogenous secretory RAGE both isoforms have not been fully elucidated [47]. There are also other variants such as dominant-negative RAGE and N-truncated RAGE [46].

Other AGE receptors besides RAGE have been reported. Some of them are macrophage scavenger receptors I and II, oligosaccharyl transferase complex protein 48, or AGER receptor 1, 80 K−H protein (AGER2), galectin-3 (AGER3), and some scavenger receptors. One of the most studied is AGER1, which is a transmembrane protein found in almost all cells and tissues of the human body. The particular interest about AGER1 is that it is believed to help in the removal of AGEs by facilitating their absorption and elimination. Furthermore, it can counteract oxidative stress and inhibit the production of NF-κB generated by the effects of RAGE [42,48]. In patients with type 2 diabetes mellitus, AGER1 is decreased, as is SIRT1, a member of sirtuin that cooperates to regulate insulin levels [49].

Natural compounds AGEs inhibitors: in vitro studies

Throughout history, humans have used plants for the treatment and prevention of various diseases. Currently, there is a growing interest in medicinal plants and phytochemicals with pharmacological properties since conventional treatments can have a high cost, secondary effects, and therapeutic limitations [50]. Therefore, natural plant compounds can be considered viable alternatives in the treatment of diabetes and chronic diseases. In this sense, the study of natural compounds capable of inhibiting AGEs or with antiglycation properties is a therapeutic target in complications of chronic diseases [51,52].

In vitro AGE inhibition assays are generally based on protein-carbohydrate model systems. The most commonly used and accepted protein model is bovine serum albumin (BSA) and to a lesser extent with HSA. BSA is made up of 585 amino acids, has a molecular weight of 66.28 kDa, and has 76% homology to HSA. It is made up of three domains (I, II, and III), each of which is divided into subdomains A and B. The secondary structure of BSA is mainly made up of alpha-helical chains (67%) and 17 disulfide bonds give it the tertiary structure at neutral pH and room temperature [53]. On the other hand, the main carbohydrates used in the model systems are simple reducing sugars such as glucose, fructose, lactose, ribose, arabinose, rhamnose, and even α-dicarbonyls such as MGO and GO. The glycation of BSA or HSA with some of these carbohydrates is carried out at physiological conditions of pH 7−7.4 with phosphate buffer, a temperature of 37 °C, and incubation times ranging from 5 to 45 days. Measurement of AGE inhibition can be done by quantifying CML by ELISA or a chromatographic method or by measuring fluorescence with an excitation wavelength of 335−370 nm and an emission wavelength of 385−440 nm, respectively [11−13,51,52,54].

Plant extracts have been extensively studied for inhibiting the formation of AGEs in model systems. These extracts can be obtained from various organic or aqueous solvents as well as with different extraction methods. These can range from conventional methods such as liquid-liquid, solid-liquid, and Soxhlet extraction to some modern unconventional methods such as supercritical fluid extraction, microwave-assisted extraction, pressurized solvent extraction (PSE), ionic liquid extraction, and ultrasound-assisted extraction [55]. Extracts rich in bioactive compounds such as polyphenols, carotenoids, flavonoids, and alkaloids that have positive effects on health can be obtained from these techniques [56]. Some works on the inhibition of AGEs with plant extracts are presented in Table 9.1.

Some studies, such as those by Séro et al. [71], demonstrated fluorescence-based inhibition of AGEs (vesperlysine and pentosidine type AGE) with 22 aqueous and ethanolic extracts from various herbs and tea samples. The extracts were made with PSE, and the model system was BSA-ribose. It is noteworthy that the ethanolic extract of Quinquina showed the lowest IC_{50} value, which was 0.1 mg/mL, in the inhibition of vesperlysine and pentosidine

TABLE 9.1 Plant extracts and their main inhibitory compounds of AGEs in protein-carbohydrate model systems (studies in vitro).

Plant	Main solvents for extraction and methods	Main compounds characterized and method	AGEs formation conditions	Main result of inhibition of AGEs and method	References
Garcinia mangostana air-dried fruit	Methanol, chloroform with column eluted using water and gradient of methanol/water	Garcimangosone D Aromadendrin-8-C glucopyranoside Epicatechin 2,3′,4,5′,6-pentahydroxybenzophenone HPLC-DAD	BSA-glucose and ribose at pH 7.4, 37°C for 4 weeks Control (+): AG	93% and 77% of inhibition at 1000 μg/mL for glucose and ribose, respectively Fluorescence 88% and 75% of inhibition at 1000 μg/mL for glucose and ribose, respectively. CML by ELISA	[57]
Annona muricata Linn. dried leaves	Ethanol, solubilized in methanol:water solution (9:1, v/v) and subjected to LLE, with different solvents: hexane, dichloromethane, ethyl acetate, n-butanol and water	Chlorogenic acid Caffeic acid Procyanidins B2 and C1 Epicatechin Quercetin Kaempferol HPLC-ESI-MS/MS	BSA-fructose and MGO at pH 7.4, 37°C for 72 h. Also, arginine-MGO at same conditions Control (+): Q	Ethyl acetate fraction, $IC_{50} = 45.7 \pm 13.5$ μg/mL for BSA-fructose assay Hexane fraction, $IC_{50} = 325.9 \pm 46.7$ μg/mL for BSA-MGO assay Ethyl acetate fraction, $IC_{50} = 437.9 \pm 89.0$ μg/mL for arginine-MGO assay Fluorescence	[58]

Olive leaves	Water and methanol	Luteolin Hhydroxytyrosol Luteolin-4′-O-β-D-glucopyranoside Luteolin-7-O-β-D-glucopyranoside Oleuropein LC-MS	BSA-ribose and fructose at pH 7.4, 37°C for 3 and 21 days Control (+): AG	43.07% of inhibition for methanol extract at 100 μg/mL in BSA-ribose assay Fluorescence	[59]
Siraitia grosvenorii fruit	Mogroside extract (solvents and conditions are not described)	Mogrosides Method is not described	BSA-glucose and at pH 7.4, 37°C for 4 weeks Control (+): AG	58.5% of inhibition at 500 μg/mL Fluorescence 71.2% of inhibition at 500 μg/mL CML by ELISA	[60]
Hippophae rhamnoides L. leaves and berries	Ethanol using UAE and heating	Sophoroside-7-rhamnoside UPLC-MS	BSA-fructose at pH 7.4, 37°C for 7 days Control (+): AG	72.2% of inhibition at 200 μg/mL of extract leaves Fluorescence	[61]
Trapa bispinosa Roxb.	Water	Compounds and method are not described	HSA-glucose at pH 7.4, 60 °C for 30 h Control (+): AG	$IC_{50} = 2.53$ μg/mL Fluorescence $IC_{50} = 12.76$ μg/mL CML by ELISA	[62]
Hordeum vulgare	Water, methanol, n-hexane, dichlorometane and ethyl acetate	α-tocopherol LC-MS and GC-MS	BSA-glucose at pH 7.4, 37°C for 2 weeks Control (+): R	72.52 ± 0.35% of inhibition at 2 mg/mL for n-hexane extract Fluorescence	[63]
Fagopyrum tataricum seeds	Ethanol	Rutin Quercetin	BSA-fructose at pH 7.4 and	>80% of inhibition at 200 μg/mL Fluorescence	[64]

