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Skin ageing and damage resulting from RCS/AGEs-mediated carbonyl stress and associated intervention strategies

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ABSTRACT: Reactive carbonyl species (RCS) derived from glycoxidation, mainly α-dicarbonyl compounds (α-DCs), can induce covalent modifications in biological macromolecules, particularly proteins and DNA, leading to formation of advanced glycation end products (AGEs). The excessive accumulation of RCS and AGEs contributes to a pathophysiological condition known as carbonyl stress. Carbonyl stress varies with age, diet, and environmental factors. It is further aggravated by oxidative stress and health conditions like hyperglycemia and renal dysfunction. Increasing evidence indicates that RCS/AGEs-mediated carbonyl stress is involved in disruption of cellular homeostasis and damage of physiological functions of the skin, clinically presenting as chronic inflammation, yellowish discoloration, accelerated aging, and other dermatological abnormalities. Consequently, targeted modulation of the RCS/AGEs axis represents a promising therapeutic strategy for cutaneous health preservation. This review provides a first systematic discussion on the role of RCS/AGEs-induced carbonyl stress in skin ageing and damage. Furthermore, the key intervention strategies against carbonyl stress are summarized, including (i) inhibition of RCS/AGE formation and exogenous intake; (ii) scavenging of preformed RCS/AGEs; (iii) blockade of AGE-receptor interactions. Notably, interventions based on dietary bioactives hold promise for designing personalized diets and developing functional foods to mitigate carbonyl stress-associated skin ageing and damage.

Keywords: Reactive carbonyl species, Advanced glycation end products, Carbonyl stress, Skin ageing, Skin damage

1. Introduction

Reactive carbonyl species (RCS) are chemically diverse multi-carbonyl compounds formed from glycoxidation and lipid peroxidation *in vivo*, and are also found in foods derived from the Maillard reaction[1]. Among these, sugar-derived RCS are generally characterized by an α-dicarbonyl structure[2], and termed as α-dicarbonyl compounds (α-DCs). α-DCs are highly electrophilic reactive and prone to condense with nucleophilic residues of macromolecules, leading to the production of advanced glycation end products (AGEs)[3]. α-DCs, to a large extent, act as precursors for AGEs. The excessive accumulation of α-DCs and/or

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AGEs culminates in carbonyl stress[4] , a pathological condition implicated in the onset and progression of diabetes- and ageing-related diseases, including atherosclerosis, renal failure, and neurological disorders among others[5,6].

In 1981, Monnier and Cerami observed that the ageing process was accelerated in the interstitial tissue and collagen of skin under high glucose condition[7]. Subsequent studies established that glycation and AGEs impair cutaneous homeostasis, potentially leading to inflammation, yellowing, sagging, wrinkles, and other skin-related issues[8-10]. Moreover, AGEs play a pathogenic role in dermatologic complications of metabolic disorders, such as diabetic cutaneous ulcers and chronic wounds[11]. The role of carbonyl stress in ageing has been concerned since the presentation of the carbonyl toxification hypothesis of biological ageing in 1995[12]. As the pursuit of anti-ageing, health and beauty grows rapidly and gains momentum, the exploration of carbonyl stress effects on skin health and ageing has emerged as an active area of research.

Carbonyl stress, characterized by the accumulation of RCS and AGEs, contributes to protein cross-linking, structural damage, and oxidative imbalance in the skin. However, the relationship between RCS/AGEs-mediated carbonyl stress and skin ageing, as well as other skin disorders, has not been systematically reviewed. A comprehensive understanding of the mechanisms underlying carbonyl-induced skin ageing is therefore crucial for developing effective strategies to prevent or mitigate cutaneous ageing and maintain skin homeostasis. This review summarizes the formation and detoxification mechanisms of sugar-derived RCS and AGEs, examines the factors that influence the skin's homeostasis of RCS and AGEs, and highlights the detrimental effects of RCS/AGEs-mediated carbonyl stress on skin health, along with potential intervention strategies. Particular emphasis is placed on dietary bioactives as a promising modulator, aligning with the growing interest in precision nutrition for skin health and offering a translational bridge between fundamental research and clinical application.

2. Endogenous formation of sugar-derived RCS and AGEs

Sugar-derived RCS, primarily α-DCs, are largely regarded as the precursors of AGEs. The chemical structures and formation pathways of typical α-DCs and AGEs are illustrated in Fig. 1.

