

The Hazards of Skin Glycation and Related Inhibitors

Subjects: Dermatology

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Skin saccharification, a non-enzymatic reaction between proteins, e.g., dermal collagen and naturally occurring reducing sugars, is one of the basic root causes of endogenous skin aging. During the reaction, a series of complicated glycation products produced at different reaction stages and pathways are usually collectively referred to as advanced glycation end products (AGEs). AGEs cause cellular dysfunction through the modification of intracellular molecules and accumulate in tissues with aging. AGEs are also associated with a variety of age-related diseases, such as diabetes, cardiovascular disease, renal failure (uremia), and Alzheimer's disease. AGEs accumulate in the skin with age and are amplified through exogenous factors, e.g., ultraviolet radiation, resulting in wrinkles, loss of elasticity, dull yellowing, and other skin problems.

Keywords: skin glycation ; anti-glycation ; AGEs inhibitors

1. The Hazards of Skin Glycation

The skin is mainly divided into three layers: epidermis, dermis, and subcutaneous tissue, and it is the organ with the largest contact area between the human body and the external environment. It not only protects the body from damage from the external environment and avoids the loss of water from the body but also has a certain cosmetic effect ^[1]. The aging of the skin is first manifested as the aging of cells. Studies have shown that with aging, the proliferation and vitality of skin fibroblasts are reduced, leading to a decrease in the secretion of elastin fibers, collagen fibers, reticular fibers, and extracellular matrix in the dermis layer of the skin. This will result in a deepening and lengthening of skin wrinkles, pigmentation, and other manifestations of aging. A distinctive feature of aging at the molecular level is the gradual accumulation of non-enzymatically modified proteins, i.e., glycation, which produces skin problems, such as wrinkles, pigmentation, and yellowing of the skin color ^[2].

1.1. The Harm of High Glucose to the Skin

Glycation is an aging reaction of naturally occurring sugars and dermal proteins ^[3], which begins in early life, develops clinical symptoms at around 30, and progressively accumulates in tissues and skin due to the glycated collagens that are difficult to be decomposed ^[4]. Advanced glycation end products (AGEs) derived from natural sugars (such as glyceraldehyde-3-PO₄, glucose-6-PO₄, and fructose) are formed several times faster than advanced glycation end products (AGEs) derived from glucose. Thus, glucose is the main source of energy for mammalian cells, fueling glycolysis and the tricarboxylic acid (TCA) cycle ^[5]. High-sugar foods activate the reward system of hypothalamic regulation to promote the intake of more foods that are easily metabolized as glucose ^[6]. A correlation has been shown between a high-sugar diet and elevated sugar levels in the blood and skin, and a low-sugar diet can reduce skin sugar levels ^[4].

In addition, the correlation between high sugar levels and skin aging can be seen in diabetic patients, where one-third of this population has skin complications ^[7]. A prominent feature of aging human skin is the fragmentation of collagen fibers, which severely damages the structural integrity and mechanical properties of the skin. Elevated levels of MMP-1 and MMP-2, increased lysyl oxidase (LOX) expression, and higher crosslinked collagen in the dermis of diabetic skin lead to the accumulation of fragmented and crosslinked collagen, thereby impairing the structural integrity and mechanical properties of dermal collagen in diabetes ^[8]. Collagen crosslinking makes it impossible for them to easily repair ^[9], resulting in reduced skin elasticity and wrinkles ^[10]. Keratinocytes and fibroblasts are the main cells involved in wound healing, but due to the high glucose (HG) microenvironment in diabetics, the functional state of these cells is impaired, thereby accelerating cellular senescence ^[11].

Long-standing high glucose regulates different metabolic pathways, leading to glycototoxicity or hyperglycemic stress ^[12]. These metabolic pathways include polyol pathways, glycolytic pathways, hexosamine pathways, protein kinase C (PKC) activation, and the formation of AGEs ^[13]. These changes accelerate the production of ROS, increase the oxidative reaction of lipids, DNA, and proteins in various tissues ^[14], and ECM disorders ^[15]. High sugar also induces senescence in

keratinocytes and fibroblasts [16], upregulates p 16, p 21, and p 53 gene expression [17], induces oxidative injury [18], apoptosis [19], activates transcription factor nuclear factor kappa B (NF- κ B) [20], promotes secretion of TNF- α , IL-1 β , IL-6, and IL-8 [21][22][23], and upregulates the expression of AGEs.

