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Natural Products as a Source of Inspiration for Novel Inhibitors of Advanced Glycation Endproducts (AGEs) Formation*

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* Dedicated to Professor Arnold Vlietinck on the occasion of his 80th birthday.

Abstract

Protein glycation, a post-translational modification found in biological systems, is often associated with a core defect in glucose metabolism. In particular, advanced glycation endproducts (AGEs) are complex heterogeneous sugar derived protein modifications implicated in the progression of pathological conditions like atherosclerosis, diabetic complications, skin diseases, rheumatism, hypertension, and neurodegenerative diseases. Undoubtedly, there is the need to expand the knowledge about anti-glycation agents that can offer a therapeutic approach in preventing and treating health issues of high social and economic importance. Although various compounds have been under consideration, only for a few data from clinical trials is available, and there is a lack of approved and registered anti-glycation agents. Next to the search for novel synthetic AGEs inhibitors, more and more the efforts of scientists are focusing on anti-glycation compounds from natural origin. The main purpose of this review is to provide a thorough overview of the state of scientific knowledge in the field of natural products from plant origin (e.g. extracts and pure compounds) as inhibitors of AGEs formation in the period between 1990 and 2019. Moreover, the objectives of the summary also include basic chemistry of AGEs formation and classification, pathophysiological significance of AGEs, mechanisms for inhibiting AGEs formation, and examples of several synthetic anti-AGEs drugs.

Key words

Advanced glycation endproducts (AGEs), natural products, medicinal plants

Abbreviations

3-DG: 3-deoxyglucosone

AIIRIs: angiotensin II receptor inhibitors

ACE: angiotensin converting enzyme

AGEs: advanced glycation end products

ALEs: advanced lipoxidation endproducts

CEL: N-ε-carboxyethyl-L-lysine

CML: N-ε-carboxymethyl-L-lysine

DOLD: deoxyglucosone-derived lysine dimer

GO: glyoxal

GODIC: glyoxal derived imidazoline crosslink

GOLD: glyoxal-derived lysine dimer

IgG: immunoglobulin G

IgM: immunoglobulin M

IL-2: interleukin 2

IL-6: interleukin 6

LDLs: low-density lipoproteins

MG-H_1: N-(5-H-5-methyl-4-imidazolon-2-yl)-L-ornithine

MGO: methylglyoxal

MODIC: methylglyoxal derived imidazoline crosslink

MOLD: methylglyoxal-derived lysine dimer

NF-kB: nuclear factor kappa light chain enhancer of activated B cells

NO: nitric oxide

PMFs: polymethoxylated flavonoids

RAGE: receptor for AGEs

RCS: reactive carbonyl species

ROS: reactive oxygen species

TGF-β: transforming growth factor-β

TNF-α: tumour necrosis factor-α

VCAM-1: vascular cell adhesion molecule-1

Introduction

Nowadays, age-related chronic inflammatory diseases like type 2 diabetes mellitus and cardiovascular diseases represent a major health problem [1]. The prevalence of those conditions is exponentially increasing since the population ages [2]. Therefore, prevention is of highest importance and clearly has a medical and economic impact. Not surprisingly, future strategies are focusing on the identification of individuals at risk for developing chronic complications by means of novel biomarkers for pathophysiological pathways; i.e. to improve risk prediction [2]. Various mechanisms have been proposed to explain the causes for initiation and progression of chronic diseases and on biochemical level, experimental and histological data suggest that protein glycation - formation of advanced glycation endproducts (AGEs), correlates with many pathological complications [3–5]. The term glycation is defined as the spontaneous, non-enzymatic reaction of glucose or other reducing sugars with an amino group of proteins, lipids and nucleic acids [6]. Protein glycation occurs predominantly on lysine, arginine and *N*-terminal residues of proteins, it involves series of complex reactions and it is considered as a post-translational modification of proteins found in biological systems [6,7]. In particular, AGEs are complex, heterogeneous, sugar derived protein modifications that have been implicated in the pathogenesis of diabetic complications, Alzheimer's disease and in the process of normal aging [8–10]. Additionally, important physiological glycating agents apart from glucose are dicarbonyl metabolites, particularly glyoxal (GO), methylglyoxal (MG) and 3-deoxyglucosone (3-DG) [11].

The classical pathway (Hodge pathway) for AGEs formation can be generally subdivided in three stages: initiation, propagation and an advanced stage (Figure 1). It usually takes several days to several weeks to complete due to the lack of enzymatic catalysis during the process. In the first step (initiation), reducing sugars (aldoses and ketoses) react with amino groups *via* a nucleophilic addition, resulting in aldimines and ketoimines (Schiff bases). Subsequently, through acid-base catalysis, the unstable and reversible Schiff base undergoes Amadori or Heyns rearrangements, resulting in 1-amino-deoxyketosyl or 2-amino-deoxyaldos-2-yl adducts (relatively stable Amadori or Heyns products) [12–14]. During the propagation phase, the Amadori products can be transformed (within a period of weeks) to reactive dicarbonyl products. They initiate glycation by undergoing further non-oxidative dehydration and rearrangement reactions to dicarbonyl compounds, including 3-DG, GO and MGO. While 3-DG is formed by non-oxidative rearrangement and hydrolysis of Amadori product (see Figure 1), MGO and GO can be produced in several additional pathways (see further). Alternatively, Amadori products can generate amines through a metal-ion-mediated catalysis and oxidation,

while the glycosyl group is dehydrated to form deoxyglucosone (DG). Further on, these early glycation products are highly prone to oxidative (glycoxidation) and non-oxidative degradation, cleavage and covalent binding, leading to a heterogeneous group of stable compounds and cross-linking of proteins, commonly called advanced glycation endproducts (AGEs). In particular, the advanced stage is characterized by intermolecular or intramolecular heterocyclic cross-linking and fragmentation that occur in the protein molecules, leading to protein denaturation and irreversible damage.

Meanwhile, AGEs can also be formed from Amadori products directly through rearrangement under both oxidative and non-oxidative conditions. In the oxidative pathway (Namiki pathway) the unstable initial products (Schiff bases) can be directly converted to oxoaldehydes (glycoxidation) [15]. Additionally, the Wolff pathway describes the metal-catalyzed autoxidation of reducing sugars leading to AGEs formation [16,17]. The products from both pathways are dicarbonyl intermediates (MGO, GO, 3-DG) and free radicals. Moreover, the oxidation of polyunsaturated fatty acids (lipoxidation pathway) can also lead to GO or MGO formation, apart from the general advanced lipoxidation end products (ALEs). Basically, AGEs can be formed by pre- and post-Amadori product reactions, and in such a way that the Amadori product is not a precursor. Therefore, AGEs are generated in both early and late stages of glycation processes. Nevertheless, the concept of early and advanced glycation adducts is rather simplifying the whole process but ensures a possibility of classifying the different glycation products [6].

AGEs Classification

Many attempts have been made to classify the diverse group of AGEs. For instance, one approach is based on their fluorescence properties and the presence of cross-linking in their structure (Figure 2): fluorescent cross-linked AGEs (pentosidine, crossline, vesperlysine A-C); non-fluorescent cross-linked AGEs (glucosepane, MOLD, GOLD); non-fluorescent non-crosslinked AGEs (CML, pyrraline, argpyrimidine) [18]. Another classification is according to the molecular structure of the glycation adduct and the mechanism of AGEs formation (Table 1) [6].

Today a variety of AGEs structures have been characterized in different human tissues associated with various pathological conditions (see Table 1), including pyrraline, pentosidine, crossline, *N*-ε-carboxymethyl-L-lysine (CML), *N*-ε-carboxyethyl-L-lysine (CEL), glyoxal-lysine dimer (GOLD), methylglyoxal-lysine dimer (MOLD), methylglyoxal-derived hydroimidazolones, glucosepane [19–22]. MGO and GO can react with lysine residues to form

CEL and CML, respectively, while the three oxoaldehydes can lead to the analogous di-lysyl cross-linked MOLD, GOLD and deoxyglucosone-derived lysine dimer (DOLD). Among the most studied AGEs, which have been detected in a wide range of tissues, are pentosidine, CML and MGO derivatives. They can be considered as biomarkers for AGEs formation [23,24].

Pathophysiological role of AGEs

AGEs formation takes place under normal physiological conditions but the equilibrium can be shifted in a state of hyperglycemia [25]. Therefore, they are referred to sometimes as glycotoxins because they can be toxic to the body when present for a prolonged period of time [26]. Most AGEs accumulate with age in long-lived tissue proteins like lens crystallins and collagen due to their slow formation rate [27,28]. Despite it was believed that AGEs accumulate only on long-lived extracellular proteins, a rapid extracellular AGEs formation on short-lived proteins and intracellular AGEs formation by reactive dicarbonyl compounds has recently become a major topic of research interest [28]. In general, the pathophysiological effects of AGEs can be related to several mechanisms of action: (i) oxidative stress; (ii) carbonyl stress; (iii) interaction with AGEs receptors (RAGE) on the cell surface [29–31]. To begin with, oxidative stress can lead to the damage of various cell components and to the activation of specific signaling pathways like nuclear factor-κB (NF-κB) (Figure 3). In general, the hypothesis of cellular damage (to cardiac muscle and neuronal cells) associated with age-related diseases and explained by excessive oxidative stress, has been formulated a long time ago. However, novel pharmaceutical targets have been characterized lately, opening new research challenges. A relatively new field of interest is the carbonyl stress, an imbalance of reactive carbonyl species (RCS) production and carbonyl scavenging mechanisms. An important step in the glycation reaction is the generation of reactive intermediate products during all stages and pathways of glycation. For example, Schiff bases are highly prone to oxidation and free radical generation, which lead to the formation of RCS, such as GO, MGO and 3-DG. Compared to ROS, these aldehydes are more stable and diffuse within or even escape from the cell and attach to targets far away from their site of formation. The phenomenon accelerates in diabetes and in glycemia. Through generation of ROS and RCS, AGEs contribute to tissue injury by alteration of extracellular matrix structures through formation of protein cross-links, and alteration of intracellular short-lived proteins like metabolic enzymes and mitochondrial protein complexes [32]. Inside cells, the impact of glycation is countered by high turnover and short half-life of many cellular proteins. Long-lived extracellular proteins, however, accumulate glycation adducts with age. Extracellular

degraded glycated proteins are recognized by specific receptors [33]. Multiple receptor independent and dependent pathways, linking AGEs to cellular and tissue dysfunction, have been proposed [34]. So far, it is well-understood that the interaction between AGE-modified proteins and AGE-specific receptors (RAGEs) on the cell surface induces the overproduction of ROS and inflammatory mediators, which lead to cellular disorder in biological systems [35]. The receptors are weekly expressed in vascular cells, smooth muscle cells, fibroblasts, and monocyte/macrophages. The link between RAGE and its ligands triggers a cascade of intracellular events, followed by the transcription of a range of genes involved in different biological systems, as well as other reactions such as the induction of oxidative stress (see Figure 3). All of these reactions lead to series of functional changes that participate in neurological and vascular complications (micro- and macrovasculopathies) in diabetes, metabolic syndrome, etc. [23,36]. There is a considerable body of evidence that the formation and accumulation of AGEs is implicated as a major factor in the progression of various pathological conditions, such as: atherosclerosis, diabetic retinopathy, nephropathy, neuropathy, wound healing, Alzheimer's disease (see Figure 3).