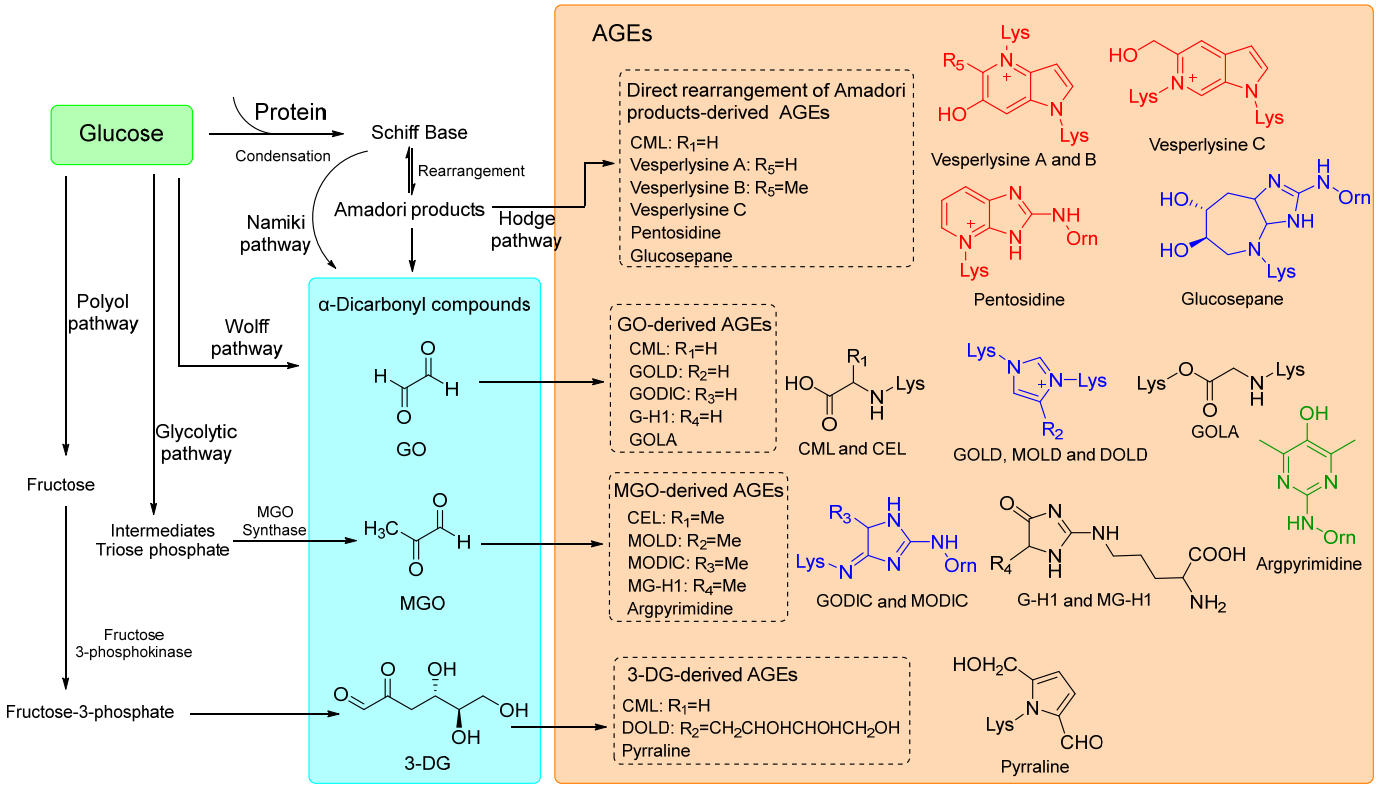

Fig. 1 Proposed pathways for the endogenous formation of sugar-derived RCS and AGEs. α-DCs including GO, MGO, and 3-DG can be generated by the Maillard reaction, the Namiki pathway, and the Wolff pathway. Additionally, MGO can be produced through the glycolytic pathway, while 3-DG can be formed via the polyol pathway. The endogenous formation of AGEs occurs through two pathways: (i) Non-enzymatic glycation: this involves a condensation reaction between α-DCs and free amine groups of proteins, DNA or lipids, followed by further rearrangements to yield stable and irreversible end-products. Representative AGEs include: (a) GO-derived AGEs: CML, GOLD, GODIC, G-H1, and GOLA; (b) MGO-derived AGEs: CEL, MOLD, MODIC, MG-H1, and argpyrimidine; (c) 3-DG-derived AGEs: CML, DOLD, and pyrraline; (ii) Hodge pathway: this involves direct rearrangement of Amadori products to form AGEs, including CML, vesperlysine A, B, and C, pentosidine, and glucosepane. The structures of AGEs are color-coded based on their crosslinking structures and fluorescence characteristics. Black: non-fluorescent, non-crosslinked; Blue: non-fluorescent, crosslinked; Green: fluorescent, non-crosslinked; Red: fluorescent, crosslinked. GO, glyoxal; MGO, methylglyoxal; 3-DG, 3-deoxyglucosone; CML: N^{ε}-(carboxymethyl)-lysine; CEL: N^{ε}-(carboxyethyl)-lysine; GOLD: glyoxal-derived lysine-lysine dimer; MOLD: methylglyoxal-derived lysine-lysine dimer; DOLD: 3-deoxyglucosone-derived lysine-lysine dimer; GODIC: glyoxal-derived lysine-arginine dimer; MODIC: methylglyoxal-derived lysine-arginine dimer; GH-1: glyoxal-derived hydroimidazolone; MG-H1: methylglyoxal-derived hydroimidazolone.