1.2. Advanced Glycation End Products Induce Skin Aging

Over time, glycation in vivo causes skin AGEs to accumulate, resulting in wrinkles, loss of elasticity, dullness, and decreased function of skin, which is one of the main mechanisms of skin aging [24]. AGEs cause pathological changes in the skin through three processes. First, AGEs interact with their specific cell receptors, altering the levels of soluble signaling molecules, such as cytokines, hormones, and free radicals. Second, in the process of non-enzymatic glycation reaction, a large number of reactive oxygen radicals are released, creating a state of oxidative stress, leading to a significantly reduced level of glutathione, VitC, and VitE in the body. This causes synthetic disorders of collagen in skin tissues. Third, AGEs alter the physical and biological properties of the original extracellular matrix proteins, such as collagen. The most important concentrations of AGEs in the skin are (from the highest to the lowest concentrations) glucosepane, CML, pentosidine, and CEL [25]. Skin autofluorescence (SAF) has been shown to be a biomarker of cumulative skin AGEs [26], and measuring facial fluorescence intensity allows for an assessment of the skin glycation index [24]. SAF is also a powerful and independent predictor for cardiovascular disease and type 2 diabetes (T2D) [27]. Most compounds on the cosmetic market focus on blocking or reversing the initial saccharification reaction, i.e., the binding between proteins and sugars, reducing the formation of early saccharification Amadori products [28].

1.2.1. Epidermis

The epidermis is the outermost layer of the skin, which has a protective function that prevents the penetration of pathogens and regulates the body's water loss [29] and provides a natural "shield" against DNA damage [30]. Keratinocytes are the main cells in the human epidermis, which rapidly differentiate into four layers after proliferation: stratum corneum, stratum granulosum, stratum spinosum, and stratum basale. Protein turnover in the epidermis is much faster, but the accumulation of AGEs can still be observed for a short term before being replaced. mRAGE expression dominates the keratinocytes of healthy human epidermis and can monitor and respond to acute and cellular responses to maintain skin homeostasis [31]. The presence of RAGE suggests that AGE-mediated activation can have potentially negative consequences even for a short period of time. AGEs have been found to inhibit wound healing in diabetic patients by modulating the expression of MMP-9 in keratinocytes through the RAGE, ERK1/2, and p38 MAPK pathways [32] and inducing apoptosis and inhibiting normal cell growth by activating NF- κ B [33].

Glyoxalase is detected in the epidermis and dermis, with GLO-1 located mainly in the basal layer of the epidermis, while GLO-2 being more prominent in the upper keratinocytes. The accumulation of AGEs can be counteracted by the enzymes GLO-1 and GLO-2 of the glyoxalase system, which works synergistically to detoxify the reactive precursors of AGEs. GLO-1 and GLO-2 are more abundantly expressed in older skin. Probably as a protective mechanism, the amounts of AGEs in the basal epidermal layer of the skin are lower. Photoexposure reduces GLO-2 production and thus promotes the accumulation of AGEs [34]. These results suggest that the glyoxalase system plays an important role in both chronological (intrinsic) aging and photoaging and acts as a defense system against skin aging [35]. The natural vitamin B₆ analog pyridoxamine has been described as an anti-glycating agent, which not only quenches MGO but also increases GLO-1 activity. In addition, polyphenols, such as resveratrol and fisetin, can also upregulate GLO-1 expression [36].