Continued

TABLE 9.1 Plant extracts and their main inhibitory compounds of AGEs in protein-carbohydrate model systems (studies in vitro).—cont'd

Plant	Main solvents for extraction and methods	Main compounds characterized and method	AGEs formation conditions	Main result of inhibition of AGEs and method	References
		Quercetin-3-glucoside HPLC with UV detector	50°C Control (+): AG		
Tribulus terrestris	Chloroform and ethanol for Soxhlet	Gitogenin Protodioscin Diosgenin HPLC-DAD	BSA-ribose at pH 7.4 and 37°C for 72 h Control (+): AG	70% of inhibition at 1000 μg/mL Fluorescence	[65]
Trichilia catigua leaves *Turnera diffusa* bark	Extracts of H_2O	Phenolic acids Catechins Flavonolignans Luteolin HPLC-DAD	BSA-glucose, fructose and MGO at pH 7.4 and 37°C for 14 days Control (+): AG	~90% of inhibition at 133 μg/mL ~80% of inhibition at 133 μg/mL Fluorescence	[66]
Pterocarpus marsupium heart wood *Artocarpus lakoocha* bark	Don't described, supplement comercial	Pterostilbene Oxyresveratrol HPLC-MS	BSA-glucose at 60°C Control (+): not mentioned	84.6% of inhibition at 100 mg/mL 100% of inhibition at 10 and 100 mg/mL Fluorescence	[67]
Cocos nucifera L. husk fibers	Ethanol	Quercetin Vanillic acid Caffeic acid	BSA-glucose and fructose at pH 7.4 and	$IC_{50} = 9.61 \pm 1.15$ μg/mL Fluorescence	[68]

		4-hydroxybenzoic Chlorogenic acid Epicatechin Catechin HPLC and UHPLC-MS/MS	37°C for 7 days Control (+): AG		
Diospyros lotus Linn. roots	Methanol fractioned with other solvents: n-hexane, chloroform, ethyl acetate, butyl alcohol, and with chromatographic columns	Di-naphthodiospyrols A–G 8-hydroxyisodiospyrin Diospyrin TLC	BSA-MGO at pH 7.4 and 37°C for 9 days Control (+): R	$IC_{50} = 190.09 \pm 2.03$ μM for di-naphthodiospyrols D Fluorescence	[69]
Micromeria biflora aerial parts	Methanol with Soxhlet	Salicylalazine TLC	BSA-MGO at pH 7.4 and 37°C for 9 days Control (+): R	86.4% of inhibition $IC_{50} = 248.7 \pm 2.09$ μM Fluorescence	[70]

Abbreviations: *AG*, aminoguanidine; *AGEs*, advanced glycation end products; *BSA*, bovine serum albumin; *CML*, *N*-carboxymethyl-lysine; *ELISA*, enzyme-linked immunosorbent assay; *GC-MS*, gas chromatography coupled with mass spectrometry; *HPLC-DAD*, high performance liquid chromatography with diode array detector; *HPLC-ESI-MS/MS*, high performance liquid chromatography electrospray ionization tandem mass spectrometry; *HPLC-MS*, high performance liquid chromatography with mass spectrometry; *HSA*, human serum albumin; IC_{50}, inhibitory concentration at 50%; *LC-MS*, liquid chromatography coupled with mass spectrometry; *LLE*, liquid-liquid extraction; *MGO*, methylglyoxal; *Q*, quercetin; *R*, rutin; *TLC*, thin layer chromatography; *UAE*, ultrasound-assisted extraction; *UHPLC-MS/MS*, ultrahigh performance liquid chromatography with tandem mass spectrometer; *UPLC-MS*, ultraperformance liquid chromatography with mass spectrometer; *UV*, ultraviolet.

compared to the other extracts evaluated. They also showed that quercetin, evaluated separately, has a greater inhibition effect, presenting an IC_{50} of 0.06 mg/mL in both assays.

Another study reported as the one by Packirisamy et al. [72], demonstrated the antiglycation effect of methanolic extracts of *Coccinia grandis* (L.). This effect was based on fluorescence in the BSA-fructose model system, and they obtained a decrease in fluorescence at 1, 2, 3, and 4 weeks compared to the control. This indicates that reducing fluorescence inhibits the formation of AGEs, and this effect is attributed to the high amount of polyphenols, flavonoids, and saponins in the extract. Similarly, Vasarri et al. [73] demonstrated the antiglycation effect with hydroalcoholic extracts of *Posidonia oceanica* (L.) *Delile* by fluorescence in the HSA-glucose model system. They also found reduced fluorescence in the presence of their extract compared to the control. However, they glycated HSA at 60°C and not at 37°C, arguing that similar results were obtained at both temperatures but in shorter times at 60°C.

Moe et al. [74] reported the antiglycation effect with medicinal plants from Myanmar, where they obtained ethanolic extracts and evaluated them in a BSA-fructose model system where they measured fluorescence. They reported that *Garcinia mangostana* extract Linn. showed a high percentage of inhibition in the formation of AGEs (82.37% ± 1.78%). In the same way, Chiung-Tsun et al. [75] used various solvents to obtain extracts from *Canarium album* L. and demonstrated the antiglycation effect. They used a BSA-glucose model system and measured glycation by fluorescence. They reported that the aqueous/ethanolic extract 1:1 showed a higher percentage of inhibition around 30% and mentioned that the result is attributed to the content of polyphenols and flavonoids that also showed an antioxidant effect by inhibiting the radical 2,2-diphenyl-1-picrylhydrazyl by 77.98 ± 0.92%.

Spagnuolo et al. [76] reported polyphenols in hazelnut skin extracts that inhibit the formation of AGEs. They measured fluorescence in a BSA-MGO model system and obtained an IC_{50} of 109.7 μg/mL in their extract, which is much lower than the individual compounds tested (gallic acid and aminoguanidine). They suggested that greater efficiency in bioactivity is obtained within a group of molecules rather than with a single purified one. Similarly, Suantawee et al. [77] inhibited glycation with aqueous extracts of *Syzygium aromaticum* (L.). They used a BSA-fructose model system, from which they measured fluorescence and CML by ELISA. They reported up to 95.2% inhibition with a concentration of 1 mg/mL of the extract. Furthermore, CML formation was inhibited by 59.2% with the same extract concentration. A possible mechanism was also mentioned in the inhibition of the formation of AGEs which could be through the elimination of ROS during the autoxidation of the carbohydrate and/or oxidative degradation of the Amadori product promoted by the extract.

In addition to the use of plant extracts, there has also been an interest in demonstrating the inhibition of AGEs with specific natural compounds, such

as polyphenols. These are compounds with biological activity, such as improving insulin resistance, glucose assimilation tolerance, and antiinflammatory effects. They can be obtained through the human diet due to the consumption of plant-based foods where they are present, such as vegetables, colorful fruits, coffee, tea, wine, and medicinal herbs. Polyphenols can be classified into three groups: flavonoids, nonflavonoids, and phenolic acids [78].