2.1 Sugar-derived RCS and formation pathways

More than 20 RCS have been identified in organisms[13]. Glyoxal (GO), methylglyoxal (MGO), and 3-deoxyglucosone (3-DG) are dominant sugar-derived RCS, as shown in Fig.1. There are several routes contributing to the formation of α-DCs, and most of which are associated with glucose or other reducing sugars and glucose metabolism[1,14].

2.1.1 Maillard reaction, Wolff pathway, and Namiki pathway

The classic Maillard reaction is a well-established pathway engaged in the generation of α-DCs[15], as well as AGEs that will be discussed later. The Maillard reaction is a complex cascade involving three main

stages[16]. The early stage is an addition reaction between the carbonyl group from reducing sugars, such as glucose and an unprotonated amino group to yield Schiff bases[17]. These Schiff bases are unstable imine derivatives that undergo acid-catalyzed rearrangements to produce stable glycated proteins known as Amadori products[17] (Fig.1). The intermediate stage consists of the degradation of Amadori products and the production of α-DCs[18]. In addition, α-DCs can be produced in early glycation, including autoxidation and dehydration of glucose via the Wolff pathway and the condensation and oxidative degradation of Schiff bases through the Namiki pathway[19,20] (Fig.1). However, the aforementioned routes are minor endogenous sources of α-DCs[21].

2.1.2 Glycolytic pathway and polyol pathway

The glycolytic pathway has been considered as the major source of MGO *in vivo*[22]. MGO is inevitably formed as a by-product of glycolysis[23]. As depicted in Fig.1., glycolysis produces triose phosphate intermediates, including glyceraldehyde 3-phosphate and dihydroxyacetone-phosphate, which can subsequently yield MGO through spontaneous non-enzymatic elimination of the phosphate group or via the catalytic action of MGO synthase[24]. The polyol pathway is associated with the production of 3-DG (Fig.1). Although glucose itself has relatively low reactivity, it can be converted to fructose via the polyol pathway [25]. 3-DG is then formed through the hydrolysis of fructose-3-phosphate, an intermediate enzymatically generated from fructose[26].

2.2 Endogenous formation of AGEs and determination in the skin

Endogenous AGEs are primarily formed through two routes[27]. One route involves the direct rearrangement of Amadori products, namely the Hodge pathway, to yield AGEs, such as N^{ε}-(carboxymethyl)lysine (CML), pentosidine, glucosepane, and vesperlysine A, B, and C. The other route is the Maillard reaction, which mediated the formation of most AGEs, with α-DCs acting as precursors[28]. In detail, the final stage of the Maillard reaction includes the condensation reaction between highly electrophilic α-DCs and nucleophilic amino acid residues of proteins, principally including lysine, arginine, and cysteine residues[24]. AGEs derived from α-DCs have variety of chemical structures, as they can be formed from different precursors such as GO, MGO, and 3-DG, and the conformations among α-DCs are interconvertible; for instance, MGO can be formed from the fragmentation of 3-DG.

Based on their physicochemical properties, AGEs can be classified into four categories, as illustrated in Fig. 1: non-fluorescent and non-crosslinked, non-fluorescent but crosslinked, fluorescent and non-crosslinked, and fluorescent and crosslinked types. The structure and fluorescence profiles are very important in the qualitative and quantitative analysis of AGEs[29]. By integrating gas chromatography-mass spectrometry (GC-MS) and high-performance liquid chromatography (HPLC), at least 12 AGEs (linear chains or crosslinks) were quantified in the skin of a healthy individual aged approximately 80 years[30]. Among these, the predominant AGEs in descending order of abundance were glucosepane, fructosyl-lysine, CML, pentosidine, and N^{ε}-(carboxyethyl)-lysine (CEL)[30,31]. The concentration of glucosepane was 20-fold higher than that of pentosidine, while CML levels were approximately 24-times greater than those of CEL.

3. Homeostasis of α-DCs and AGEs in the skin

There are multiple natural detoxification pathways that organisms mitigate α-DCs and AGEs-mediated carbonyl stress. Consequently, under normal *in vivo* conditions, including in the skin, α-DCs and AGEs maintain a relative state of equilibrium, despite continuous acquisition (Fig. 2).