1.2.2. Dermis—Fibroblast

Fibroblasts are the main repair cells in the dermis but also the main cells that secrete collagen, and their normal proliferation and growth have great significance for maintaining the normal structure and physiological function of the skin. AGEs induce fibroblast senescence, matrix molecule proliferation (type I collagen, type III collagen, and type IV collagen), and metalloproteinase production (MMP1, MMP2, and MMP9) [37]. They also promote apoptosis, reduce hyaluronic acid (HA) synthesis, and reduce elastase-type matrix metalloproteinase (ET-MMP) activity. Finally, they regulate cell dysfunction by interacting with cell membranes and accelerating the leakage of lactate dehydrogenase (LDH) from cells [38]. AGEs modify intracellular molecules, including intermediate filament waveforms and proteasomes. The intermediate filament waveform is the main target of CML in human skin fibroblasts. DNA is also sensitive to glycation. GO causes DNA strand breaks, and MGO produces extensive DNA–protein crosslinking. RAGE levels have been found to increase over time, particularly in fibroblasts in the epidermal basal and upper dermis in elderly patients, and those interactions between AGE and RAGE lead to slower cell replication and induce a pro-inflammatory cascade [39]. On the other hand, fibroblasts may play an important role in skin AGEs degradation and photoaging skin AGEs accumulation. AGEs can be internalized by fibroblasts through receptor-mediated endocytosis and further degraded by lysosomal proteases or proteasomes. Among them, protease D plays a major role in the degradation of intracellular AGEs [40].

1.2.3. Dermis—Extracellular matrix (ECM)

The extracellular matrix (ECM) is a complex, non-cellular network produced primarily by fibroblasts, including proteoglycans, hyaluronic acid, adhesion glycoproteins (fibronectin and laminin), and fibrin (collagen and elastin), as well as growth factors and cytokines [41]. They provide the mechanical strength and elastic resilience to the skin. ECM saccharification is manifested as increased skin hardness, decreased elasticity, activation of RAGE, and induction of fibroblast senescence and apoptosis [42]. AGEs can regulate the expression of ECM proteins and alter the expression and synthesis of the enzymes responsible for their degradation. AGEs have been reported to reduce ET-MMT activity in a dose-dependent manner and have a regulatory effect on matrix metalloproteinases (MMPs) [43]. The production of AGEs is primarily through non-enzymatic glycation of proteins in ECM. Longevity molecules are particularly susceptible to glycation, making collagen a common target for active compound modification due to its abundance and slow turnover rate. Glucosepane is the most abundant AGE that crosslinks the collagen of aging human skin. Due to its abundance, glucosepane is thought to play a major role in increasing skin stiffness and hardness. CML is one of the main AGEs in the skin and serves as an indicator of collagen glycation [44]. Fluorescent pentosidine is a recognized marker for general AGE accumulation, and the presence of pentosidine may indicate a significant increase in the level of glucoside and other AGEs [45]. In addition, glycated collagen induces CML expression in the dermis and epidermal compartments, resulting in an aging phenotype of poor stratification of the epidermal layer and keratinocyte cytoplasmic vacuolization [46]. If collagen is severely crosslinked, collagenase fails to degrade the modified collagen, causing AGEs to accumulate in the dermal skin [38].

1.3. UVA Induces Advanced Glycation End Products of the Skin

UVA exposure combined with dermal glycation are two catalysts for skin aging [47]. The accumulation of glycation products increases with age and is amplified by ultraviolet exposure [48]. AGEs produce superoxide anion radicals (O_2^-) and hydroxyl radicals (OH^\bullet) after UVA irradiation, increase oxidative stress in the dermal matrix [49], damage human dermal fibroblasts, and accelerate the formation of the sugar oxidation products pentosidine and CML in actinic elastic tissues. Elastin crosslinked with AGEs cannot be degraded by elastase. UVA irradiation combined with AGEs enhances MMP1 and MMP3 mRNA expression, which induces protein expression of fibrin 1 and tropoelastin and reduces the expression of glyoxalase, which detoxifies harmful precursors of AGEs. Because glycated collagen and elastin are highly resistant to MMP degradation, a large accumulation of glycated proteins [50] leads to skin aging and elastic tissue proliferation [51]. In addition, keratinocytes secrete AGEs in response to UV irradiation, which stimulates melanin production through ERK and CREB signaling of RAGE, leading to skin pigmentation [52].