Currently, there are more than 8000 polyphenol structures, and more than 4000 of them belong to the flavonoid group. Most plant polyphenols are found as glycosides, that is, attached to different sugars at different positions on the polyphenol backbone. Flavonoids have a general structure in their skeleton of C6−C3−C6, of which the C6 units (ring A and ring B) are benzene rings that may or may not be hydroxylated [79]. Flavonoids are subdivided into classes such as flavonols, flavones, anthocyanidins, anthocyanins, flavones, and isoflavones. While the nonflavonoids are mainly stilbenes and lignans, resveratrol and pinoresinol are examples of compounds from those groups, respectively. Phenolic acids can be subdivided into benzoic acid derivatives, such as gallic acid and protocatechuic acid, and cinnamic acid derivatives, including coumaric, chlorogenic, caffeic, and ferulic. Other polyphenols are tannins, coumarins, and curcuminoids [79,80]. A scheme for the classification can be visualized in Fig. 9.7.

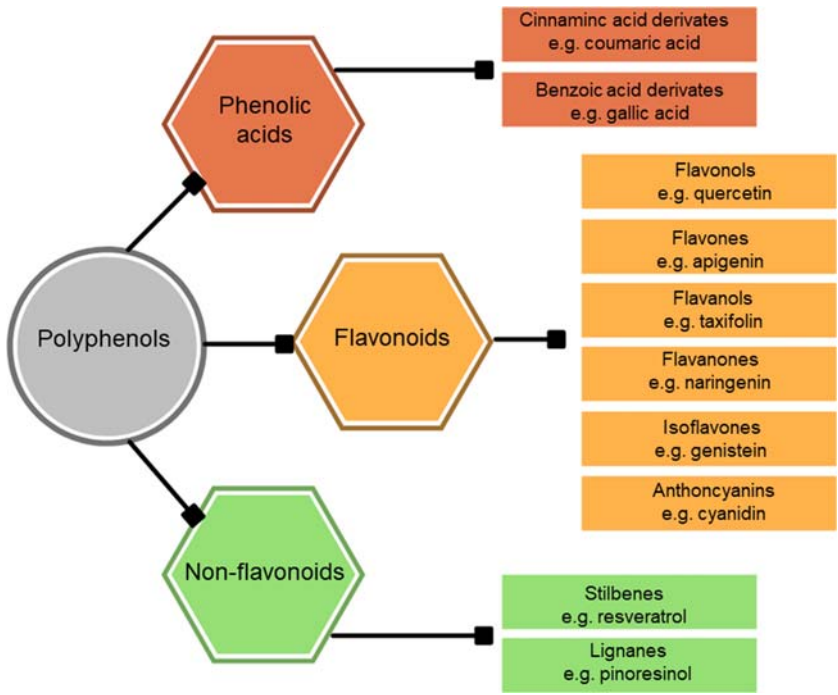

FIGURE 9.7 Polyphenols classification general scheme.

In addition to polyphenols, other natural compounds have demonstrated an antiglycation and/or inhibitory effect on the generation of AGEs. Some examples of compounds are fatty acids, alkaloids, vitamins, terpenes, polysaccharides, and even peptides. Examples of AGE inhibition assays with the above compounds are described in Table 9.2.

The study of Bhuiyan et al. [105] can be highlighted among the studies of polyphenols summarized in Table 9.2. In that study, 14 different polyphenols were evaluated to assess their antiglycation effect in BSA-ribose, glucose, and MGO model systems and supplemented with physiological concentrations of Cu^{2+}, Zn^{2+}, and Mg^{2+} ions to determine their impact on the generation of AGEs. They reported that the flavonoid quercetin inhibited the MGO system, while other polyphenols such as catechins, gallic acid, and isoflavones did so for the ribose and glucose systems. They demonstrated the antiglycation effects of the polyphenols employed by metal chelation, MGO trapping, and ROS trapping. Another study like that of Meeprom et al. [106], used isoferulic acid to inhibit the formation of fluorescent AGEs and CML in BSA-glucose and fructose model systems. They reported inhibition by fluorescence of 71.4% and 73% at a concentration of 5 mM in BSA-fructose and glucose model systems, respectively. While in the case of CML, it was measured by ELISA and reported 47% and 21.9% inhibition at the same concentration in BSA-glucose and fructose model systems, respectively.

Wang et al. [107] demonstrated antiglycation of lyophilized epigallocatechin gallate (EGCG) and its derivatives esterified with aliphatic fatty acids. They developed a BSA-glucose model system and measured fluorescence and CML by ELISA. They reported that EGCG inhibited around 60% of the generation of fluorescent AGEs and 70% of CML formation. They also mention that EGCG esters with acetic acid and saturated fatty acids with 6, 8, 12, and 18 carbons showed slightly greater inhibition than EGCG and significant differences between them. While esters did not show significant differences in CML inhibition compared to EGCG. Another study by Liu et al. [108] used the flavones eriodictyol and naringenin to inhibit AGEs in the BSA-MGO model system by fluorescence. Eriodictyol and naringenin, both at concentrations of 200 μM, were able to inhibit AGEs by 39.04% and 29.69%, respectively. In addition, molecular docking analysis showed that eriodictyol presented an affinity energy of −8.96 kcal/mol as well as two hydrogen bond interactions in the amino acids Lys350 and Leu480 of BSA, explaining the greater inhibitory activity of AGE than naringenin due to the hydroxyl group in the position C-3′ of the B ring.

Shen et al. [109], used resveratrol to inhibit AGEs in the BSA-fructose, MGO, and arginine-MGO model systems. Measuring fluorescence, resveratrol presented a maximum inhibition of $57.94 \pm 0.10\%$ at a concentration of 300 μg/mL in the BSA-fructose system, while in the BSA-MGO system they obtained $85.95 \pm 6.61\%$ inhibition at the same concentration. For the model system, arginine-MGO at the same concentration inhibited approximately

TABLE 9.2 Natural compounds inhibitory of AGEs in protein-carbohydrate model systems (studies in vitro).

Natural compound	Used concentration	AGEs formation and conditions	Main result of AGEs inhibition and method	References
Gallic acid Ascorbic acid	1.1 μg/mL 15 μg/mL	BSA-fructose at pH 7.4, 37°C for 2 weeks Control (+): AG	15.06 ± 1.62% of inhibition 37.83 ± 1.82% of inhibition Fluorescence	[81]
Chlorogenic acid Syringic acid	150 μg/mL 150 μg/mL	BSA-glucose at pH 7.4, 37°C for 21 days Control (+): AG	49.07 ± 2.16% inhibition 65.47 ± 3.53% inhibition Fluorescence	[82]
Rosmarinic acid	400 μg/mL	BSA-glucose at pH 7.4, 37°C for 7 days Control (+): AG	97.4% of inhibition Fluorescence 82.7% and 75.2% of inhibition of CML and CEL, respectively by UPLC-MS/MS	[9]
Ellagic acid	100 μM	Total protein soluble eye lens-fructose at pH 7.4, 37°C for 3 weeks Control (+): AG	~75% of inhibition Fluorescence	[83]
Cinnamic acid	200 μM	HSA-MGO at pH 7.4, 37°C for 14 days Control (+): AG	23.7% of inhibition Fluorescence	[84]
Rutin Quercetin	100 μM 100 μM	BSA-glucose at pH 7.4, 37°C for 30 days Control (+): AG	~85% of inhibition ~50% of inhibition Fluorescence	[85]