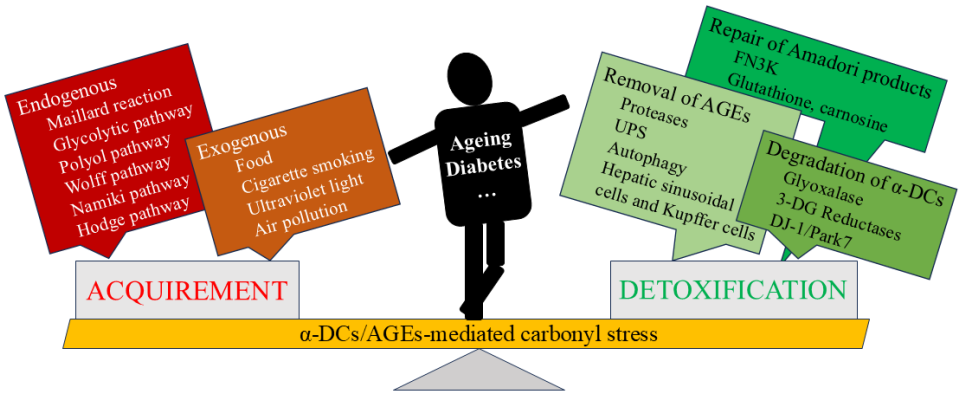

Fig. 2 Dynamic equilibrium of α-DCs/AGEs-mediated carbonyl stress: acquisition versus detoxification under physiological conditions. Endogenous formation of α-DCs and AGEs occurs through multiple metabolic pathways, including the Maillard reaction, glycolytic pathway, polyol pathway, Wolff pathway, Namiki pathway, and Hodge pathway. Exogenous sources include dietary intake and cigarette smoke exposure among others. The human body maintains multiple natural detoxification pathways against α-DCs/AGEs-mediated carbonyl stress, including degradation of α-DCs, repair of Amadori products, and removal of AGEs. Disruption of this equilibrium occurs in aging and pathological states (e.g., diabetes, renal dysfunction), when increased production and impaired detoxification/excretion lead to net accumulation of carbonyl stress markers. FN3K, fructosamine 3-kinase; UPS, ubiquitin-proteasome system; 3-DG, 3-deoxyglucosone.

3.1 Acquisition pathways and affecting factors

The sources of α-DCs and AGEs in the skin can be both endogenously generated as discussed above, and exogenously acquired through the intake of ultra-processed foods and exposure to ultraviolet ray, cigarette smoking, and environmental pollutants. Increasing evidence suggests that the endogenous production and accumulation of α-DCs/AGEs in the skin progressively rise with age as part of normal physiological metabolism[32,33]. For example, a study found that levels of argpyrimidine and N^{ε}-(5-methyl-4-imidazolon-2-yl)-*L*-ornithine (MG-H1) were twice as high in tail tendons of old mice compared to young ones[34]. Another study performed on different age groups of human volunteers identified an age-dependent accumulation of α-DCs and AGEs in the skin[35]. The contents of CML, CEL, and pentosidine were approximately tripled from 20 to 80 years of age[35]. Furthermore, emerging evidence suggests that the deleterious accumulation of carbonyl stress is insignificant in young individuals, but begins at a certain age and progressively exerts toxic effects as one ages[36].

Prolonged hyperglycemia is a crucial pathological contributor to the circulating pool of α-DCs and AGEs[37]. In the diabetic murine model, AGE levels in serum were significantly higher than that in the control, with α-DCs and particularly MG being the primary source of these glycated modifications[38]. In tissues where diabetic complications occur, a 2- to 4-fold increase in MG-H1-protein adducts was detected[39]. Similarly, high levels of CML were detected in the skin of renal failure-complicated diabetics[35]. In this scenario, a recent notion proposed that AGEs span the spectrum from cause to consequence of diabetes, representing a

"common soil" underlying the pathophysiology of the metabolic disorders[40]. Specifically, hyperglycemia-induced accumulation of AGEs exacerbates insulin resistance, inflammation, and oxidative stress, which in turn promotes the generation of more AGEs, thus creating a feed-forward-driven pathological loop that mediates metabolic dysfunction.

Oxidative stress is another key factor involved in the endogenous formation of AGEs. When organisms undergo persistent oxidative stress, the body's original antioxidant defense system becomes compromised, leading to excessive production of RCS and consequently, the formation and accumulation of AGEs[41,42]. Additionally, oxidative stress enhances the generation of 3-DG, a precursor of AGEs, via the polyol pathway[41]. In a detrimental feedback loop, excessive AGEs bind to their receptor (RAGE), thereby amplifying the production of reactive oxygen species (ROS) and perpetuating a vicious cycle of oxidative damage. In primary mesangial cells, cytosolic ROS levels markedly increased followed a 7-day exposure to AGEs[43]. An nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and protein kinase C (PKC)-α-dependent pathway was suggested to be involved in the AGEs-mediated ROS generation[43]. In addition, ROS was involved in the formation and stabilization of crosslinks of early glycation products[44].