Hyperglycemia results in an accumulated amount of AGEs in the blood vessels, which induces proliferation of smooth muscle cells, thickening of the intima (plaque formation and sedimentation) and rigidity and stiffness of the vessels. Moreover, AGEs stimulate foam cell formation by lipid and protein glycosylation. The low-density lipoproteins (LDLs) are not discarded in the normal way and then accumulate in the monocytes to form foam cells. The reason for this is that the LDL receptor does not recognize the glycated LDLs. The AGE-RAGE complex induces *atherosclerosis* by enhanced expression of VCAM-1 (vascular cell adhesion molecule-1) on the endothelial cells, and the production of cytokines. As a result, VCAM-1 promotes adhesion of the monocytes to the endothelial cells. Then, the monocytes differentiate to macrophages which transform to foam cells by lipid uptake. Generally, pathological glycation of collagen is the major cause of tissue dysfunction due to cross-linking that could cause decreased elasticity, increased thickness and rigidity of the vessel lumen. As a result, the vascular damage associated with diabetes is the key for microvascular complications like neuropathy, nephropathy and retinopathy [37]. The AGE-RAGE complex increases the production of cytokines (interleukin-2 (IL-2), interleukin-6 (IL-6)) and growth factors (tumor necrosis factor-α, TNF-α) (see Figure 3), which are responsible for the development of macrovascular complications like generalized atherosclerotic plaques. Additionally, during the glycoxidative stress, NF-κB activates the production of TNF-α which leads to enhanced ROS

production, in other words, AGEs formation keeps the ongoing of the oxidative stress (see Figure 3) [32].

Retinopathy is the major cause of blindness in diabetic patients. The accumulation of AGEs leads to thickening of the capillary basement membrane, enhanced permeability of the capillaries, and apoptosis of pericytes. Hyperglycemia stimulates an excessive expression of RAGE on pericytes and endothelial cells, causing deterioration of the pericytes. The loss of pericytes is the clinical expression of retinopathy. Moreover, a high level of AGEs in retinal cells includes expression of vascular endothelial growth factor which causes destruction of the blood-retinal barrier and microvascular hyper-permeability, which finally leads to blindness or poor vision [38].

Diabetic nephropathy, which is considered as the most life-threatening condition in diabetic patients, is associated with basal membrane thickening and decreased filtration [39]. The sedimentation of proteins in the glomerular space plays a significant role in the reduction of filtration. AGEs stimulate an extreme RAGE expression, which encourages cell inflammation signaling pathways, such as NF-κB activation, as well as generation of cytokines and growth factors. The transforming growth factor-β (TGF-β) is increasing the synthesis of collagen matrix components, which leads to higher thickness of the basement membrane, increased vascular permeability and reduced barrier activity [40]. Further evidence for glomerular injuries comes from immunohistochemical studies that have identified a number of AGEs like CML, pyrraline and pentosidine in renal tissues of diabetic patients [41].

In general, diabetes can affect the central, peripheral and autonomic systems. The manifestation of *diabetic neuropathy* can be characterized by functional abnormalities (reduced blood flow) and structural changes like axonal degeneration, fibre demyelination and neuronal apoptosis. Particularly, AGEs react with plasma proteins like IgM and IgG to activate the demyelination of the peripheral neurons. The complex AGE-RAGE induces ROS formation and several intercellular signaling pathways. ROS promotes both AGEs formation and AGEs quenching of nitric oxide (NO). Consequently, the NO level in the cells is decreased, which results in nerve ischemia (lack of oxygen) and then nerve dysfunction [42].

Wound healing in diabetic patients is hindered by the AGE-RAGE complex which stimulates production of pro-inflammatory factors resulting in collagen degradation [43].

The increased number of AGEs can cause extensive cross-linking, oxidative stress and neuronal cell death representing the neuropathological and biochemical characteristics of *Alzheimer's disease*, hampering the function of proteins or tissues [44].

Mechanisms of inhibiting AGEs formation

The serious implementation of AGEs in the genesis of many pathological conditions has initiated the process to identify and develop AGEs inhibitors that suppress their formation. The inhibitory mechanism of AGEs formation (Figure 4) can be accomplished by, for instance blocking the sugar attachment to proteins, attenuating glycoxidation and oxidative stress through trapping or scavenging some intermediates including reactive dicarbonyls, free radicals and nitrogen species produced in the process of glycation, and breaking down formed cross-links [45,46]. Glycation is a major source of ROS and RCS that are generated by both oxidative (glycoxidative) and non-oxidative pathways [47]. Therefore, potential AGE inhibitors are difficult to distinguish from general anti-oxidants, such as plant polyphenols. Contrary to the glycation of proteins by glucose, RCS such as MGO and GO exhibit both extracellular and intracellular glycating properties, and are involved in non-oxidative glycation reactions and the formation of AGEs *in vivo*. Glycation inhibitors, whose activity is based on antioxidant properties, may not effectively inhibit non-oxidative protein glycation [48]. Knowing the link between glycation and oxidation, it could be hypothesized that antioxidants might possess antiglycoxidative activities [47]. The investigation and discovery of so called "AGEs-breakers" also represent a therapeutic approach for lowering the risk of diabetic or other pathogenic complications caused by AGEs formation [45]. So far, a large number of compounds have been reported as inhibitors of glycation and AGE-protein cross-link formation. Additionally, the term "AGEs-breakers" was suggested by Cerami and described compounds which may cleave glycation derived cross-links and reverse the damaging effects of glycation associated with aging and diseases [49]. Another mechanism of action for the AGEs inhibitors may be related with the key enzyme in the polyol pathway – aldose reductase. During chronic hyperglycemia, excessive glucose uptake in the tissue affects the aldose reductase, leading to reduction of various sugars to sugar alcochol (e.g. glucose to sorbitol), increased fructose production, consequently, active formation of reactive carbonyl species [50]. Alternatively, any inhibitors of the enzyme aldose reductase can be considered as potential agents against AGEs formation.

AGEs inhibitors

Nowadays, there is an increased interest in agents with anti-glycation activity that could play a key role for prevention and amelioration of AGE-mediated health problems. The currently known AGEs inhibitors can be generally divided into two groups: synthetic compounds and natural products.

Synthetic compounds

According to a previous review which investigated the current clinical therapies with anti-AGEs effect, the applied agents can be summarised in several groups (see Table 2) [28]. The inhibition of free radicals generation derived from glycation processes and inhibition of protein modification is considered as one of the mechanisms of anti-glycation activity. Many data have shown that typical antioxidants / nutrients such as (5) vitamin B1 (thiamine) and (4) B6 (pyridoxamine) inhibit *in vitro* and *in vivo* AGEs formation [51]. Another preventive or therapeutic approach is to use nucleophilic anti-RCS molecules such as (1) aminoguanidine, pyridoxamine or (7) metformin. They could inhibit AGEs, remove RCS, and prevent the interaction of AGEs with RAGE. Despite the reported inhibitory capacity against AGEs formation, many synthetic inhibitors have been withdrawn from clinical trials due to relatively low efficacy, poor pharmacokinetics, and unsatisfactory safety [52].

Natural products

Current studies attempt to search for effective phytochemical compounds from dietary plants, fruits, and herbal medicines to inhibit AGEs formation [53]. In the past three decades has been a significant increase in the anti-AGEs agents from natural origin. The rate of scientific publications tripled in this time. In the current review, the references were selected by a search of papers retrieved using Web of Science for the period 1990-2019, and the key words “natural products” and “AGEs” Figure 5.

Considering the toxic or side effects of synthetic molecules in clinical trials, natural products can be more promising candidates as potent AGEs inhibitors. Phytochemicals exhibit several antiglycation mechanisms, including effects on glucose metabolism, amelioration of oxidative stress, scavenging of dicarbonyl species, and up/down-regulation of gene expression [54]. So far, some plant extracts and their phenolic ingredients have been evaluated for activity against AGEs formation, and also for their antioxidant activity [55]. Therefore, natural products with strong inhibitory properties on AGEs formation have great potential for further investigation as preventive drugs against AGE-associated diseases and disorders [45]. However, it remains unknown whether phytochemicals possess protective effects against glycotoxin-induced damage. While the anti-AGEs activity of a wide variety of synthetic molecules has already been evaluated, the chemodiversity of natural products such as secondary metabolites of vegetal origin still needs to be thoroughly explored [56]. Many plant products and their active constituents have been reported for prevention and treatment of various pathological conditions

in the human body: various plant extracts (Table 3), fractions or pure compounds (Table 4) have been excessively tested for inhibiting AGEs formation [26].

Plant extracts

Chrysanthemum morifolium Ramat. (Asteraceae) contains large amount of (27) chlorogenic acid, flavonoid glucoside and aglycon (e.g. (38) apigenin) varieties, and *Chrysanthemum indicum* L. (Asteraceae) is a rich source of (24) caffeic acid, luteolin and (44) kaempferol. The two *Chrysanthemum* species extracts demonstrated strong inhibition of AGEs formation, in particular, CML and pentosidine in BSA/ glucose (fructose) assay [57]. The inhibitory effects of *Chrysanthemum* extracts at concentration of 5 mg/ml were stronger than aminoguanidine at concentration of 1 mM used as a positive control.

The ethyl acetate-soluble fraction of the stem and leaves extract of *Erigeron annuus* L. (Asteraceae) contains quinic acid derivatives such as 3,5-di-*O*-caffeoyl-epi-qunic acid which showed an IC_{50} of 6.06 µM in the BSA/ glucose assay (while the IC_{50} of aminoguanidine was 961 µM), and prevented opacification of rat lenses [58].

Cinnamon (*Cinnamomum verum* J. Presl, Lauraceae), a traditional spice, has been shown to attenuate the symptoms of metabolic syndrome like insulin resistance, hyperglycemia, increased protein glycation, inflammation. It was found that the ethyl acetate extract from the bark, containing (33) catechin, (34) epicatechin and procyanidin B2, inhibited CML and pentosidine formation. Additionally, the presence of catechins was proved to reduce MGO to the physiological level [26,54].