Continued

TABLE 9.2 Natural compounds inhibitory of AGEs in protein-carbohydrate model systems (studies in vitro).—cont'd

Natural compound	Used concentration	AGEs formation and conditions	Main result of AGEs inhibition and method	References
Kaempferol Galangin Polydatin Carnosic acid	100 μg/mL 100 μg/mL 100 μg/mL 100 μg/mL	BSA-fructose at pH 7.4, 50°C for 24 h Control (+): AG	70.7% of inhibition 70.9% of inhibition ∼15% of inhibition ∼45% of inhibition Fluorescence	[86]
Hesperidin	50 μM	HSA-MGO at pH 7.4, 37°C for 72 h Control (+): AG	71.2% of inhibition Fluorescence	[87]
Cyanidin	1 mM	BSA-glucose and MGO at pH 7.4, 37°C for 14 days Control (+): AG	43.5% of inhibition Fluorescence 54% of inhibition CML by ELISA	[88]
Epicatechin gallate Epigallocatechin gallate	44.2 μg/mL 44.2 μg/mL	BSA-fructose at pH 7.4, 50°C for 24 h Control (+): AG	87% of inhibition 85% of inhibition Fluorescence	[89]
Oncocalyxone A	10.35–662.25 μM	BSA-glucose and fructose at pH 7.4, 37°C for 7 days Control (+): AG	$IC_{50} = 87.88 \pm 3.08$ μM Fluorescence	[90]
Resveratrol Oxyresveratrol Piceatannol	45 mM	BSA-acrolein and MGO at pH 7.4, 37°C for 7 days Control (+): AG	65.69% of inhibition 69.65% of inhibition 96.84% of inhibition Fluorescence	[91]

Phloroglucinol	1 mM	BSA-glucose, fructose, MGO and GO at pH 7.4, 37°C for 6 days Control (+): AG and PG	~55% of inhibition Fluorescence	[92]
Moracin M	10 μM	BSA-glucose and fructose at pH 7.4, 37°C for 1 week Control (+): AG	65.75% of inhibition Fluorescence	[93]
Thymoquinone	20 μM	BSA-glucose at pH 7.4, 37°C for 28 days Control (+): AG	28.04% of inhibition Fluorescence	[94]
Palmatine	29.2–146.02 μM	BSA-glucose and MGO at pH 7.4, 37°C for 7 days Control (+): AG, GL and MET	$IC_{50} = 2.0 \pm 0.25$ μM Fluorescence	[95]
Arborinine Betulinic acid Ursolic acid Cajaninstilbene acid Anhydrofusarubin Methyl ether of fusarubin	Don't described	BSA-glucose at pH 7.4, 60°C for 24 h Control (+): R	$IC_{50} = 234.36 \pm 1.91$ μg/mL $IC_{50} = 320.31 \pm 5.22$ μg/mL $IC_{50} = 308.26 \pm 1.24$ μg/mL $IC_{50} = 187.83 \pm 2.74$ μg/mL $IC_{50} = 220.60 \pm 1.26$ μg/mL $IC_{50} = 212.54 \pm 0.16$ μg/mL Fluorescence	[96]
Eugenol	15 mM	BSA-dextrose monohydrate at pH 7.4, 37°C for 7 days Control (+): AG	58% of inhibition Fluorescence	[97]
Oleanolic acid	500 μg/mL	BSA-fructose at pH 7.4, 50°C for 24 h Control (+): AG	>90% of inhibition Fluoresence	[98]

Continued

TABLE 9.2 Natural compounds inhibitory of AGEs in protein-carbohydrate model systems (studies in vitro).—cont'd

Natural compound	Used concentration	AGEs formation and conditions	Main result of AGEs inhibition and method	References
Vitamin B1 (thiamine)	500 μM	HSA-glucose at pH 7.4, 37°C for 30 days Control (+): AG	~55% of inhibition Fluorescence	[99]
Polysaccharides from *Coreopsis tinctoria*	2 mg/mL	BSA-glucose at pH 7.4, 37°C for 14 days Control (+): AG	>60% of inhibition Fluorescence	[100]
Polysaccharides from *Opuntia macrorhiza*	10 mg/mL	BSA-glucose at pH 7.4, 37°C for 14 days Control (+): AG	71.5% of inhibition Fluorescence	[101]
Aloin with casein peptides from *Aloe vera*	0.25 mg/mL and 0.5 mg/mL, aloin and peptide, respectively	HSA-glucose at pH 7.4, 37°C for 42 days Control (+): AG	~80% of inhibition Fluorescence	[102]
Peptides from *Vicia faba*	5 mg/mL	BSA with glucose and fructose at pH 7.4, 37°C for 19 days Control (+): AG	49.51% of inhibition Fluorescence	[103]
Carnosine	5 mM	BSA-glucose and fructose at pH 7.4, 60°C for 48 h Control (+): AG	~50% of inhibition Fluorescence	[104]

Abbreviations: *AG*, aminoguanidine; *AGEs*, advanced glycation end products; *BSA*, bovine serum albumin; *CEL*, *N*-carboxyethyl-lysine; *CML*, *N*-carboxymethyl-lysine; *GL*, glimepiride; *GO*, glyoxal; *HSA*, human serum albumin; IC_{50}, inhibitory concentration at 50%; *MET*, metformin; *MGO*, methylglyoxal; *PG*, pioglitazone; *Q*, quercetin; *R*, rutin; *UPLC-MS*, ultraperformance liquid chromatography with mass spectrometer.

100% of the formation of AGEs. They mention that resveratrol is a strong antiglycation agent and can trap α-dicarbonyls as MGO. The study by Sun et al. [110] demonstrated the ability of curcumin to inhibit AGEs in the HSA-MGO model system by fluorescence. They reported inhibition greater than 80% at 10^{-7} M and demonstrated the ability of curcumin to trap MGO.

Peake et al. [111] studied other natural compounds, such as saturated and unsaturated fatty acids, to inhibit AGEs in the BSA-MGO and GO model systems. They measured fluorescence generation and CML and CEL formation by LC-MS/MS in both model systems. The arachidonic, eicosapentaenoic, and docosahexaenoic fatty acids showed a decrease in the fluorescence of the model systems with respect to the control (aminoguanidine). In addition, saturated fatty acids showed a decrease in the production of CML and CEL in both model systems using fatty acids with endothelial cells to reduce the AGE-RAGE interaction. On the other hand, Huang et al. [112] used the alkaloid leonurine to inhibit the formation of AGEs in a porcine insulin model system with MGO. They reported up to 76.53 ± 5.06% inhibition using leonurine at 0.5 mM. Furthermore, they showed that leonurine can trap MGO due to the guanidino group in its chemical structure, thus preventing MGO from continuing to react with other molecules.