Aside from endogenous production, several exogenous pathways, particularly dietary intake also increase the systemic burden of AGEs in human body[45]. Approximately 30% of dietary AGEs are absorbed by the intestine[46]. They can then enter the systemic circulation and distribute throughout various tissues and organs, including the skin. A Rotterdam study (NTR6831), a population-based cohort of primarily European ancestry, demonstrated a positive association between dietary CML intake and skin AGE levels, but exclusively in participants without diabetes or chronic kidney disease (CKD)[47]. Interestingly, this association was not significant when individuals with diabetes and CKD were included in the analysis. These observations aligned with a recent intervention study in elderly diabetic patients with CKD, where a two-month AGE-restricted diet failed to alter AGE levels in skin or urine[48]. These findings collectively indicate that in pathological conditions with markedly accelerated AGE accumulation, endogenous metabolic pathways appear to dominate over exogenous dietary AGE intake. This interpretation is biologically plausible given that both diabetes (through chronic hyperglycemia) and CKD (via reduced renal clearance) are established promoters of AGE accumulation. In diabetic/CKD populations, the substantial baseline AGE burden in skin may mask potential modest dietary effects. Furthermore, disease-specific dietary modifications could confound the observed relationships. Nevertheless, current evidence regarding dietary AGE-tissue AGE relationships in these high-risk populations remains limited by insufficient sample sizes, warranting further investigation. In foods, the main factors determining AGE content include nutrient composition (protein > fat > carbohydrate), temperature (high-temperature cooking such as frying, grilling, and baking > water-based preparation such as boiling and steaming) and duration of heat application, humidity, pH, and the presence of trace metals[49]. With the exponential increase in the consumption of highly processed food in modern diet, AGEs and associated carbonyl stress may be a more striking link between eating style and human health.

Additionally, higher levels of AGEs were also detected in the skin when exposed to sustained cigarette smoking, ultraviolet light or air pollution[50-52].

3.2 Detoxification pathways

The innate defense system in human body counteracts α-DCs/AGEs-mediated carbonyl stress through three distinct detoxification pathways (Fig. 3): degradation of AGE precursors, repair of Amadori products, and removal of AGEs.

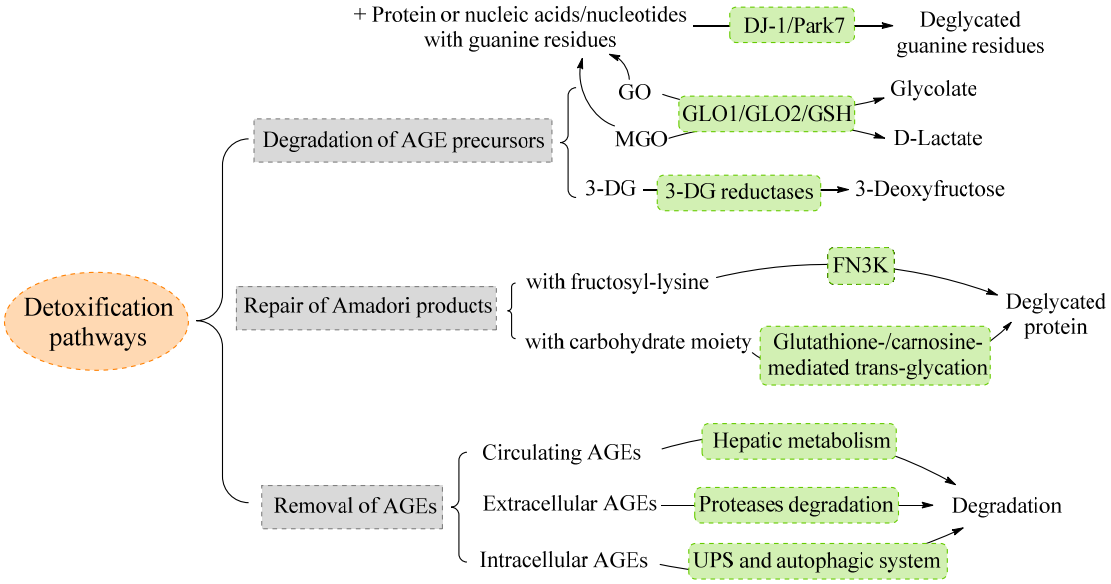

Fig. 3 Detoxification pathways counteracting α-DCs/AGEs-mediated carbonyl stress. Three natural detoxification mechanisms in human body are indicated by gray boxes, including degradation of AGE precursors, repairment of Amadori products, and removal of AGEs. Enzymatic and metabolic pathways involved in detoxification are highlighted in green boxes. GO, glyoxal; MGO, methylglyoxal; 3-DG, 3-deoxyglucosone; GLO1, glyoxalase I; GLO2, glyoxalase II; GSH, reduced glutathione; FN3K, fructosamine 3-kinase; UPS, ubiquitin-proteasome system.

As dominant precursors of AGEs, GO and MGO are detoxified by the glyoxalase system, which includes glyoxalase I (GLO1) and glyoxalase II (GLO2), along with reduced glutathione (GSH). MGO can be converted into non-toxic D-lactate while GO is converted into glycolate and excreted[53,54]. Additionally, 3-DG is metabolized by 3-DG reductases. Recently, the DJ-1/Park7 family has been established as deglycase enzymes, functionally analogous to the classical glyoxalase system. The detoxification pathway of DJ-1/Park7 is capable of repairing early glycation intermediates and reversing glycated guanine residues in both nucleic acids and nucleotides to their free form, specifically targeting modifications induced by MGO and GO[55,56].