Figure 1 shows the effects of UV exposure combined with AGEs on the skin.

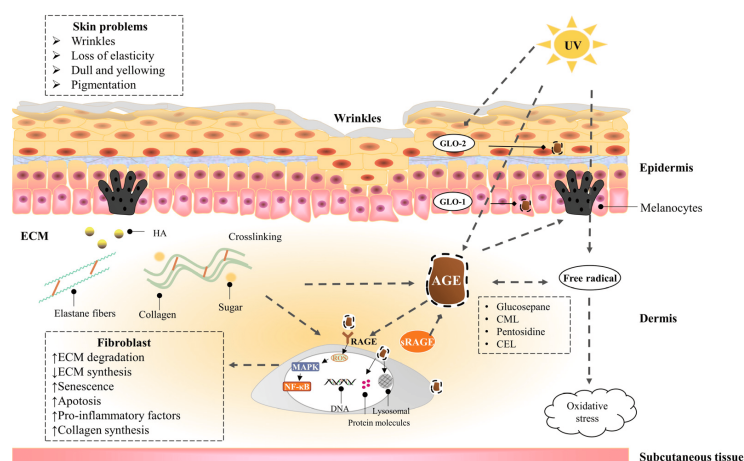


Figure 1. The effects of UV exposure combined with AGEs on the skin. A dotted line with an arrow indicates an induced effect; a dotted line with a diamond shape indicates a suppressive effect. AGEs in the skin are endogenously generated or exogenously ingested, including CML, CEL, pentosidine, and glucosepane, etc. Collagen is more likely to be glycated due to the slow turnover rate. On the one hand, AGEs act directly on cells, leading to a decrease in cell function by activating inflammatory signaling pathways and oxidative stress through cell surface receptors, as well as by modifying cell membranes and intracellular molecules, resulting in skin problems, such as dullness, pigmentation, and wrinkles. On the other hand, AGEs crosslink with collagen and elastin in ECM and promote the secretion of melanin, causing skin problems, such as macula and loss of elasticity. In addition, UV exposure can exacerbate skin glycation by promoting the generation of AGEs, exacerbate oxidative stress, and reduce epidermal GLO-2 production, leading to the accumulation of

AGEs. AGEs can be degraded by proteases through receptor-mediated fibroblast endocytosis; the glyoxalase system can detoxify the reactive precursors of AGEs; sRAGE can competitively bind to AGEs with RAGE.

2. Inhibitors of Advanced Glycation End Products

AGEs inhibitors are mainly divided into five categories: (1) carbonyl trapping agents that weaken carbonyl stress; (2) metal-ion chelators or scavenging free radicals, inhibiting sugar and lipid oxidation reaction; (3) crosslinking breakers that reverse AGEs crosslinking; (4) activating the anti-glycation system—many kinds of herbal extracts and natural compounds inhibit glycation by enhancing the anti-glycation system in the body; (5) RAGE antagonists. These include: anti-RAGE antibodies, sRAGE, and RAGE inhibitors; FPSZM1, a specific and potent chemical inhibitor of AGE receptor, which could improve diabetic nephropathy [53] and A β -mediated brain disorder [54]; Azeliragon, an oral small molecule antagonist of RAGE in Phase 3 development for mild cognitive impairment [55]. Small molecules are also in development to inhibit Diaphanous.1, the intracellular RAGE adaptor [56]. Inhibiting oxidative stress and inflammation in tissues by blocking the interaction of AGEs with RAGE is another new way to inhibit the process of late glycation. **Figure 2** shows the action sites that inhibit the formation of AGEs in vivo.