Abdullah et al. [113] demonstrated the antiglycation effect of vitamin B3 (niacin) in the HSA-glucose model system. They reported a 64.36% inhibition by fluorescence at a concentration of 500 μM. They also performed molecular docking assays and reported an affinity energy of −5.3 kcal/mol, and the main interactions between niacin and HSA highlight a hydrogen bond in Arg257 as well as two hydrophobic interactions with Leu238 and Ala291. Such interactions may prevent HSA glycation and consider niacin as an antiglycation and potential antidiabetic agent. In addition, Joglekar et al. [114] demonstrated the inhibitory effect on protein glycation using the terpene limonene with the BSA-glucose model system in the presence of urea. Where limonene inhibited 66% of the generation of AGEs in terms of fructosamine at 100 μM, a higher value than that of aminoguanidine (23%).

Sobhy et al. [115] demonstrated the effect of antiglycation with different phytosterols in a BSA-glucose model system. Inhibition was measured by fluorescence, and 33.89%, 19.64%, and 52.44% were obtained with stigmasterol, β-sitosterol, and γ-oryzanol, respectively, at a concentration of 0.1 mg/mL. According to their molecular docking analysis, phytosterols interacted with BSA at glycation sites such as Lys127, 357, 434, 524, and Arg185, thereby preventing AGE formation and its effects. Linping et al. [116] extracted polysaccharides from the mushroom *Boletus snicus* and determined antiglycation in the BSA-glucose model system. Two polysaccharides named BSP-1b and BSP-2b with molecular weights of 59.21 and 128.74 kDa were used. Inhibition by fluorescence was reported with a 26. 23% and 45.21% for BSP-1b and BSP-2b, respectively, at a concentration of 250 μg/mL. They refer

to the fact that BSP-2b showed greater inhibitory activity, which may be linked to its molecular weight and composition concerning BSP-1b.

It seems paradoxical that amino acids or peptides can inhibit the generation of AGEs when they can generate them. However, several studies demonstrate it, such as the one reported by Kuerban et al. [117], in which peptides were formed through alkaline and enzymatic hydrolysis of *Lens culinaris* proteins. They used a BSA-glucose-fructose model system and measured the generation of AGEs by fluorescence. Two peptides called BLH and RLH were evaluated at a concentration of 5 mg/mL, which inhibited the BSA-glucose system by 28.5% and 50.4%, respectively. While for the BSA-fructose system, BLH and RLH were inhibited by 34.3% and 62.3%, respectively. They assumed that the antiglycation effect of peptides may be due to exposure to lysine and arginine protein residues containing the electrophilic amino group of the side chain. Another example of protein compounds with antiglycation properties is mentioned by Nurilmala et al. [118], who used enzymatic hydrolysis and purification by chromatographic columns in collagen and hydrolysate from *Thunnus albacares* skin on model systems of BSA-glucose and fructose. Fluorescence results showed that collagen did not present antiglycant activity; however, its hydrolysate presented $4.36 \pm 2.18\%$ inhibition, and its fractions presented higher percentages, such as F3, with $24.45 \pm 2.41\%$ inhibition.

The aforementioned studies showed that amino acids can inhibit or reduce glycation by hindering the union between proteins and carbohydrates by competitive inhibition, thus offering protection. In this sense, peptides also have the same capacity because they have bioactivity, low toxicity, and structural diversity; however, the antiglycation property will depend on their composition, sequence, and length of amino acids. Therefore, amino acids and peptides prevent the generation of AGEs through the competitive formation of Schiff's bases for their amino groups, substituting those of proteins, capturing reactive carbonyls, and eliminating free radicals due to their antioxidant properties [119].

Main mechanisms of inhibiting AGEs formation

The ability to inhibit the formation of AGEs in several natural compounds has been proven, and, therefore, these are considered as antiglycation compounds that can be used in the prevention and/or treatment of chronic diseases such as diabetes mellitus. There are reports in the literature on the main inhibition mechanisms of AGEs, and they are summarized in Fig. 9.8.

The inhibitory mechanisms include: (1) Reduction in the production of free radicals: during glycation in the first stage of MR, free radicals are produced, and the generated Schiff bases that are susceptible to oxidation produce free radicals and reactive dicarbonyls. Therefore, compounds with antioxidant capacity can inhibit the formation of AGEs. (2) Reduction in the production of Schiff's bases and Amadori products: blocking the carbonyl or dicarbonyl

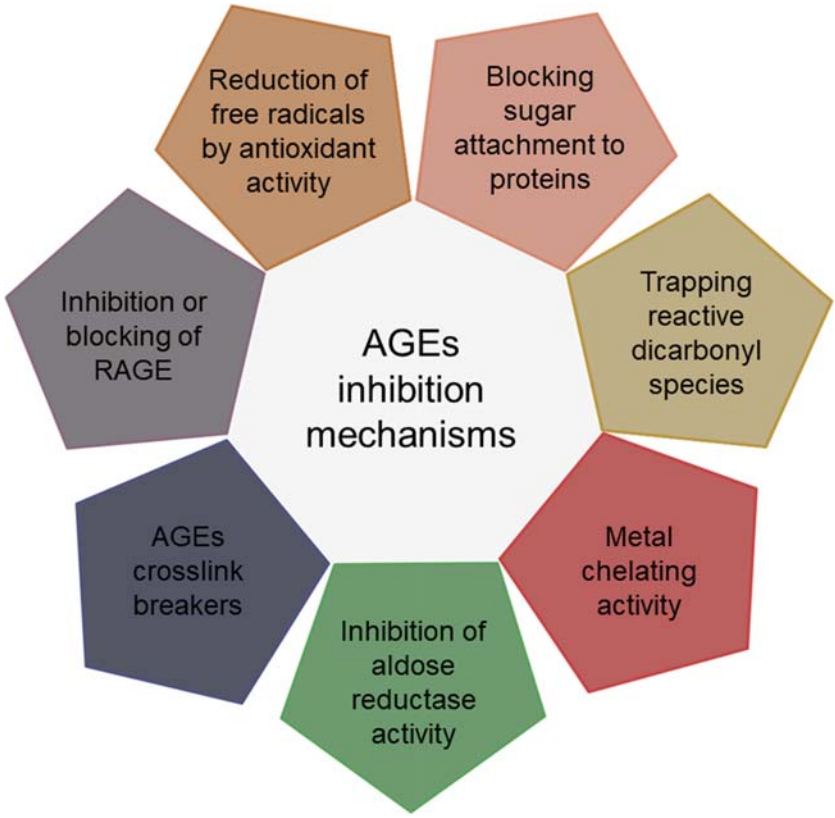

FIGURE 9.8 Main mechanisms known for the inhibition of AGEs.

groups of reducing sugars, or those that bind to amino groups, can inhibit the production of AGEs. (3) Trapping reactive dicarbonyl species: capture such species as MGO and GO and form adducts through nucleophilic addition. (4) Metal chelation: the chelation of metal ions such as Fe and Cu is of interest since these cause glucose autoxidation and lipid peroxidation, forming AGEs and ALEs, which is another inhibition mechanism. (5) Inhibition of aldolase reductase activity: This enzyme converts glucose into sorbitol via polyols, and this is oxidized into fructose by the action of the enzyme sorbitol dehydrogenase. It is known that fructose can produce a greater amount of dicarbonyls, such as MGO and AGEs, with respect to glucose, so compounds that inhibit aldolase reductase are related to the inhibition of AGEs. (6) Cross-link breakers: Compounds capable of cleaving and breaking AGE-protein cross-links are also of interest. (7) Block or inhibit RAGE function and reduce the subsequent development of oxidative stress and inflammation [120,121]. These

mechanisms apply to many synthetic and natural compounds, such as polyphenols.