Certain Amadori products, such as fructosyl-lysine, are refractory to degradation by the glyoxalase system. To circumvent this limitation, fructosamine 3-kinase (FN3K) facilitates the phosphorylation of fructosyl-lysine residues, promoting their removal from proteins[57]. Alternatively, a non-enzymatic trans-glycation mechanism mediated by glutathione and carnosine can cleave the carbohydrate moiety from glycated proteins, thereby restoring their native conformation and biological activity[58]. Of note, this route exhibits specificity for Amadori products without affecting AGEs.

Regarding preformed AGEs, they can be eliminated through multiple metabolic pathways. Circulating AGEs undergo hepatic metabolism primarily mediated by resident macrophages, including hepatic sinusoidal cells and Kupffer cells[59]. Extracellular AGEs can be degraded by proteases and excreted via renal clearance[58], with potential involvement of matrix remodeling enzymes in this clearance process[60]. The metabolism of intracellular AGEs may be associated with the ubiquitin-proteasome system (UPS) and autophagic system[61,62]. These two systems may operate independently or synergistically, with autophagy potentially serving as a compensatory mechanism for AGE removal when UPS capacity is exceeded or impaired [63]. However, the precise molecular mechanisms governing their functional interplay and regulatory factors in the detoxification process remain poorly characterized.

The detoxification pathways are crucial for maintaining homeostasis, as α-DCs and AGEs are continuously generated endogenously and acquired exogenously. During physiological ageing, the balance slowly but steadily shifts toward accumulation more than degradation due to a gradual decline in detoxification function. As a result, α-DCs/AGEs-mediated carbonyl stress emerges, exerting its detrimental effects on skin proteins and other molecules, and ultimately leading to the phenotypic manifestations of skin ageing[64]. However, under pathological conditions such as diabetes mellitus and renal insufficiency, the homeostatic regulation of α-DCs and AGEs becomes severely compromised. The concomitant exacerbated production and impaired excretion leads to an exponential rise in systemic carbonyl stress, precipitating various dermatological complications including impaired wound healing, chronic pruritus, and increased susceptibility to cutaneous infections[65,66]. Clinical studies revealed that hemodialysis patients had a plasma AGE concentration up to 40-fold higher than healthy controls, with correspondingly elevated cutaneous accumulation[67,68]. These findings underscore the great significance of maintaining α-DCs/AGE homeostasis for both cutaneous health and overall physiological well-being.

4. Pathogenic roles of RCS/AGEs-mediated carbonyl stress in the skin

The skin consists of three major layers: the epidermis, dermis, and hypodermis, each with distinct anatomical structures and functions. Carbonyl stress mediated by RCS/AGEs can damage all skin layers, particularly the epidermis and dermis, leading to inflammation, yellowing, ageing, and other skin issues (Fig. 4). The associated mechanisms are extremely complex, which from molecular to cellular level, may involve disruption of gene expression, modification of protein structures, activation of RAGEs, inhibition of cell migration and proliferation, and promotion of cell senescence and apoptosis.

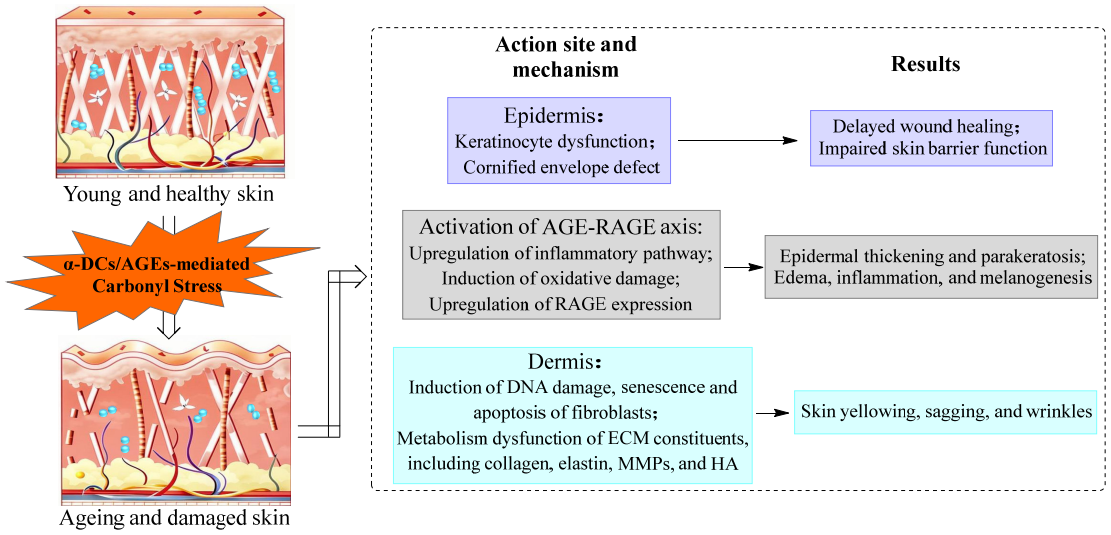

Fig. 4 Action scheme and damage effects of α-DCs/AGEs-mediated carbonyl stress on skin.