S-ethylcysteine and *S*-propylcysteine in garlic (*Allium sativum* L., Amaryllidaceae) extract are strong antioxidants and free-radical scavengers, inhibiting CML formation and the plasma HbA_{1c} (glycated hemoglobin) [26,45]. In an *in vitro* BSA/ fructose model the IC_{50} of the extract was 16.8 µg/ml and lower than that of aminoguanidine at 27.7 µg/ml [59].

Ilex paraguariensis A. (Aquifoliaceae) (maté) contains high level of antioxidants, which are proved in *in vitro* models to inhibit the second phase of the glycation reaction, namely, the free radical-mediated conversion of Amadori products to AGEs [26,45]. In another study was shown that *I. paraguariensis* and its main component chlorogenic acid inhibited fructose formation of AGEs with amino acids at conditions compatible with those in the digestion system. The value for the maté tea was 83% inhibition at 50 µg/ml concentration, and for caffeic and chlorogenic acid the IC_{50} was 0.9 mM [60].

Rosmarinus officinalis L. (Lamiaceae), which main contains are (21) rosmarinic acid, (22) carnosic acid and carnosol, possesses antioxidant activity and anti-glycation properties

comparable to aminoguanidine [26]. An *in vitro* BSA/ glucose model revealed that rosmarinic acid and carnosic acid at 400 µg/ml inhibit fluorescent AGEs by 90%, and CML and CEL by 82.7% and 75.2% and 71.4% and 64.2%, respectively. Moreover, addition of 400 µg/ml rosmarinic acid and carnosic acid inhibited fluorescent AGEs by more than 90% both in the BSA/ GO and BSA/ MGO models, the formation of CML by 64.9% and 53.9% in the BSA/GO assay, and CEL by 28.9% and 24.3% in BSA/ MGO assay, respectively [61].

Camellia sinensis L. (Theaceae), which is a rich source of (-)-epigallocatechin 3-*O*-gallate (EGCG) and (-)-epicatechin 3-*O*-gallate (ECG), has strong antioxidant properties and inhibition of the accumulation of CML, CEL and the activation of RAGE [26]. In an glucose-glycated BSA models addition of green tea extract reduced the fluorescence intensity by 64.6% (while 72.8% for aminoguanidine). Also, the green tea extract was proved to inhibit the α-glucosidase and α-amylase resulting in delayed post-prandial hyperglycemia [62].

The exocarp 80% aqueous methanol extracts from *Citrus reticulata* Blanco x *Citrus sinensis* L. (Rutaceae), and *Citrus reticulata* x *Citrus paradisis* Macfad. decreased AGEs formation by lowering the levels of carbonyl compounds in adipocyte cells *in vitro* [54].

A standardized extract from *Ginkgo biloba* L. (Ginkgoaceae) (EGb 761), containing 24% flavonoids and 6% terpenoids, was proved to inhibit the RAGE activation in microvascular endothelial cells induced by hypoxic and hypoglycemic conditions [26].

The fruit of *Garcinia mangostana* L. (Clusiaceae) (mangosteen) contains catechins, procyanidins, anthocyanin and xanthones, such as α-mangostin. A study investigating the effect of mangosteen pericarp extract on the elasticity of the skin suggested that the water-soluble polyphenols in the water extract from mangosteen inhibit oxidation, resulting in the inhibition of the pentosidine formation *in vivo* and *in vitro* [63]. Oral administration of water extract of mangosteen at 100 mg/day to volunteer patients for 3 months reduced the serum pentosidine content and the skin autofluorescence intensity, improving the total skin condition.

The methanolic extract of the leaves of *Origanum majorana* L. (Lamiaceae) showed inhibition of AGEs formation *in vitro* and in streptozotocin-induced diabetic rats [64]. Besides the antioxidant activity of the extract, the *in vitro* studies demonstrated inhibiting protein glycation (IC_{50} = 0.310 ± 0.054 mg/ml in the BSA/ glucose assay) and trapping abilities of reactive carbonyl species such as methylglyoxal (IC_{50} = 0.190 ± 0.028 mg/ml). Treatment of streptozotocin-diabetic mice with the *Origanum majorana* extract and glibenclamide (as a positive control) for 28 days showed beneficial effects on renal metabolic disorders including glucose levels and AGEs formation compared to diabetic control and the positive control.

The methanol extract of *Thymus vulgaris* L. (Lamiaceae), containing the flavonoids (45) quercetin, eriodictyol, 5,6,4′-trihydroxy-7,8,3′-trimethoxyflavone and cirsilineol, suppressed the levels of AGEs formation measured through a fluorescent assay (82% AGEs inhibition at 1 mg/ml methanolic extract) [65].

Aralia taibaiensis L. (Araliaceae) showed particularly potent inhibition of the late glycation and the formation of AGEs. The antiglycation properties were addressed to the triterpenoid saponin content in the *n*-butanol extract [66]. The results from testing 1 mg/ml of the extract showed 77.44% inhibition in the hemoglobin-δ/ glucose assay (while the value for the 50 mM aminoguanidine was 20.17%); 77.63% in the BSA/ glucose assay (while the value for the 50 mM aminoguanidine was 76.52%) and 68.19% in the Gk-peptide/ ribose assay (while the value for the 50 mM aminoguanidine was 65.11%). The mechanism of action of the plant extract could be explained by scavenging free radicals, reduce oxidative damage, enhance insulin sensitivity and regulation of the enzymes related to the glucose metabolism.

The widely consumed aromatic food spice cumin (*Cuminum cyminum* L., Apiaceae) showed antiglycation properties in the BSA/ fructose intrinsic fluorescence assay. The seeds flavor constituents like sesquiterpenoids, monoterpenoids, and chalcone derivatives, demonstrated a potent role in this biological effect in the *in vitro* assay (AGEs inhibition > 50% *vs* 35%, respectively, and for aminoguanidine as a positive control) [67].

Isolated natural compounds

In this review, the selection of the enlisted and discussed pure compounds from medicinal plants is according to the established classification of plant secondary metabolites.

Resveratrol (18) is a natural antioxidant found in grapes has been described to inhibit AGEs-induced proliferation and collagen synthesis in vascular smooth muscle [68].

Additionally to its anti-oxidant and anti-inflammatory properties, (19) curcumin was reported to be a potent inhibitor of AGEs formation and cross-linking of collagen in diabetic rats [69]. It prevented the accumulation of AGE-collagen in diabetic animals; also, Hu et. al reported trapping of MGO by curcumin in cell-free systems and in human umbilical vein endothelial cells (HUVECs). Thus, curcumin may prevent MGO-induced endothelial dysfunction by directly trapping MGO [26,70]. In another study, additional mechanisms on how curcumin abolished AGEs-induced effects was through modulating the RAGE expression and interfering with the NF-κB pathway. In conclusion, curcumin is a potential protective agent against AGEs formation and AGEs-induced disruption through several mechanisms of action [71].

Phenolic acids are among the most widely distributed plant non-flavonoid phenolic compounds which can exert antioxidant activity by scavenging hydroxyl radicals, acting as chain breaking and reducing agents [72]. They can be divided in two main types: benzoic acid and cinnamic acid derivatives. Examples of cinnamic acid derivatives are: caffeic acid, chlorogenic acid, (28) ferulic acid, rosmarinic acid, while the benzoic acid derivatives include compounds derived from gallic acid.

Rosmarinic acid (21) and (22) carnosic acid are two commercially-available active constituents of rosemary extract that can possess anti-AGEs properties in *in vitro* models: BSA/ glucose, BSA/ glyoxal and BSA/ methylglyoxal assay [61]. In the BSA/ glucose assay 400 µg/ml rosmarinic acid reduced AGEs formation by 97.4%, while with 50 µg/ml carnosic acid the inhibition rate was three times higher. Rosmarinic acid decreased the MGO formation when added at concentrations higher than 25 µg/ml and did not show effect on GO concentration at the levels lower than 50 µg/ml.

A gallic acid derivative (23) 7-*O*-galloyl-D-sedoheptulose isolated from *Cornus officinalis* L. (Cornaceae), significantly reduced the expression of RAGE in type 2 *db/db* mice (20 or 100 mg/kg body weight/day, *per os*, administered every day for six weeks), decreased the fluorescent AGEs and reactive oxygen species in the liver, as well as, the expression of oxidative stress- and inflammation-related proteins [73].

Silymarin (29), flavonolignan obtained from *Silybum marianum* L. (Asteraceae), in addition to its free-radical scavenging properties, it has shown *in vitro* inhibitory effects on the late-stage glycation and subsequent cross-linking [26].

Kavalactones – (30) DL-kawain, methysticine, are a class of lactone compounds isolated from *Alpinia zerumbet* Pers. (Zingiberaceae), which is used in the preparation of traditional food in the Okinawan islands and are thought to contribute to the longevity of the people in this region [74]. The prevention of AGEs formation was investigated by the BSA/ glucose assay where both kawain (IC_{50} = 43.5 ± 1.2 µM) and methysticine (IC_{50} = 45.0 ± 1.3 µM) inhibited the process significantly better than aminoguanidine (IC_{50} = 231.0 ± 11.5 µM).

Mangiferin (32) – a major xanthone glucoside in the roots of *Anemarrhena asphodeloides* Bunge (Asparagaceae) traditionally used in the Chinese medicine, has been reported for its anti-diabetic and anti-inflammatory effects in diabetic cardiomyopathy rat model. Mangiferin reduced AGEs production and expression of RAGE, preventing the release of inflammatory cytokines and inhibited accumulation of ROS [75].

Flavonoids have been extensively investigated as AGEs inhibitors. In general, it is difficult to draw a clear line between the structural characteristics of flavonoids for inhibition of protein

glycation and radical scavenging activities. However, Matsuda *et al.* suggested the following requirements which should be present in the structures of potential AGEs inhibitors: (1) an increasing number of hydroxyl groups in position 3′, 4′, 5, 7 is associated with increased inhibitory activity; (2) flavones are more active than the corresponding flavonols, flavanones and isoflavones; (3) methylation or glycosylation of the 4′-hydroxyl group of flavones, flavonols and flavanones reduces activity; (4) methylation or glycosylation of the 3-hydroxyl group of flavonols tends to increase activity; (5) glycosylation of the 7-hydroxyl group of flavones and isoflavones reduces activity [76]. During the past few decades, a vast number of flavonoids have been reported to possess promising antiglycation activity.

Significant inhibition of AGEs formation by (33) (+)-catechin – a major metabolite of lotus seedpod oligomeric procyanidins, was demonstrated in a study by Wu *et al.* The anti-glycation properties of the compound were related to its potent activity of trapping dicarbonyl intermediates (IC_{50} value 0.049 ± 0.019 mg/ml; scavenging MGO activity 78.25 ± 2.99 %) and antioxidant capacities [77].