Natural compounds AGEs inhibitors: in vivo studies

In addition to in vitro studies, the ability to inhibit AGEs of natural compounds has also been demonstrated in vivo studies, either in experimental animals or in humans. This inhibition occurs when measuring levels of AGEs in blood and/or tissues after the implementation of natural compounds. However, it is worth mentioning that when demonstrating the antiglycation and/or inhibitory effects of AGEs, these compounds should not show toxicity in the tests. Some works of plant extracts or natural compounds in vivo studies in animals and humans are summarized in Table 9.3.

Regarding natural extracts, Khan et al. [134] used *Illicium verum* hook. F. dry fruits in a Sprague− Dawley diabetic rat model ($n = 6$). They induced the formation of diabetes with streptozocin (STZ). They were fed ethanolic extracts of *I. verum* for 7 weeks and AGEs in the kidneys were measured by fluorescence. They obtained a ∼5% reduction of AGEs in arbitrary units (AU)/mg protein in rats treated at 500 and 1000 mg/kg of body weight compared to nondiabetic rats. In addition, with said extract, urea, creatinine, and liver enzyme levels were reduced, which is positive since AGEs are usually involved in diabetic nephropathy, glomerulosclerosis, and oxidative stress. The main compounds related to the effects are attributed to 1-methoxy-4-(1-propenyl)-benzene (anethole) and 4-methoxy-benzaldehyde analyzed by GC-MS. Another study on antiglycation is that of Jovanović et al. [135], where they evaluated the mushroom *Lactarius deterrimus* and the chestnut *Castanea sativa* in albino Wistar rats ($n = 8$) induced to diabetes mellitus by STZ. They evaluated ethanolic extracts at 60 mg/kg for 4 weeks and measured by immunoblot the amount of CML and RAGE in the liver and kidneys, as well as serum fructosamine levels. They obtained that the combined extracts in diabetic rats reduced protein glycation in serum (∼70%) with respect to nondiabetics in liver and kidneys. And the same effect was obtained with CML levels. While RAGE levels were about 30% lower with the *C. sativa* extract than when combined with *L. deterrimus*. Previous HPLC-DAD studies revealed that the *L. deterrimus* extract contains p-hydroxybenzoic acid and unsaturated fatty acids, while the *C. sativa* extract contains ellagic acid, gallic acid derivatives, and flavonoid structures.

Also, antiglycation of individual natural compounds has been reported. In the study by Joglekar et al. [136], the monoterpene cymene was evaluated as an inhibitor of AGEs in vivo in Wistar rats ($n = 6$) and diabetes mellitus was induced with STZ. They administered cymene at a dose of 20 mg/kg for 60 days and measured AGEs and pentosidine by fluorescence. They obtained tail tendon values of AGEs of 35.2 ± 1.5 and pentosidine of 22.01 ± 1.4 AU/mg collagen, lower values compared to diabetic rats' 58.6 ± 0.6 and

TABLE 9.3 Plant extracts and natural compounds inhibitory of AGEs in studies in vivo (animals and humans).

Natural compound	Study group	Doses and time	Sample analyzed and method for AGEs	Main result of inhibition of AGEs	References
Trigonella foenum cinnamon	Wistar rats $n = 6$ Treatment with STZ	2% and 8% w/w 30 days	Serum and kidney Fluorescence	Changes not significant compared with diabetic and control rats	[122]
Coffea arabica L. beans	Wistar rats $n = 10$ Treatment with alloxan	7.2 mL/kg 50 days	Serum Fluorescence	~30% of inhibition	[123]
Olea europaea L.	Wistar rats $n = 8$ Treatment with STZ	200 and 400 mg/kg 6 weeks	Kidney ELISA	~50% of inhibition	[124]
Phloretin Epigallocatechin 3-gallate [6]-gingerol	C57BL/6J mice $n = 11$ Feed with HFD	25 and 75 mg/kg 16 weeks	Heart and kidney Fluorescence	67% and 86% of inhibition in heart and kidney, respectively 96% and 80% of inhibition in heart and kidney, respectively 66% and 81% of inhibition in heart and kidney, respectively	[125]
Ellagic acid	Wistar-NIN rats $n = 8$ AIN-93 diet ad libitum and treatment with STZ	0.2% and 2% 12 weeks	Retina Immunoblotting (CML)	~60% of inhibition	[126]
Curcumin	Wistar rats $n = 10$ Curcumin combination with aminoguanidine in yoghurt Treatment with STZ	45–90 mg/kg 45 days	Liver and kidney Fluorescence	~60% of inhibition in liver and ~30% of inhibition in kidney	[127]

Continued

TABLE 9.3 Plant extracts and natural compounds inhibitory of AGEs in studies in vivo (animals and humans).—cont'd

Natural compound	Study group	Doses and time	Sample analyzed and method for AGEs	Main result of inhibition of AGEs	References
Trapa bispinosa Roxb.	Patients at relatively advanced ages $n = 63$ 38–42 years	100 mg/day extract Until late pregnancy or failure	Serum and follicular fluid LC-ESI-MS/MS (CML) HPLC (pentosidine)	Not change in CML and ~5% inhibition in pentosidine	[128]
Ginger (*Zingiber officinale*)	Patients with peritoneal dialysis $n = 36$ 29–79 years	1000 mg/day 10 weeks	Serum ELISA (CML and pentosidine)	Increase ~25% of CML and ~40% of inhibition of pentosidine	[129]
Centella asiatica	Patients with DMT2 and dry skin $n = 53$ <60 years	2 × 1.100 mg and 0.25 g 28 days	Skin and serum ELISA (CML)	~10% inhibition of CML in topical application	[130]
Omega-3 fatty acid	Patients with diabetic nephropathy $n = 30$ 45–85 years	1000 mg/day 12 weeks	Serum Fluorescence	~9% of inhibition	[131]
Taurine	Patients with DMT2 $n = 23$ 30–60 years	3 g/day 8 weeks	Serum ELISA (pentosidine)	~10% of inhibition	[132]
Vitamin D	Patients with DMT2 $n = 24$ 30–60 years	100 μg 3 months	Serum ELISA	~30% of inhibition	[133]

Abbreviations: *AG*, aminoguanidine; *AGEs*, advanced glycation end products; *BSA*, bovine serum albumin; *CML*, *N*-carboxymethyl-lysine; *DMT2*, diabetes mellitus type 2; *ELISA*, enzyme-linked immunosorbent assay; *GO*, glyoxal; *HFD*, high fat diet; *HPLC*, high performance liquid chromatography; *HSA*, human serum albumin; *LC-ESI-MS/MS*, liquid chromatography electrospray ionization tandem mass spectrometry; *MGO*, methylglyoxal; *STZ*, streptozotocin.