4.1 Epidermal keratinocyte dysfunction and delayed wound healing

Keratinocytes, representing the predominant cell type of the epidermal layer, play a pivotal role in cutaneous wound repair. Diabetic wound, characterized by delayed healing process, is documented to exhibit excessive apoptosis of keratinocytes. A mechanistic study revealed that AGEs were involved in the delayed healing by up-regulating matrix metalloproteinase 9 (MMP-9), which exerted a pro-apoptotic effect on keratinocyte through FasL (Fas ligand)/Fas (Apo-1/CD95) pathway[69]. Additionally, dysregulation of autophagy and decreased aquaporin-3 (AQP3) expression in keratinocytes stimulated by AGEs were considered to contribute to the delay of wound healing in diabetic skin[70,71]. A comparative study reported that the plantar epidermis in type 2 diabetes (T2DM) was thicker and the plasticity was lower compared to age-matched controls[72]. The level of pentosidine measured in plantar epidermis was higher in the diabetic subjects than in controls. Under non-diabetic condition, keratinocytes exposed to AGEs for 72 h lost their capacities of migration and proliferation with the effect being dose-dependent[73]. In addition, direct exposure to α-DCs such as GO and MGO was found to promote cell death and alter various protein expressions in human keratinocytes[74].

4.2 Cornified envelope defect and impaired skin barrier function

The cornified envelope (CE) is a lipid-protein crosslinked structure that replaces the plasma membrane surrounding keratinocytes. The complete composition and ordered organization of CE are crucial for reinforcing skin barrier function. In an *in vitro* tissue-engineered skin model, exposure to 200 μmol/L of GO for 31 days resulted in sustained accumulation of CML, leading to an epidermal differentiation defect with the lack of two predominant CE proteins loricrin and filaggrin [75]. Notably, co-treatment with a glycation inhibitor almost completely reversed these pathological changes[75]. Regarding the effect of glycation on lipids, the reconstructed skin model showed that ceramide and cholesterol in the epidermis were increased[76] by glycation whereas saturated fatty acid was decreased[77]. Assessment of the barrier function using excised mouse skin confirmed that GO-induced glycation disrupted both inside-out and outside-in epidermal lipid barriers[77].

4.3 Proliferation inhibition and induction of senescence and apoptosis in dermal fibroblasts

Fibroblasts are the primary cellular population in the dermis, and their normal proliferation and growth are essential to maintain skin health. Emerging evidence indicates that α-DCs/AGEs-mediated carbonyl stress may contribute to the senescence and apoptosis of fibroblasts. For instance, a time- and dose-dependent increase of apoptosis was observed in human adult dermal fibroblasts exposed to AGEs[78]. Investigations into the mechanisms revealed that AGE-stimulated apoptosis was linked to the formation of ROS, nitric oxide, and ceramide, which activated the mitogen-activated protein kinases (MAPK) pathway and subsequently induced the activation of the proapoptotic transcription factor forkhead box transcription factor O1 (FOXO1). Silencing FOXO1 resulted in a reduction of approximately 75% in AGE-induced apoptosis, underscoring the functional importance of FOXO1 activation in the apoptosis of glycosylated fibroblasts. An *in vivo* study found that MG-modified collagen disrupted the redox homeostasis, triggering endoplasmic reticulum stress and apoptosis in the tail skin fibroblasts of mice. The underlying mechanism of MG-collagen involved the activation of the protein kinase R-like kinase (PERK)-eukaryotic initiation factor 2α (eIF2α) pathway and caspase-12[34]. In murine skin fibroblasts, AGEs were formed after exposure to RCS for 4 h, contributing to the senescence process of fibroblasts through the modification of histones and the sirtuin SIRT1, which resulted in an accumulation of acetylated proteins[79].

In addition to proteins, carbonyl stress also damages DNA in fibroblasts, leading to inhibited cell proliferation. An *in vitro* study performed in human CF3 fibroblasts found that GO treatment caused DNA strand breaks while MGO produced extensive DNA-protein crosslinking[80]. The genotoxic effect of α-DCs was attributed to carbonyl stress-mediated intracellular histone glycoxidation, leading to oxygen-dependent DNA cleavage. Skin ageing is partly attributed to glycation-derived DNA damage in both nuclei and mitochondria, which contributed to the suppression of fibroblast proliferation[81].

4.4 Modification of molecules in dermal ECM and skin ageing

The extracellular matrix (ECM) of the dermis serves as a complex structural support network of the skin, characterized by dynamic structures and diverse biofunctions. Primarily secreted by fibroblasts, the dermal ECM is composed of a varied array of functional molecules such as fibrous proteins (collagen and elastin), adhesion proteins (fibronectin and laminin), proteoglycans, and glycosaminoglycans[82].