Plantagoside (42) (5,7,4′,5′-tetrahydroxyflavone-3′-*O*-glucoside) and its aglycone (5,7,3′,4′,5′-pentahydroxyflavone) obtained from the 50% ethanolic extract of *Plantago major* L. (Plantaginaceae) seeds were proven to inhibit the formation of AGEs in physiological conditions and inhibiting protein cross-linking glycation. The fluorometric BSA assay reported IC_{50} 1.2 μM for plantagoside and IC_{50} 18.0 μM for the aglycone which was 83- and 5.5-times stronger, respectively, than the one of aminoguanidine (IC_{50} 100.0 μM) used as a positive control [78]. Additionally, 18.0 μM plantagoside was identified to inhibit AGEs formation in physiological level.

Kaempferol (44), well known anti-oxidant flavonol aglycon, was detected to inhibit the early stages of AGEs formation by scavenging MGO in physiological conditions forming mono-MGO and di-MGO adducts. The data showed that MGO was trapped up to 60% by 0.25 mM aminoguanidine (although, the inhibitory activity was not dose dependent), in contrast to the same concentration of kaempferol, where the remaining MGO decreased significantly to 32% in a dose-dependent manner [79].

Quercetin (45) is another example of flavonol aglycones which was proved to inhibit MGO-mediated AGEs formation, as well as glucose- and ribose-mediated AGEs formation [80]. 100 μM exhibited 50% inhibition of MGO which was the highest result among other polyphenols tested in the assay such as (-)-epicatechin, gallic acid, hesperetin, (47) rutin, kaempferol. Another study compared the anti-glycation properties of quercetin and aminoguanidine, the generally used positive control in various fluorescent assays: hemoglobin-δ-gluconolactone (δ-

Glu) assay, MGO/ HSA (human serum albumin), GO/HSA, Gk-peptide (*N*-acetyl-glycyl-lysine methyl ester)/ ribose tests [81]. In the GO/HSA, 500 µM quercetin inhibited almost 75% of the post-Amadori glycation, while 10 mM of aminoguanidine reached 72.5% inhibition. In the Gk-peptide/ ribose assay, which is used to evaluate the inhibiting properties of the compound against cross-linking, 200 and 500 µM quercetin inhibited 61.5% and 69.6% of the late glycation products over a period of 14 days. As for aminoguanidine, the 62% inhibition in the same test was achieved in concentration of 10 mM.

In an *in vitro* screening assay, (47) rutin exhibited significant inhibitory effect at the intermediate stage of AGEs formation by trapping MGO with an IC_{50} value of 71.8 µM [26].

Polymethoxylated flavonoids (PMFs), particularly (50) 5-*O*-demethyl nobiletin isolated from the chloroform fraction of *Citrus depressa* Hayata (Rutaceae) peel, had significantly higher AGEs inhibitory activity (IC_{50} = 64.2 ± 3.6 µM) than aminoguanidine (IC_{50} = 484.3 ± 7.3 µM) measured *in vitro* through fluorimetric methods [82].

Amentoflavone (51), biflavonoid isolated from the methanol leaves extract of *Calophyllum flavoramulum* Hend. &Wyatt-Sm. (Calophyllaceae), was found to possess potent anti-AGEs activity *in vitro*: IC_{50} = 0.05 mM, while the activity of quercetin, used as a reference compound, was moderately strong: IC_{50} = 0.5 mM [83]. Amentoflavone can exert its anti-AGEs activity through various mechanisms like radical scavenging, chelation of divalent metal ions as well as trapping dicarbonyl species.

Geraniin, which is the main ellagitannin in the crude extract from *Nephelium lappaceum* L. (Sapindaceae) peels, is effective inhibitor of the carbohydrate enzymes: α-glucosidase and α-amylase, therefore it has the potential to interrupt carbohydrate digestion and the absorption of glucose resulting is suppressed postprandial hyperglycemia. Additional, *in vitro* studies proved the significant aldose reductase inhibiting properties, consequently, decreasing the formation of AGEs [84]. It has been demonstrated that geraniin has antioxidant, immune-modulation, antimicrobial, anticancer properties besides the promising therapeutic effects on hypertension, cardiovascular diseases and metabolic dysregulation.

Twelve triterpenoid saponins isolated form the extract of root bark of *Aralia taibaiensis* Z.Z. Wang & H.C. Zheng (Araliaceae), plant excessively used for the treatment of diabetes mellitus in the traditional Chinese medicine, exhibited both antioxidant and antiglycation properties. The activity against AGEs formation was detected through hemoglobin-δ-gluconolactone assay, BSA/ glucose assay and Gk-peptide/ ribose assay and it was significantly higher for the 3-*O*-[α-L-arabinofuranosyl-(1-4)-β-D-glucuronopyranosyl]-oleanolic acid (TA24); 3-*O*-{β-D-glucopyranosyl-(1-2)-[β-D-glucopyranosyl-(1-3)]-β-D-glucuronopyranosyl}-oleanolic acid

(TA21) and 3-*O*-{β-D- glucopyranosyl-(1-2)-[β-D-glucopyranosyl-(1-3)]-β-D-glucuronopyranosyl}-oleanolic acid 28-*O*-β-D-glucopyranosyl ester (TA9) [85].

Astragaloside V from the crude extract of Astragali Radix has shown inhibition of formation of CML and pentosidine in *in vitro* samples [26,50,86].

Other groups of compounds include: anthraquinones ((53) emodine), carotenoids, especially lutein and β-carotene from the ethyl acetate fraction of the green microalgae *Chlorella zofingiensis* Donz. (Oocystaceae), contribute to the strong antiglycation activity of this species; unsaturated fatty acids such as linoleic acid, arachidonic acid and eicosapentaenoic acid from *Nitzschia laevis* Hassall (Bacillariaceae) were reported as inhibitors of glycation. Moreover, (56) ursolic acid was suggested to play a significant role in patients with diabetes in reducing hyperglycemia, hepatic glucose production, hyperlipidemia and the influx of glucose through the polyol pathway.

Considering that AGEs are major pathogenic propagators in many human diseases, and especially in diabetes and its complications, it is of great importance to identify anti-glycation substances and to examine their mode of action. It is important to note that one AGE inhibitor will not act on all pathways, therefore, it is difficult to accept the existence of a magic bullet. Nevertheless, the current review seeks to address the lacuna in contemporary research for new potential drugs or lead compounds with AGEs inhibiting properties. However, despite the tremendous efforts of many scientists in the field, none of the discussed natural products or extracts have progressed to clinical trials or even systematic preclinical studies. The reason for this can be found in the current lack of validated analytical methods for the unambiguous determination of AGEs inhibiting properties of particular candidates. Future work involving advanced analytical techniques and suitable sample preparation steps is expected in order to reveal the positive hits among plant compounds as inhibitors of AGEs formation.

Conclusion

Pathophysiological accumulation of AGEs *in vivo* has been associated with the progression of many health disorders. The current review aimed to summarise the reports in the past three decades for plant-derived natural products with anti-glycation activity. A vast number of plant extracts and pure compounds exhibit their AGEs inhibitory activity through several mechanisms of action, for example: trapping dicarbonyl intermediates, hyperglycemic activity, decrease expression of RAGE, potent free radical scavenging activity. Additionally, some of them possess other pharmacological properties as anti-inflammatory, reduction of insulin resistance which can contribute to improving the overall glycemic control and endothelial

function. In general, the promising anti-glycation activity of the extracts is in a tight correlation with their total phenolic content. However, many nonphenolic compound such as terpenoids, flavonoids, alkaloids demonstrated high potential to reduce the non-enzymatic glycosylation. The plant-derived AGEs inhibitors represent attractive novel therapeutic agents that can join forces with the already existing synthetic drugs in the treatment and/ or prevention of health issues with major importance like diabetes, neurodegenerative disorders, and aging. On the contrary to synthetic agents, the full potential of plant products has been still unrevealed and requires further comprehensive analysis in order to expand our knowledge on the antiglycation phytomolecules. However, a crucial aspect to identify the potent and promising AGEs inhibitors from natural origin is the use of validated analytical methods for precise determination of their AGEs inhibiting properties. Consequently, this can determine the outcome for developing medications using plant products, conducting clinical trials, and eventually, having new therapeutic agents reaching the market.

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Conflict of Interest Statement

The authors declare no conflict of interest.

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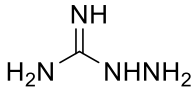
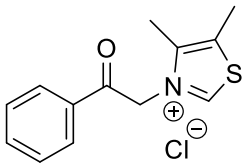
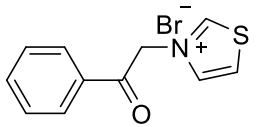
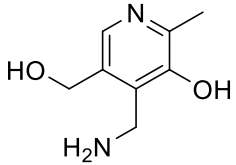
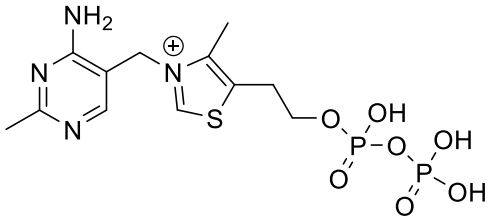
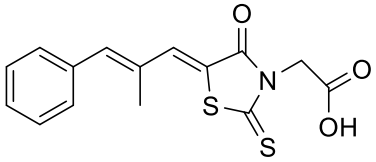
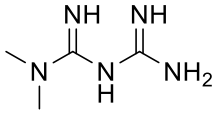
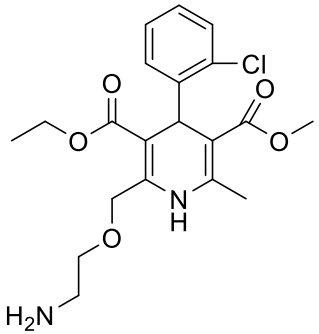
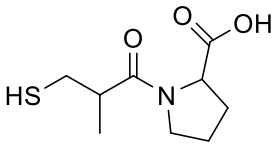
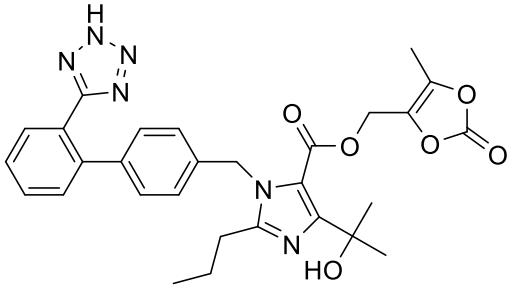
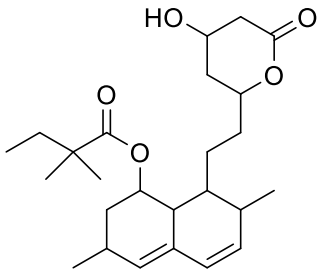
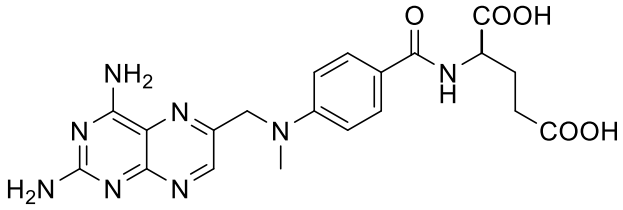
Table 1. Molecular structures and pathophysiological properties of some glycation products.