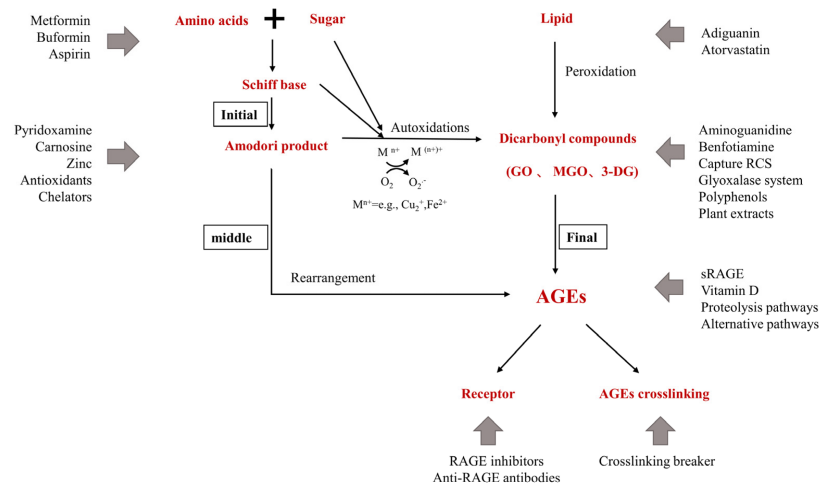


Figure 2. Action sites that inhibit the formation of AGEs in vivo. M^{n+} refers to transition metals. Endogenous AGEs are formed through the Maillard reaction in three main stages: early, middle, and final. The glyoxalase system include Glyoxalase I (GLO-1) and II (GLO-2) system; the proteolysis pathways include UPS and ALPS; alternative pathways include DJ-1/Park7 pathway, OPH, aldehyde dehydrogenases (ALDHs), aldo-keto reductases (AKRs), and acetoacetate degradation.

2.1. Pre-Amadori Inhibitors

Aminoguanidine (AG) is an inhibitor of late glycation reactions in vitro found in clinical trials and is an excellent dicarbonyls scavenger that captures reactive carbonyl precursors, such as MGO, GO, and 3-DG. Amadori compounds are important intermediates for AGEs formation in vivo, and CML must be formed primarily by oxidative cleavage of Amadori's Enediol intermediate between C₂-C₃ of the ligated sugar. AG was found to have no significant effect on the CML produced during the incubation of Amadori proteins. Therefore, AG is an important pre-Amadori inhibitor. AG is toxic at higher concentrations and has been forbidden in human clinical trials [57]. AG inhibits the development of diabetic complications in animal models of diabetes but does not inhibit the formation of late glycation end products of skin collagen in diabetic rats [58]. Benfotiamine, a synthetic thiamine precursor, activates the enzyme transketolase to accelerate the precursors of AGEs toward the pentose phosphate pathway, thereby reducing the production of AGEs [59].

2.2. Post-Amadori Inhibitors

Pyridoxamine (PM), one of the natural forms of vitamin B₆, uniquely targets the post-Amadori pathway through metal-ion chelation and blocking oxidative degradation of Amadori intermediates [60]. Good post-Amadori inhibitor compounds should form stable metal-ion complexes with a higher equilibrium constant than the Amadori compound [61]. PM also has the ability to scavenge toxic carbonyl products from sugar and lipid degradation, inhibit reactive oxygen species [62][63], and increase the activation of the detoxifying enzyme GLO-1 [64]. The *ilex paraguariensis* (IP) extract is also a post-Amadori inhibitor due to its inhibition of the second stage of glycation reaction and conversion of free-radical-mediated Amadori products to AGEs [65].

2.3. Crosslinking Breaker

Thiazole salts are AGEs crosslinking breakers, such as OPB-9195 and ALT-711 (alagebrium). OPB-9195 inhibits AGE formation (particularly pentosidine and CML) through the chelation of metal ions and carbonyl trapping [66]. ALT-711 is the first compound in the thiazole class, which has been reported to break down established AGE-related cross-links. Another prototypic AGE cross-link breaker is N-phenacylthiazolium bromide (PTB) which break down protein cross-links by cleaving α -diketone structure. Similar effects have been observed with rosmarinic acid, tannins, and flavonoids [67]. There are also other potent AGEs destroyers, such as curcumin and ALT-946 [68].