51.25 ± 1.4, respectively. Therefore, they infer that cymene is a powerful compound with antiglycant activity and a cross-linking breaker from collagen. Another example, Yilmaz et al. [137], evaluated resveratrol as an antiglycant of plasma and liver products in rats treated with MGO. They used Sprague−Dawley rats ($n = 6$) and administered resveratrol at 10 mg/kg BW and MGO at 100 mg/kg body weight for up to 10 weeks. Plasma and liver were obtained, and the levels of AGEs were measured by fluorescence. They mentioned that resveratrol reduced levels of AGEs in plasma; however, these levels were not changed in the liver of rats treated with MGO. They conclude that resveratrol can be considered an agent against glycooxidative stress in vivo treatment with MGO.

On the other hand, there are studies where levels of AGEs or the antiglycation effect in humans with plant extracts and/or natural compounds are measured. Sohrab et al. [138] used pomegranate (*Punica granatum*) juice to see its effect on AGEs in adults with type 2 diabetes mellitus. Forty-four patients between 49 and 63 years old consumed the juice at an amount of 250 mL/day for 12 weeks. Plasma was taken to quantify CML and pentosidine using ELISA kits. No significant changes were obtained for plasma concentrations of CML and pentosidine after treatment with pomegranate. This is attributed to the fact that the patients in the study did not have elevated basal concentrations of AGEs, and the exposure time of 6 months can highlight plasma concentrations of AGEs. Another example is the study by Sanchis et al. [139], in which they used phytate in patients with type 2 diabetes mellitus and decreased the levels of AGEs. Thirty-three patients older than 18 years with the disease participated, who followed a special diet and were administered phytate in capsules of 380 mg three times a day for 12 weeks, and then the amount of AGEs in serum was measured by an ELISA kit. They reported a reduction in the levels of AGEs after the administration of phytate, which went from 7.8 ± 0.4 to 5.8 ± 0.3 U/mL, that is, a reduction of ∼25% and, in addition, they presented a reduction of 3.8% of HbA1c that could be due to inhibition of protein glycation. Therefore, they consider phytate as a dietary supplement that decreases levels of AGEs, possibly due to the chelation of Fe^{3+}. In the same way, Van den Eyden et al. [140] used quercetin 3-glucoside and (−)-epicatechin in patients with type 2 diabetes mellitus to decrease levels of AGEs and MGO. The study involved 37 participants aged 20−40 years who were administered quercetin 3-glucoside at 160 mg/d and (−)-epicatechin at 100 mg/d for 4 weeks. They measured plasma concentrations of AGEs, CEL, CML, MGO, GO, and 3-DG by UPLC-MS/MS and pentosidine by HPLC with a fluorescence detector. They reported that with quercetin 3-glucoside, there was a 10.6% reduction of MGO, while for GO, 3-DG and AGEs (fluorescent and nonfluorescent) did not change significantly. Furthermore, treatment with (−)-epicatechin did not modify the plasma concentrations of MGO, GO, 3-DG, and AGEs.

Natural compounds inhibitors of RAGE

Returning to the mechanisms of AGE inhibition, we can detail those natural compounds that inhibit RAGE formation and/or block the AGE-RAGE interaction, thereby preventing the production of NF-κB, ROS, proinflammatory cytokines, and adhesion molecules that are relevant in chronic diseases. Natural compounds can reduce RAGE expression levels through expressed mRNA or protein. This can be done in vitro in cell culture studies or in vivo in experimental animals. Natural compounds that inhibit RAGE expression levels are displayed in Table 9.4.

Okada and Okada [153] used methanolic extracts from different edible plants to see the inhibitory effect of RAGE on human endothelial cells (HUVEC). HUVEC cells were subjected to high concentrations of glucose, and methanolic extracts with 10 and 100 μL were used to measure the production of RAGE by ELISA. They found that of the 21 plant extracts they tested, three of them decreased RAGE production to 10 μL compared to the control (RAGE at 20 pg/mL). These extracts showed RAGE values <20 pg/mL, which were onion peel (*Allium cepa* L.), onion rhizome, and cowpea (*Vigna unguiculata* (L.) *Walp*.), with cow pea being the one that showed the greatest decrease with a value of RAGE ~ 10 pg/mL. Also, burdock (*Arctium lappa* L.) in 100 μL showed a decrease in RAGE. Therefore, they support these plant extracts as an improvement in diabetes complications. Moreover, Guzmán et al. [154] used scalarin from *Euryspongia* cf. *rosea* on PANC-1 and MIA PaCa-2 pancreatic cancer cells and inhibit RAGE. Cells were incubated with scalarin at concentrations ranging from 1.4−22.5 μM and an antibody against RAGE was used for western blotting. They reported that scalarin reduced RAGE expression levels by 30%−50% in PANC-1 at concentrations of 11.3 and 22.5 μM and in MIA PaCa-2 at 5.6, 11.3, and 22.5 μM, an inhibition very similar to curcumin at 30 μM. However, curcumin turned out to present greater cytotoxicity than scalarin in cell lines, so scalarin turned out to be a better agent to inhibit RAGE.

In addition to cell studies, in vivo studies have been conducted to elucidate the inhibitory effect of plant extracts and natural compounds on RAGE expression. Wu et al. [155] tested lotus seedpods of *Nelumbo nucifera* Gaertn with oligomeric procyanidins to inhibit RAGE expression in high-fat diet rats. Ethanolic extracts of lotus seedpod were administered to Sprague−Dawley rats ($n = 10$) for 12 weeks. RAGE mRNA levels in liver samples were measured by quantitative real-time polymerase chain reaction. They reported that RAGE mRNA levels increased 4.5-fold in rats fed a high-fat diet compared to the normal control group, and rats fed a high-fat diet and 0.5% (w/w) extract showed a decrease of RAGE very similar to the normal control group. HPLC analyses of the extract suggest that the main compounds responsible for such effects are probably monomers, dimers, and trimers of procyanidins, as well as other compounds such as catechin/epicatechin,

TABLE 9.4 Plant extracts and natural compounds inhibitory of RAGE expression in cell lines and studies in vivo (animals).

Natural compound	Model of study	Concentration	Sample and method of inhibition of RAGE	Main result of inhibition of RAGE	References
Amaranthus lividus *Amaranthus tricolor*	SH-SY5Y cells	20–100 μg/mL	RT-qPCR	~60% decrease of mRNA levels in both plant extracts	[141]
Bombax ceiba L. calyx	HEK-293 cells	1–20 μg/mL	Immunoblotting	~30% inhibition of expresión	[142]
Kigelia africana leaves	EA.hy926 cells	10–200 μg/mL	Western blot	~70% inhibition of protein levels	[143]
Pterostilbene	RAW264.7 cells	10 μM	RT-qPCR	~50% inhibition of expresión	[144]
Paeoniflorin	HBZY-1 cells	25 and 50 μM	Western blot	~50% inhibition of expresión	[145]
Quercetin	MIA Paca-2 cells	6.25–50 μM	Western blot	~30% inhibition of expresión	[146]
Auricularia auricular	ICR mice $n = 10$ Feed with D-galactose	500 and 1000 mg/kg	Hippocampus tissue Western blot	~50% inhibition of expresión	[147]
Scrophularia striata aerial parts	Wistar rats $n = 6$ Treatment with STZ	100 and 200 mg/kg b.w. 60 days	Kidney RT-qPCR	~50% inhibition of expresión	[148]