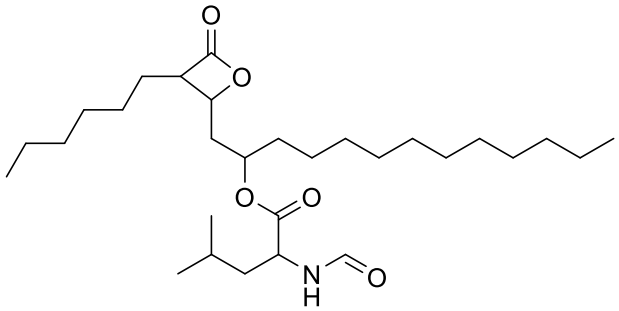
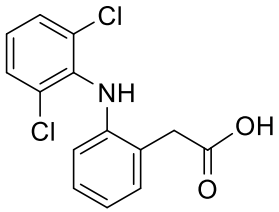
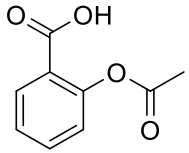
Classification	Glycation product	Pathophysiology	References
α-dicarbonyl intermediates	MGO	nephropathy, atherosclerosis, tissue injury and protein cross-linking	[45,46,87–89]
monolysine adducts	CML	skin collagen cross-linking, progression of cardiovascular diseases	[19,88,90]
	CEL	accumulating in tissue proteins, progression of cardiovascular diseases	[90,91]
	pyrraline	plasma proteins and skin collagen cross-linking	[20,91]
imidazolium crosslinks	GOLD (glyoxal-lysine dimer)	a major crosslink in serum proteins of uremic and haemodialysis patients	[92,93]
	MOLD (methylglyoxal-lysine dimer)	cross-link formed in lens protein, a major crosslink in serum proteins of uremic and haemodialysis patients	[21,92,93]
	DOLD (3-deoxyglucasone-derived lysine dimer)	not yet detected in tissue proteins	[21,92]
	glucosepane	cross-linked AGE in old human collagen and human eye lenses, associated with stiffness of arteries, joints and lenses in diabetes	[92]
fluorophores	argpyrimidine	cataractous lenses	[91]
	pentosidine	lens proteins and skin collagen cross-linking	[22,88]
	vesperlysine A, B, C	cross-linked products formation	[94]

Table 2. Synthetic inhibitors of AGEs formation based on their mechanism of action or their chemical structure.

Drug class	Compound	Stage of glycation	Mechanism of action	References
Specific AGEs inhibitors and AGEs breakers	 **(1) Aminoguanidine**	late stage	Trapping α-dicarbonyl intermediates by nucleophilic reaction (carbonyl scavenging activity).	[89,91,95–99]
	 **(2) Alagebrium chloride (ALT-711)**	late stage	Chemical cleavage of the carbon-carbon bond in *α*-dicarbonyl-containing cross-linked structures.	[28,45,97]
	 **(3) N-phenacylthiazolium bromide (PTB)**	late stage	Reacting with and cleaving covalent AGEs-derived protein cross-links.	[45]
B vitamins and synthetic derivatives of B vitamins	 **(4) Pyridoxamine (vitamin B6)**	late stage	Blocking the oxidative degradation of glucose-derived Amadori intermediates by binding catalytic metal ions interferes the post-Amadori oxidative reactions or quenching dicarbonyl compounds.	[91,100,101]

	 **(5) Thiamine pyrophosphate, benfotiamine (synthetic derivative)**	late stage	Benfotiamine shunts the triose glycolytic intermediates towards the reductive pentose pathway.	[40,91,97,102]
Aldose reductase inhibitors	 **(6) Epalrestat**	multistage inhibitor	Trapping 3-DG and inhibiting the CML formation.	[28,103]
Glucose-lowering medications	 **(7) Metformin**	multistage inhibitor	Trapping MGO and other dicarbonyls.	[91,104,105]
Blood pressure-lowering medications	Calcium antagonists  **(8) Amlodipine**	late stage	Radical scavenging properties, inhibiting the production of dicarbonyl precursors by chelation of metal ions and blocking hydroxyl radicals at the pre-Amadori step.	[106]

	ACE inhibitors		late stage	Inhibiting formation of fluorescent AGEs (pentosidine).	[92,107]
		(9) Captopril			
	AIIRIs		late stage	Inhibiting formation of fluorescent AGEs (pentosidine).	[92]
		(10) Olmesartan			
Lipid-lowering medications			late stage	Antioxidant properties, consequently decreasing the lipid peroxidation and the AGEs production.	[28]
		(11) Simvastatin			
Medications against rheumatic diseases			late stage	Decreasing serum and urinary pentosidine levels.	[28]

	(12) Methothrexate			
Weight-reduction therapies		late stage	Decreasing the level of serum AGEs, urinary pentosidine and serum CML.	[28]
	(13) Orlistat			
NSAIDs		early stage	Blocking sugar attachment to proteins due to non-covalent binding.	[48,91,92]
	(14) Diclofenac			
		early stage	Blocking the attachment of reducing sugars to proteins due to acetylating the free amino groups.	[45,91]
	(15) Acetylsalicylic acid			

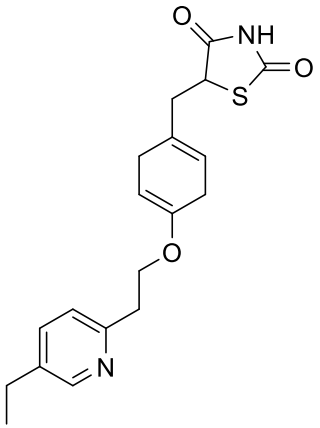
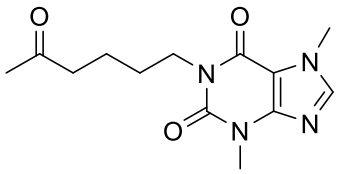
Antidiabetic thiazolidinedione	 **(16) Pioglitazone**	early stage	Inhibiting glycation and AGEs formation due to direct interaction between the hydrazine nitrogen atom of pioglitazone and a carbonyl group; antioxidant effects.	[46,89,108]
Agents against diabetes-induced peripheral vascular diseases	 **(17) Pentoxifylline**	early stage	Moderate activity for inhibiting glycation related to antioxidant properties.	[91]

Table 3. Medicinal plant extracts inhibiting AGEs formation.

Plant	Extract	Antiglycation activity	Reference
Allium sativum skin	50% ethanolic extract	Inhibiting AGEs formation in an *in vitro* BSA/ fructose assay. Strong antioxidant and free-radical scavenging properties.	[26,59]
Alpinia zerumbet rhizome	hexane	Inhibiting the Amadori products formation and trapping reactive dicarbonyl compounds.	[109]
Apocynum venetum L. (Apocynaceae) leaves	water	Antioxidant properties and protection against glucose-mediated protein modification *in vitro*.	[110,111]
Aralia taibaiensis root bark	*n*-butanol	Inhibiting AGEs formation *in vitro*: BSA/ glucose, Gk-peptide/ ribose and hemoglobin- δ / glucose assay.	[66]
Astragalus membranaceus L. (Fabaceae) roots	methanol	Hypoglycemic effect, decreasing the aldose reductase and increase the insulin level. Additionally, inhibit the CML and pentosidine formation.	[112]
Calendula officinalis L. (Asteraceae) whole plant	methanol	Inhibiting protein glycation in BSA/ glucose *in vitro* assay, potent antioxidant activity.	[113]
Camellia sinensis leaves	water	Inhibited AGEs formation in the BSA/ MGO and BSA/ ribose models by	[26,62]

		trapping α -dicarbonyl compounds. Reducing the post-prandial hyperglycemia.	
Chrysanthemum sp. flowers	water	Inhabiting CML and pentosidine formation in an *in vitro* BSA/ glucose (fructose) assay by free radical and metal scavenging.	[57]
Cinnamomum verum bark	ethyl acetate	Inhibiting CML and pentosidine formation. Mimicking insulin activity.	[26,54]
Citrus sinensis seeds; *Citrus reticulata* x *C. sinensis* peels *C. reticulata* x *Citrus paradisis* peels	water; 80% methanol	Inhibiting AGEs formation in BSA/ glucose assay; HSA/ MGO assay. Potent free radical scavenging activity.	[114,115]
Cuminum cyminum seeds	methanol	Inhibiting AGEs formation in BSA/ fructose assay.	[67]
Curcuma longa L. (Zingiberaceae) rhizome	methanol	Inhibiting free radicals and HbA_{1c} formation, antioxidant effect, hypoglycemic effect and preventing lipid peroxidation.	[116,117]
Empetrum nigrum L. (Ericaceae) fruit	80% ethanol	Inhibiting the formation of fluorescent AGEs in concentration-dependent manner, potent radical scavenging activity.	[118]
Erigeron annuus leases and stems	methanol	Inhibition of RLAR (rat lens aldose reductase), AGEs formation, AGEs/	[58]

		BSA cross-linking, and cataractogenesis.	
Garcinia mangostana pericarp	water	Inhibiting the formation of pentosidine.	[63]
Garcinia subelleptica (Clusiaceae) leaves	ethyl acetate	Inhibiting protein glycation in several *in vitro* models: BSA/ glucose experiment, fructosamine adduct and α - dicarbonyl compounds formation.	[82]
Glycyrrhiza glabra L. (Fabaceae) roots	methanol	Inhibiting AGEs formation through radical scavenging properties. Antioxidant and hypoglycemic activity.	[119]
Hypericum perforatum L. (Hypericaceae) aerial part	methanol	Free radical scavenging activity, inhibiting lipid peroxidation, and inhibiting the advanced glycation in an BSA/ glucose assay.	[120]
Ilex paraguariensis leaves and stems	water	Inhibition of the free-radical-mediated conversion of Amadori products to AGEs.	[26,60]
Juglans regia L. (Juglandaceae) bark	methanol	Inhibiting protein glycation in BSA/ glucose in *in vitro* assay, antioxidant activity.	[113]
Knoxia valerianoides Thovel ex Pitards (Rubiaceae) root	methanol	*In vitro* inhibition of AGEs formation in BSA/ fructose and glucose assay, and inhibition of rat lens aldose reductase activity.	[99,121]