2.4. Indirect Advanced Glycation End Products Inhibitors

A small number of AGEs inhibitors play a role in the early stages of glycation by disturbing the initial binding between sugars and amino groups and indirectly reducing the formation of AGEs and ALEs. Since AGEs are mostly produced by non-enzymatic glycation of sugars and lipids, hypoglycemic and lipid-lowering drugs can inhibit the production of AGEs in vivo. For example, Atorvastatin (a lipid-lowering drug) inhibits the further formation of Schiff bases and AGEs by interfering with the initial binding between reducing sugars and amino groups [69]; Metformin is used to treat type II diabetes mellitus by inhibiting the production of reactive oxygen species by reducing the expression of the AGEs receptor (RAGE) [70] and capturing MG and other dicarbonyls produced during glycation. Buformin inhibits the formation of AGEs by trapping the carbonyl groups of ammonia and MGO and is a more effective inhibitor of AGEs formation than metformin [71]; Aspirin, or acetylsalicylic acid, inhibits the glycation process by acetylating the proteins' free amino groups, thereby blocking the attachment of reducing sugars.

2.5. Natural Advanced Glycation End Products Inhibitors

Synthetic AGE inhibitors have safety concerns and side effects, so natural products with lower toxicity are the most promising alternatives for developing natural medicines with anti-glycation activity. It has been reported that tea, herbal tea, vegetables, fruits [72], yogurt, and other foods have an inhibitory effect on the saccharification reaction. A large number of experiments in vitro and in vivo have shown that natural compounds have the potential to combat the formation and accumulation of AGEs, including phenols, oligosaccharides and polysaccharides, carotenoids (e.g., β -carotene), saponins [73], and unsaturated fatty acids.

Plants have long been used in traditional medicine techniques to treat various diseases and are also a source of new natural medicines discovery. Plant extracts have great anti-aging potential and are rich in a variety of active ingredients, which can inhibit the formation of AGEs by scavenging free radicals, capturing dicarbonyl carbon, etc. [74]. For example, *C. ternatea* flower extract (CTE) prevents protein glycation by trapping carbonyl groups and scavenging free radicals [75]. The polyphenolic components of peanut peel include gallic acid, catechin, and resveratrol, which reduce toxicity caused by AGEs and reduce the levels of reactive oxygen species and pro-inflammatory cytokines [76]. Citrus fruit extract significantly reduces the level of protein carbonyl compounds [77]. *Akebia quinata* fruit extracts (AQFE) can act as an anti-skin aging agent by preventing oxidative stress and other complications associated with AGEs formation [78]. Phenolic components of milk thistle flowers have anti-glycation activity in vitro and on human explants. Polyphenol-rich clove extract, due to its antioxidant properties, is able to inhibit the formation of AGEs and protein glycation [79]. The polyphenol compounds of hazelnut bark extract can reduce the formation of AGEs in vitro [80]. The hydrophobic extract of *dunaliella salina*, rich in colorless carotene phytoene and phytofluene, has anti-glycation and anti-inflammatory activity and helps reduce the signs of aging (wrinkles) [81]. Cinnamon is a traditional spice, which contains some phenolic components in its aqueous extracts, such as catechin, epicatechin, and procyanidin B2, which inhibit the formation of AGEs through antioxidants and direct capture of active carbonyl substances [82]. Black galangal extract inhibits the formation of fluorescent AGEs, pentosidine, CML, and intermediates 3-DG, GO, and MGO, and it acts on the decomposition of AGEs, thereby reducing the accumulation of AGEs in vivo [67]. *Salvia officinalis* L. methanol extract, including rosmarinic acid, resveratrol, quercetin, rutin, and luteolin-7-O-glucoside, exerts anti-glycation effects through antioxidation and inhibition of fluorescent substances and carbonyl groups [83]. Pomegranate fruit extract (PE), its phenolic constituents (punicalagin, ellagic acid, and gallic acid), and products of the degradation of ellagitannin (urolithin A and urolithin B) [84] all have effective anti-glycation activities [85].