Continued

TABLE 9.4 Plant extracts and natural compounds inhibitory of RAGE expression in cell lines and studies in vivo (animals).—cont'd

Natural compound	Model of study	Concentration	Sample and method of inhibition of RAGE	Main result of inhibition of RAGE	References
Kappaphycus alvarezii (Doty) Doty ex P.C.Silva thalli	Wistar rats $n = 6$ Treatment with STZ	0.17 and 0.255 mg/mL 4 weeks	Kidney RT-qPCR	~30% inhibition of expresión	[149]
Mangiferin	Wistar rats $n = 12$ Treatment with STZ	40 mg/kg 28 days	Heart Western blot	~20% inhibition of expresión	[150]
Salvianolic acid A	Sprague–Dawley rats $n = 8$ Feed with HFD Treatment with STZ	1 mg/kg/day 8 weeks	Kidney Western blot	~90% inhibition of expresión	[151]
Hesperidin	APP/PS1 mice $n = 20$	40 mg/kg 90 days	Brain Western blot	~50% inhibition of expresión	[152]

Abbreviations: *AGEs*, advanced glycation end products; *EA.hy926*, human umbilical vein cell line; *HBZY-1*, rat glomerular mesangial cells line; *HEK-293*, human embryo kidney cell line; *HFD*, high fat diet; *MIA Paca-2*, human pancreatic cancer cell line; *mRNA*, messenger ribonucleic acid; *RAW264.7*, mouse macrophage cell line; *RT-qPCR*, quantitative reverse transcription polymerase chan reaction; *SH-SY5Y*, thrice cloned subline of the neuroblastoma cell line; *STZ*, streptozotocin.

gallocatechin/epigallocatechin, quercetin glycoside, quercetin glucuronide, and proanthocyanidin dimer gallate, among others. On the other hand, as reported by Giridharan et al. [156], used schisandrin B against intracerebroventricular infused β-amyloid induced neuronal dysfunction in rats and expression of RAGE. They used male Sprague−Dawley rats ($n = 8$) and administered β-amyloid and schisandrin B at 25 or 50 mg/kg for 28 days. The cerebral cortex was obtained from rats, and the level of RAGE was measured by Western blot. β-amyloid was able to increase the number of RAGE-positive cells in the cerebral cortex compared to control, and administration of schisandrin B was able to significantly reduce the number of RAGE-positive cells. They detailed that it is important because RAGE is associated with β-amyloid deposits in the brain and contributes to the development of Alzheimer's. Furthermore, they suggest that this inhibition of expression is due to the RAGE/NF-κB/MAPK axis.

Conclusions

AGEs derived from MR are responsible for generating complications in chronic degenerative diseases such as diabetes mellitus, Alzheimer's, atherosclerosis, and kidney problems, among others. This occurs because these compounds interact with the RAGE receptor of cells, causing inflammation and oxidative stress. Commercially available natural compounds obtained from plant extracts can inhibit the production of AGEs in vivo and in vitro through various mechanisms. In addition, they can also decrease the expression of RAGE to avoid the effects of the mentioned AGEs. Therefore, natural compounds that have a positive effect, which can be considered non-pharmacological alternatives for the prevention and treatment of chronic diseases linked to AGEs.

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Abbreviations

1-DG	1-deoxyglucosone
3-DG	3-deoxyglucosone
AFGP	Alkyl formyl glycosyl pyrroles
AGER1	Advanced glycation end products receptor 1
AGER2	Advanced glycation end products receptor 2
AGER3	Advanced glycation end products receptor 3
AGEs	Advanced glycation end products
Akt	Protein kinase B

Ala	Alanine
ALEs	Advanced lipoxidation end products
Arg	Arginine
ARP	Amadori rearrangement product
AU	Arbitrary units
BSA	Bovine serum albumin
CEL	n-Carboxyethyl-lysine
CML	n-Carboxymethyl-lysine
DAD	Diode array detector
DHAP	Dihydroxyacetone phosphate
DN-RAGE	Receptor of advanced glycation end products with dominant-negative
DPPH	2,2-diphenyl-1-picrylhydrazyl
EGCG	Epigallocatechin gallate
ELISA	Enzyme-linked immunosorbent assay
ERK	Extracellular signal-regulated kinase
esRAGE	Receptor of advanced glycation end products endogenous secretory
G3P	Glyceraldehyde-3-phosphate
GC-MS	Gas chromatography coupled with mass spectrometry
GO	Glyoxal
GODIC	Imidazolium cross-link derived from glyoxal and lysine-arginine
GOLD	Glyoxal-lysine dimer
HbA1c	Glycated human hemoglobin
HMF	Hydroxymethylfurfural
HMGB1	High mobility group box-1 protein
HPLC	High performance liquid chromatography
HSA	Human serum albumin
HUVEC	Human endothelial cells
IC_{50}	Inhibitory concentration at 50%
IgG	Immunoglobulin G
IGPs	Intermediate glycation products
IL	Interleukin
ILE	Ionic liquid extraction
JAK	Janus kinase
JNK	c-Jun N-terminal kinase
LC-MS/MS	Liquid chromatography coupled with tandem mass spectrometry
Leu	Leucine
Lys	Lysine
Mac-1	Macrophage 1 antigen
MAE	Microwave-assisted extraction
MAPK	Mitogen-activated protein kinase
MGO	Methylglyoxal
MHC	Major Histocompatibility Complex
MIA PaCa-2	Human pancreatic cancer cell line
MODIC	Imidazolium cross-link derived from methylglyoxal and lysine-arginine
MOLD	Methylglyoxal-lysine dimer
MRPs	Maillard reaction products
MS/MS	Tandem mass spectrometer
NADPH oxidase	Nicotinamide adenine dinucleotide phosphate-oxidase

NF-κB	Nuclear factor kappa B
NT-RAGE	Receptor of advanced glycation end products n-truncated
OST-48	Oligosaccharyl transferase complex protein 48
PANC-1	Human pancreatic cancer cell line
PI3K	Phosphoinositide 3-kinase
PRRs	Pattern recognition receptors
PSE	Pressurized solvent extraction
qPCR	Quantitative realtime polymerase chain reaction
RA	Rheumatoid arthritis
RAGE	Receptor of advanced glycation end products
RM	Maillard reaction
ROS	Reactive oxygen species
RT-qPCR	Quantitative reverse transcription polymerase chan reaction
SAPK	Stress-activated protein kinases
SFE	Supercritical fluid extraction
SIRT1	NAD-dependent deacetylase sirtuin-1
sRAGE	Receptor of advanced glycation end products soluble
STAT	Signal transducer and activators of transcription
STZ	Streptozocin
TGF-β	Transforming growth factor beta
TNF-α	Tumor necrosis factor alpha
UAE	Ultrasound-assisted extraction
UHPLC	Uultrahigh-pressure liquid chromatography
UPLC-MS/MS	Ultraperformance liquid chromatography with mass spectrometer
VCAM-1	Vascular cell adhesion molecule-1

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