Matricaria recutita L. (Asteraceae) leaves	70% methanol extract	Potent inhibition on the rat lens aldose reductase, AGEs formation and reactive oxygen species.	[122]
Melissa officinalis L. (Lamiaceae) leaves	water	Inhibiting the pentosidine formation in BSA/ fructose model. Improving tissue damage in blood vessels and skin elasticity.	[123]
Mentha arvensis L. (Lamiaceae) leaves	water	Reduction of fructosamine formation, dicarbonyl compounds formation and glycated albumin, free radical scavenging activity.	[124]
Nigella sativa L. (Ranunculaceae) seeds	water	Scavenging reactive carbonyl and oxygen species.	[125]
Origanum majorana leaves	methanol	Inhibiting AGEs formation *in vitro* (BSA/ glucose assay, BSA/ MGO assay, Amadori screening assay, Glycation of hemoglobin) and in streptozotocin-induced diabetic rats.	[64]
Panax ginseng L. (Araliaceae) root	different solvents: water, 70% ethanol, 55% ethanol	Reducing AGEs formation through alleviating oxidative stress.	[45,126]
Polygonum multiflorum Thunb. (Polygonaceae) root	80% ethanol	Scavenging free radicals, inhibiting lipid peroxidation and protein glycation.	[127]
Punica granatum L. (Lythraceae) fruit	fruit juice	Antiglycation effect through inhibiting the α-amylase and α-glucosidase, and	[128,129]

		metal chelating activity.	
Rhus verniciflua Stokes. (Anacardiaceae) bark	ethanol	Inhibiting aldose reductase and AGEs formation in a BSA/ glucose assay, potent antioxidant activity.	[130]
Rosmarinus officinalis leaves	50% ethanolic extract	Inhibiting AGEs formation in an *in vitro* BSA/ fructose assay. Potent antioxidant and antiglycation activity.	[26,59,61]
Solanum lycopersicum L. (Solanaceae) fruit	tomato paste	Inhibiting glucose autoxidation and trapping reactive dicarbonyl compounds.	[26,54,131]
Thymus vulgaris whole plant	methanol	Inhibiting AGEs formation in a BSA *in vitro* model and fructosamine formation detected through the reduction of NBT.	[65]
Trigonella foenum-graeceum L. (Fabaceae) seeds	70% ethanolic extract	Hypoglycemic and antioxidant effect, decreasing the lipid peroxidation.	[132]
Vaccinium spp. (Ericaceae) leaves	ethanol	Inhibiting Amadori product formation and trapping reactive dicarbonyl compounds.	[133]
Vitis vinifera L. (Vitaceae) skin	water	Scavenging free radicals and dicarbonyl species.	[134]

Table 4. Pure compounds inhibiting AGEs formation presented according to the classification of plant secondary metabolites.

Classification	Compound	Antiglycation activity	Reference
Stilbenes	**(18) resveratrol**	Inhibiting AGEs formation in BSA/ fructose, BSA/ MGO, arginine/ MGO models. A competitive inhibitor of α-amylase and α-glucosidase.	[135]
Chalcones	**(19) curcumin**	Inhibiting AGEs formation through trapping MGO, modulating the RAGE expression, interfere with the NF-κB pathway.	[69]
	(20) phloridzin	Inhibiting the absorption of glucose in the small intestines and the renal resorption, resulting in overall decrease of hyperglycemia in animal models. Additional anti-inflammatory activity, antioxidant properties and anti-AGEs effect in BSA/ glucose *in vitro* model.	[136,137]
Phenolic acids	**(21) rosmarinic acid, (22) carnosic acid**	Efficiently inhibit AGEs formation in part by decreasing glycation and by reducing the level of reactive precursors (such as methylglyoxal) for glycation	[61]

	(23) 7-*O*-galloyl-D-sedoheptulose	Reduced renal glucose, AGEs formation, and oxidative stress in diabetic rats, showing beneficial effect on the early stages of diabetic kidney disease.	[73]
	(24) caffeic acid	Inhibiting AGEs formation in the *in vitro* BSA/ glucose model, decrease the expression of proinflammatory mediators. In general prevents and delays the vascular disfunction in diabetes.	[138]
	(25) ellagic acid	Preventing *iv vivo* accumulation of AGEs (CML) and ameliorate renal changes in diabetic rats.	[139,140]
	(26) vanillic acid	Inhibiting reactive dicarbonyl intermediates (MGO), ROS formation and CML formation, consequently, preventing the development of diabetic neuropathy.	[141]
	(27) chlorogenic acid	Inhibiting the AGEs cross-linking to collagen in an AGE-ELISA assay and dicarbonyl intermediates (MGO).	[142]
	(28) ferulic acid	Preventing glucose-, fructose-, and ribose-induced protein glycation, as well as MGO-induced protein glycation and oxidative protein damage in BSA.	[143]
Kavalactones	**(30) kawain and methysticine**	Inhibiting protein glycation in BSA/ glucose assay.	[74]

Coumarins	**(31) umbelliferone**	Inhibiting α-glucosidase and the pancreatic amylase as a result decreasing the postprandial hyperglycemia. Inhibiting α-dicarbonyl compounds formation.	[144]
Flavanols	**(33) (+)-catechin**	Greater antiglycation activity due to carbonyl scavenging and antioxidant activity.	[111]
	(34) (-)-epicatechin	Trapping ROS and RCS (e.g. MGO).	[145]
	(35) (-)-epicatechin gallate	Suppressing the carbonylation and the formation of amyloid cross-β structures of BSA and the AGEs formation through a BSA/ fructose model, additionally trapping MGO.	[146]
	(36) (-)-epigallocatechin-3-gallate	Decreasing the AGE-stimulated gene expression and production of TNF-α, and AGE-mediated activation of NF-κB.	[147]
Flavones	**(37) luteolin**	Potent inhibitor on the early stage of protein glycation (δ-Glu assay), preventing the HbA_{1c} formation.	[47]
	(38) apigenin	Inhibiting AGEs formation through trapping MGO, suppressing the production of ROS and inflammatory cytokines and adhesion molecules.	[148]

	(39) diosmin	Decreasing glycosylated hemoglobin and increasing hemoglobin and plasma insulin.	[149]
	(40) vitexin	Inhibiting AGEs formation in an in vitro BSA/ glucose and BSA/ MGO assays because of trapping dicarbonyl intermediates and free radical scavenging capacity.	[150]
Flavanones	**(41) naringenin**	Inhibiting AGEs formation in an *in vitro* BSA/ MGO assay.	[151]
	(42) plantagoside	Inhibiting protein glycation and in physiological conditions protein cross-linking glycation.	[78]
	(43) liquiritin	Increasing the AGEs-reduced superoxide dismutase activity, decreasing RAGE expression and blocking NF-κB activation. Consequently, has a protection effect on AGEs-induced endothelial disfunction.	[152]
Flavonols	**(44) kaempferol**	Effect on the intermediate stage of AGEs formation by trapping MGO.	[79]
	(45) quercetin	Inhibit AGEs formation *via* chelating metal ions, trapping MGO, and trapping ROS. The activity was more potent than aminoguanidine.	[80,81]
	(46) hyperoside	Inhibiting AGEs induced upregulation of RAGE.	[153]

	(47) rutin	Metal chelating properties. Inhibiting pentosidine formation in collagen/ glucose model.	[154]
	(48) myricetin	Decreasing the insulin resistance. Demonstrates anti-inflammation, anti-oxidative stress, anti-aldose reductase, anti-non-enzymatic glycation and anti-hyperlipidemic activity.	[155]
Anthocyanins	**(49) cyanidin 3-*O*-Glc**	Inhibiting dicarbonyl compounds and reducing fructosamine formation, affecting the initiation and the intermediate state of protein glycation. Potent ROS scavenging activity.	[156]
PMFs	**(50) 5-*O*-demethyl nobiletin**	Inhibiting protein glycation in several *in vitro* models: BSA/ glucose experiment, fructosamine adduct and α-dicarbonyl compounds formation.	[82]
Biflavonoids	**(51) amentoflavone**	Inhibiting protein glycation in an *in vitro* assay using fluorescent measurement.	[83]
Naphthoquinones	**(52) juglone**	Inhibiting prolyl-isomerase-1 (regulating the protein function through post phosphorylation) which acts against vascular oxidative stress, endothelial disfunction and inflammation.	[157]

Anthraquinones	**(53) emodin**	Inhibiting fructose-, MGO-, and glyoxal-induced HAS. The antiglycation effect is due to binding capacity and stabilization of the HAS protein structure.	[158]
Tannins	geraniin	Inhibiting α-glucosidase and α-amylase which leads to decreased postprandial hyperglycemia. Anti-AGEs activity through inhibiting the aldose reductase *in vitro*.	[84]
Terpenes	**(54) thymol**	Inhibiting AGEs formation in a BSA/ MGO model by trapping dicarbonyl intermediates and free radicals.	[159]
	3-*O*-[α-L-arabinofuranosyl-(1-4)-β-D-glucuronopyranosyl]-oleanolic acid	Inhibiting protein glycation in several *in vitro* models: BSA/ glucose experiment, Gk-peptide ribose and hemoglobin-δ-gluconolactone assay.	[85]
	astragaloside V	Inhibiting the CML and pentosidine formation in an *in vitro* BSA/ ribose model. A promising candidate for preventing diabetic complications.	[112]
	ginsenoside Rb1	Improving insulin resistance, having anti-obesity, anti-hyperglycemic, and anti-diabetic effect by inhibiting protein glycation, the aldose reductase activity.	[160]
	(55) oleanolic acid	Inhibiting fructosamine and α-dicarbonyl compounds formation due to potent antioxidant activity and trapping	[161]

		MGO. Binding to lysine and arginine residues of the BSA prevents the attachment of the BSA to sugars.	
	(56) ursolic acid	Inhibiting AGEs formation by attenuating the aldose reductase and sorbitol dehydrogenase activity – the two major enzymes in the polyol pathway.	[162]
Alkaloids	**(57) berberine**	Preventing microvascular complications in diabetes due to protective effect on high glucose-induced endothelial disfunction *in vitro* with increased NO and endothelium-dependent vasodilatation.	[163]