2.6. Polyphenolic Compounds

As major and ubiquitous phytochemicals, including flavonoids, phenolic acids, alfa, and lignans, polyphenols exert AGEs inhibition through ROS inhibition, dicarbonyls capture (MGO and GO), and disruption of protein crosslinking [81][86]. Glycation and oxidative stress are closely related, with all steps of sugar oxidation producing oxygen radicals and ultimately resulting in the formation of AGEs. In addition, glycated proteins activate membrane receptors such as RAGE

through AGEs and induce intracellular oxidative stress and pro-inflammatory states [87]. Therefore, compounds that scavenge free radicals can effectively inhibit glycation. For example, resveratrol (3,4',5-Trihydroxystilbene) is a plant polyphenol that reduces oxidative stress [88] and inhibits AGEs-induced proliferation, collagen synthesis, and RAGE receptors [89]. Asiatic acid (AA), a pentacyclic triterpenoid, occurs naturally in many vegetables and fruits. AA pretreatment effectively protects HaCaT cells from subsequent AGE-BSA-induced oxidative and inflammatory stresses, exerting an anti-glycation effect [90]. The natural antioxidant "ellagic acid" (EA) exerts its inhibitory effect on AGEs in diabetic rats by inhibiting glycated intermediates (including dicarbonyls) and interrupting the auto-oxidation pathway [91].

Flavonoids (flavones, flavanones, isoflavones, and flavonols) are the most common class of polyphenol compounds and have shown significant inhibitory effects on protein glycation and AGEs formation. These mechanisms may involve capturing reactive amino groups, so that they cannot react with glucose or scavenging carbonyl compounds, chelating with trace metal ions that catalyze glycation, scavenging hydroxyl radicals, and inhibiting oxidative degradation of various intermediates [92]. For example, garlic can inhibit protein glycation and dicarbonyls in vitro; quercetin is a phenolic compound found in garlic [93], which has a more effective anti-glycation effect than aminoguanidine [94]. Dietary antioxidants such as quercetin can prevent free radical toxicity [95]. Rutin (flavonoids) is found in fruits and vegetables, making it unable to react with glucose through mechanisms such as capturing reactive amino groups. All five metabolites formed after ingestion effectively inhibit the formation of CML [92]. Anthocyanins are the main flavonoids in blackcurrants that effectively prevent the formation of AGEs by capturing methylglyoxal [96].

Phenolic acids are secondary metabolites that are widely present in plants, including a large distribution of hydroxycinnamic acid (coumalic acid, caffeic acid, ferulic acid, coumarin) and hydroxybenzoic acid (Protocatechuic acid, gallic acid, hydrobenzoic acid, and ellagitannin). These metabolites are also found to have anti-aging potential. For example, ferulic acid inhibits the formation of fluorescent AGEs and CML and reduces fructosamine levels. This leads to the prevention of protein oxidation through the reduction in protein carbonyl formation and protein thiol modification [97]. Isoferulic acid (IFA) is a powerful antioxidant and has an effective inhibitory effect on protein glycation and sugar oxidation [98]. Cinnamic acid and its derivatives reduce the levels of fructosamines, the formation of CML, and the level of amyloid cross- β structures [99].

2.7. Other Advanced Glycation End Products Inhibitors

Carnosine is a naturally occurring dipeptide (beta-alanyl-L-histidine), which hinders the formation of protein carbonyl groups and has the ability to chelate transition metal ions, prevent MG-induced glycation, and reduce sugar-induced crosslinking [100], leading to a significantly lower AGEs levels in the epidermis and reticular dermis of human skin explants [101]. Piperazine-2,5-dione reduces the number of late glycation end products accumulated in human dermal fibroblasts with age. Vitamin D therapy may help lower AGEs levels, significantly reduce NF- κ B activation, and increase sRAGE levels [102]. Zinc has antioxidant, anti-inflammatory, and anti-apoptotic potential. Zinc deficiency may stimulate the formation of AGEs, while zinc supplementation may inhibit the formation of AGEs and protein carbonyl groups through a variety of signaling pathways and improve AGEs-induced apoptosis and oxidative stress [103].

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