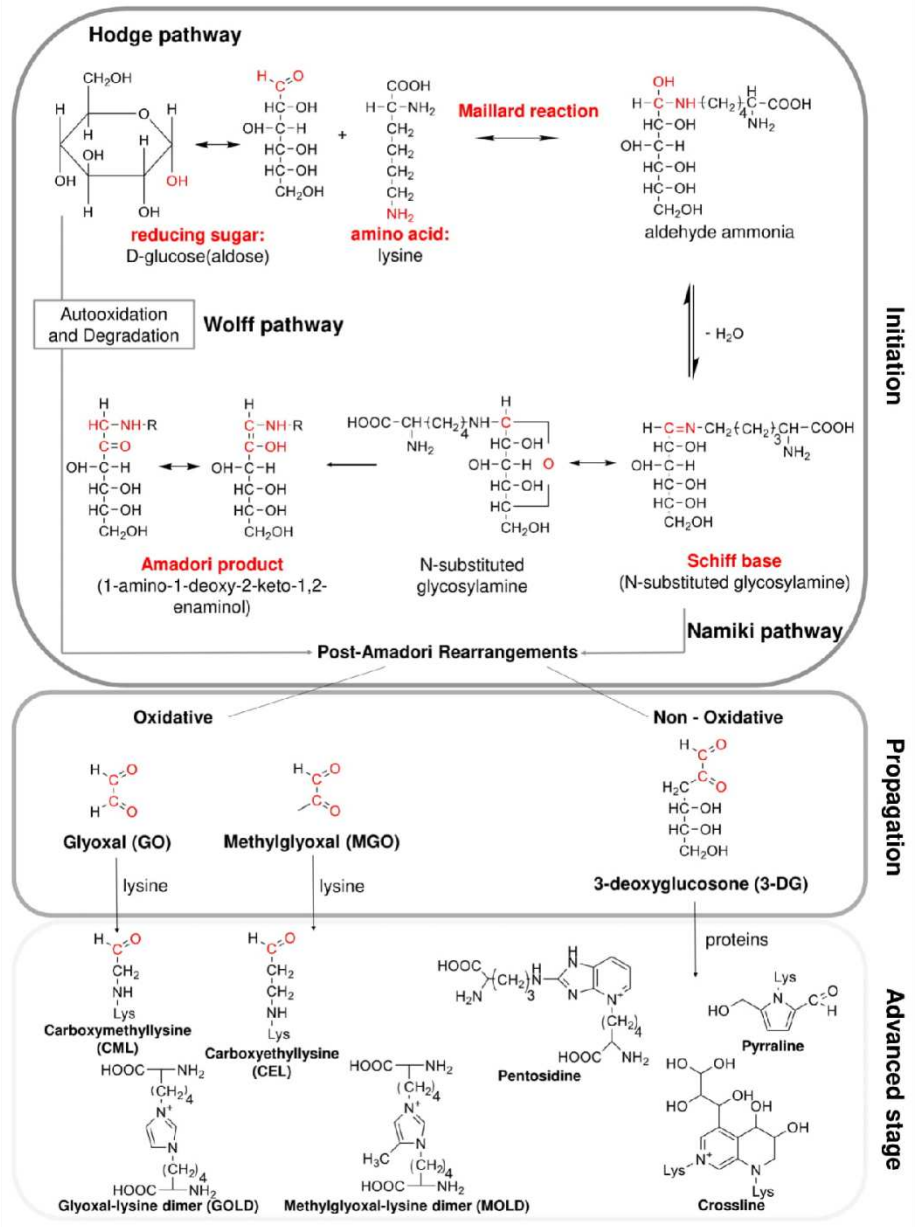

Hodge pathway
reducing sugar:
D-glucose(aldose)
amino acid:
lysine
Maillard reaction
aldehyde ammonia
Autooxidation and Degradation
Wolff pathway
- H2O
Amadori product
(1-amino-1-deoxy-2-keto-1,2-enaminol)
N-substituted glycosylamine
Schiff base
(N-substituted glycosylamine)
Namiki pathway
Post-Amadori Rearrangements
Initiation
Oxidative
Non - Oxidative
Glyoxal (GO)
Methylglyoxal (MGO)
3-deoxyglucosone (3-DG)
lysine
lysine
proteins
Propagation
Carboxymethyllysine (CML)
Carboxyethyllysine (CEL)
Pentosidine
Pyrraline
Glyoxal-lysine dimer (GOLD)
Methylglyoxal-lysine dimer (MOLD)
Crossline
Advanced stage

Figure 1. General scheme of the Advanced Glycation Endproducts (AGEs) formation pathway (Hodge pathway) going through Schiff base and Amadori product formation. However, AGEs can be formed by pre- and post-Amadori product reactions, and in such a way that the Amadori product is not a precursor. Alternatively, the reactive dicarbonyl species can be formed directly from Schiff base degradation (Namiki pathway) or through the metal-catalyzed autoxidation of reducing sugar (Wolff pathway).

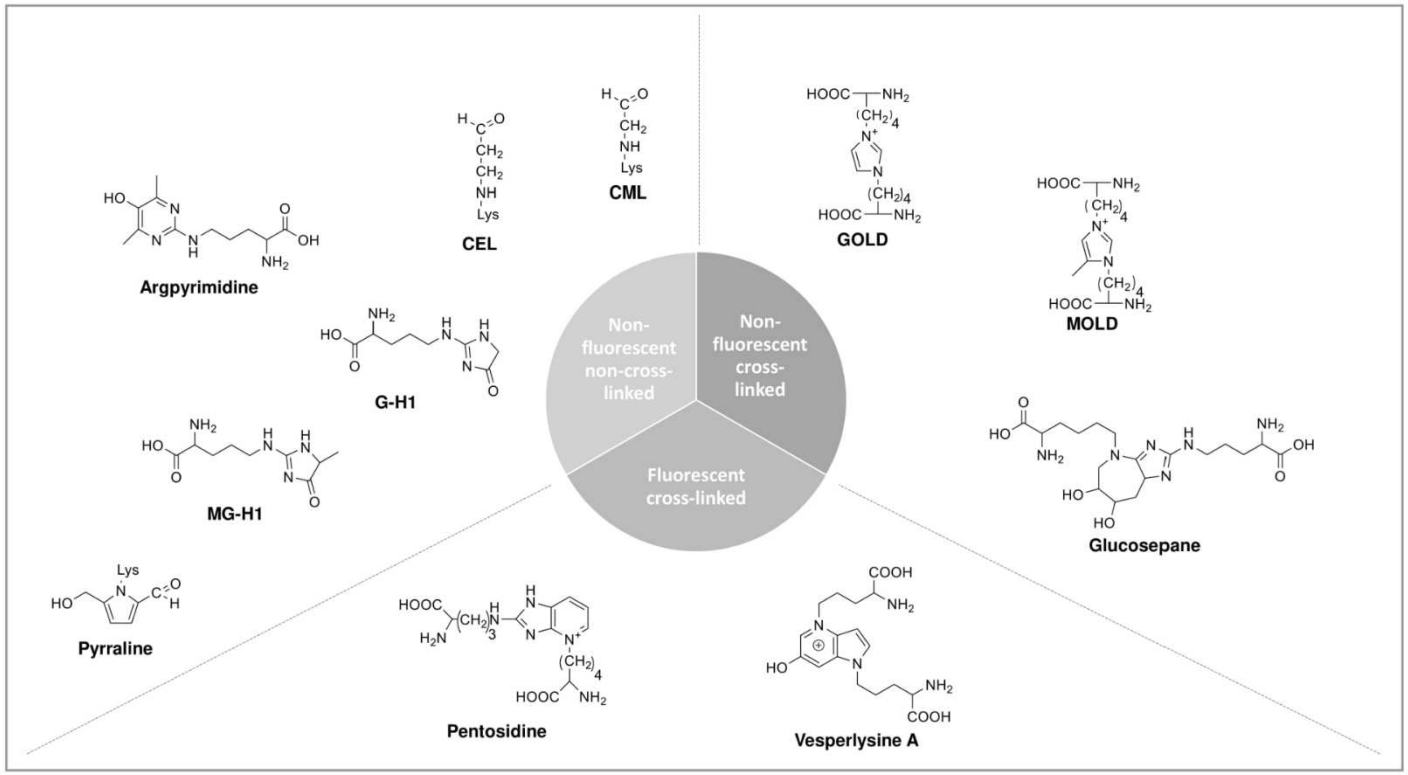


Figure 2. AGEs classification based on their fluorescent properties and the presence of cross-linking in the structure, namely, non-fluorescent cross-linked, fluorescent cross-linked and non-fluorescent non-cross-linked AGEs.

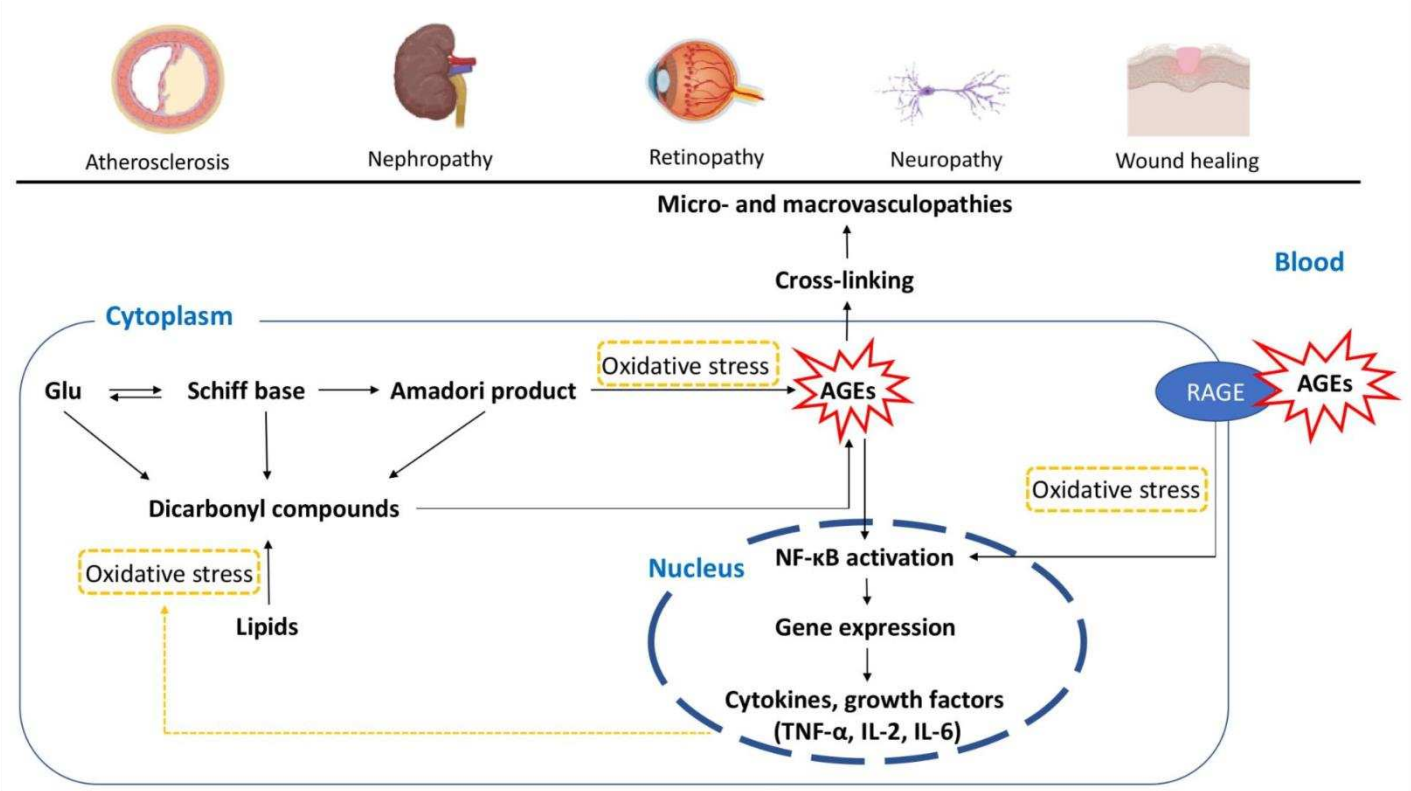

Atherosclerosis
Nephropathy
Retinopathy
Neuropathy
Wound healing
Micro- and macrovasculopathies
Blood
Cross-linking
Cytoplasm
Oxidative stress
AGEs
RAGE
AGEs
Glu
Schiff base
Amadori product
Oxidative stress
Dicarbonyl compounds
Nucleus
NF-κB activation
Oxidative stress
Lipids
Gene expression
Cytokines, growth factors
(TNF-α, IL-2, IL-6)

Figure 3. Pathophysiological significance of protein glycation. Interaction of AGEs with RAGE causing oxidative stress and initiating inflammation cascade that involves NF-κB activation; IL-2, IL-6, TNF-α synthesis; and cross-linking formation which lead to the development of micro- and macrovasculopathies implicated in atherosclerosis, diabetic nephropathy, retinopathy, neuropathy, and wound healing.

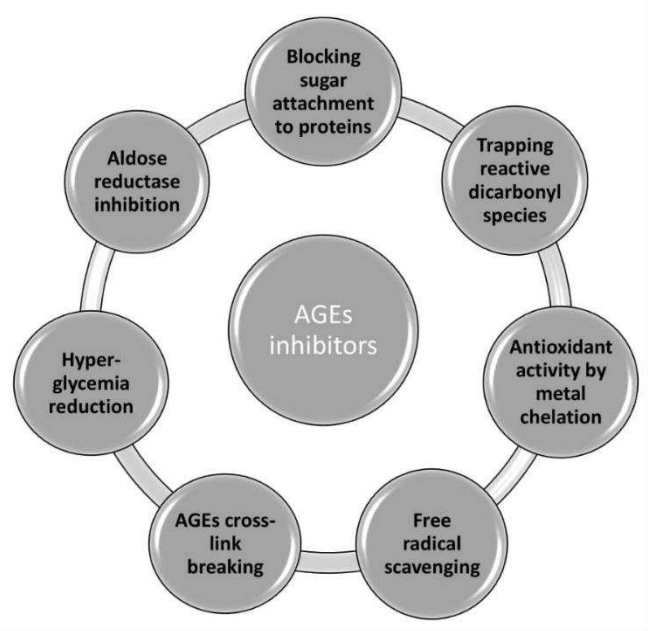


Figure 4. Different mechanisms of inhibiting AGEs formation.

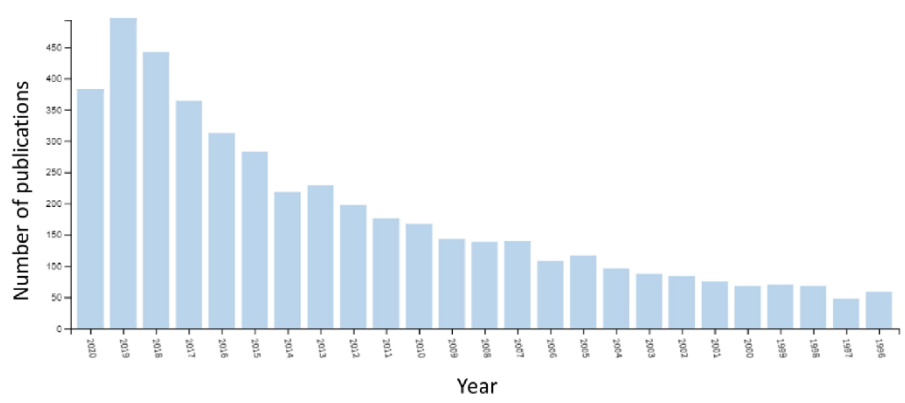
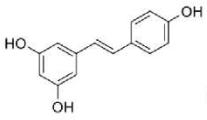


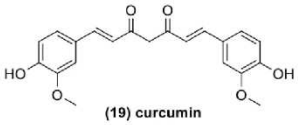
Figure 5. Publication frequency in the research of natural products as potential inhibitors of AGEs over the period 1990-2019. The database used was Web of Science and the search terms were: “natural products” and “AGEs”, which reviled a total count of 4.251 publications.

Stilbenes

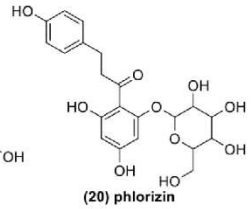


(18) resveratrol

Chalcones

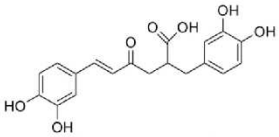


(19) curcumin

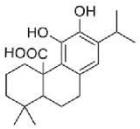


(20) phlorizin

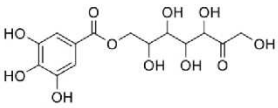
Phenolic acids



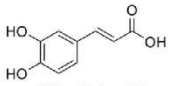
(21) rosmarinic acid



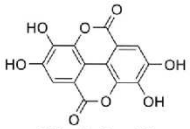
(22) carnosic acid



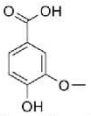
(23) 7-*O*-galloyl-D-sedoheptulose



(24) caffeic acid

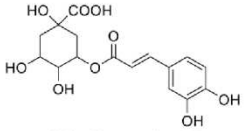


(25) ellagic acid

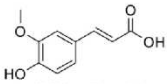


(26) vanillic acid

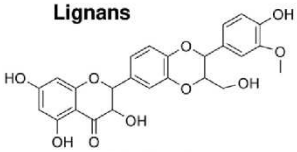
Lignans



(27) chlorogenic acid

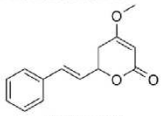


(28) ferulic acid



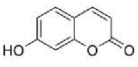
(29) silymarin

Kavalactones



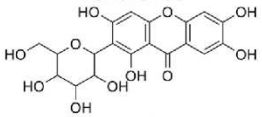
(30) kawain

Coumarins



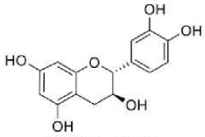
(31) umbelliferone

Xanthones

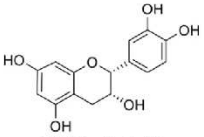


(32) mangiferin

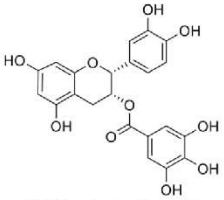
Flavanols



(33) (+)-catechin



(34) (-)-epicetechin

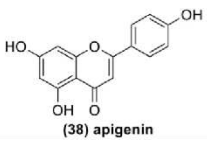


(35) (-)-epicatechin gallate

(36) epigallocatechin-3-gallate

Flavones

(37) luteolin



(38) apigenin

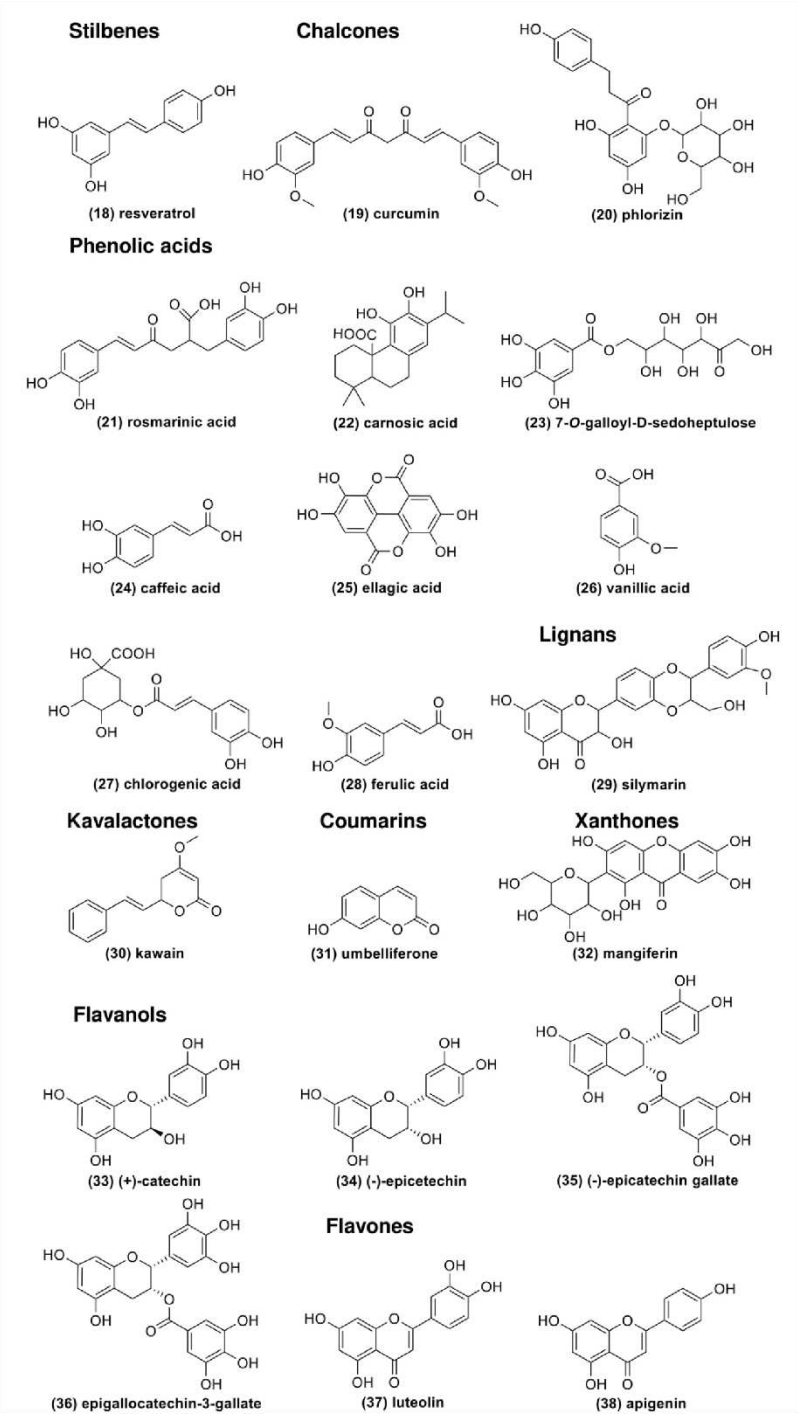


Figure 6. Chemical structure of natural products with AGEs inhibiting properties.