RCS/AGEs-mediated carbonyl stress can dysregulate the expression of ECM proteins such as collagen and elastin. The compromised mechanical properties of the skin contribute, to some extent, to ageing process. Collagen is the most abundant ECM protein, accounting for nearly 80% of the fat-free dry weight of human skin[83]. Its half-life is approximately 15 years[84]. In contrast, elastin comprises 2%–4% dry skin weight and has a half-life of more than 70 years. Due to their abundance and slow turnover rates, collagen and elastin are primary targets for carbonyl stress-induced modifications in skin. An *ex vivo* study on human skin revealed that carbonyl stress significantly and linearly increased glycosylation of epidermal and dermal collagen while moderately elevating elastin glycation adducts in the dermis[85]. Glycated collagens gradually accumulate with age, causing collagen to undergo color changes from brown to yellow. Elastin can stretch up to eight times its

length, providing elasticity and recoil to the skin[86]. Shintaro *et al*. observed that *in vitro* glycation induced increased amount of AGEs in skin, collagen yellowing, and degeneration of the fibrous structure of elastin[87]. Laughlin *et al*. collected facial cheek biopsies from young women to explore the relationship between AGE accumulation and skin appearance[88]. Results indicated that individuals with dull and yellow skin exhibited significantly higher levels of AGEs. Recently, a specific AGE known as AGEY, characterized by its intense yellow color, was identified in cultured human keratinocytes and human skin tissues, and shown to contribute to skin yellowness[89].

Matrix metalloproteinases (MMPs) are essential for maintaining ECM homeostasis, particularly through targeting the degradation of various collagens to contribute to skin remodeling. The interstitial collagenases MMP-1 and -13 preferentially degrade collagens I and III, whereas the gelatinases MMP-2 and -9 are mainly responsible for the degradation of collagen IV, the principal basement membrane component, and also collagen I when complexed with tissue inhibitor of MMP (TIMP-2) and MMP-14[90]. MMP-3 demonstrates broad substrate specificity, cleaving multiple ECM components such as collagen IV, proteoglycans, fibronectin, and laminin[91]. Experimental evidence from a recombinant skin model indicated that skin glycosylation promoted the enzymatic activity of MMP-1, -2, and -9[92]. Results from Lohwasser *et al*. also corroborated that AGEs modulated ECM-related gene expression in fibroblasts, resulting in excessive MMP-2 production and consequent basement membrane disruption[93]. Furthermore, MMPs-mediated degradation of collagen is particularly susceptible to carbonyl stress, resulting in decreased degradability and impaired dermal regeneration. A study using intact tail tendon from mouse demonstrated that approximately 75% of native fibrillar collagen was degraded after exposure to MMP-1, MMP-8, and MMP-13 for 4 h, whereas AGE-modified fibrils were only degraded by 40%–50%[94]. Additionally, a 35% decline in modulus, stress, and strain at break was observed in native fibers after MMPs-mediated collagenolysis; however, this reduction was limited to 20% following glycation treatment. These findings suggest that AGEs weaken the structural and mechanic integrity of collagen fibers, impairing MMP-mediated tissue remodeling, which may contribute to ECM pathology and further accelerate skin ageing.

Beyond collagen and other major ECM proteins, additional ECM molecules are also susceptible to RCS/AGEs-induced carbonyl stress. A representative example is hyaluronic acid (HA), an essential glycosaminoglycan in ECM, whose levels inversely correlate with AGE accumulation. This AGE-associated HA depletion may lead to dryness in ageing skin[95].

4.5 Activation of AGE-RAGE axis and skin damage

The receptor for advanced glycation end products (RAGE) is a non-specific multi-ligand pattern recognition receptor, present in various adult tissues at low levels but highly expressed in the lung and skin. The distribution of RAGE in the skin has been found to be dynamically regulated. Specifically, the expression of RAGE is up-regulated in the skin when exposed to sunlight, and increased along with ageing, particularly in the basal layer of epidermis and fibroblasts of the upper layer of dermis[96]. AGEs can bind to RAGE, thereby activating multiple signaling pathways, including nuclear factor κB (NF-κB), Janus kinase/signal transducer

and activator of transcription (JAK/STAT), phosphatidylinositol 3-kinase (PI3K)/AKT, and mitogen-activated protein kinases/extracellular signal-regulated kinase (MAPK/ERK). These pathways collectively mediate multifaceted detrimental effects on the skin via pro-inflammatory cytokine upregulation, oxidative stress induction, cell cycle dysregulation, and altered ECM biosynthesis [97,98].

RAGE's prominent role is its involvement in the inflammatory cascades. Upon direct crosslinking or indirect binding with RAGE, AGEs trigger the activation of transcription factors NF-κB and upregulate the expression of pro-inflammatory cytokines such as TNF (tumor necrosis factor)-α, IL (interleukin)-1β, IL-6, and IL-8[99]. Furthermore, AGE-RAGE interaction stimulates ROS production and in turn promotes NF-κB-mediated inflammatory response[37]. As a consequence, the inflammatory process is prolonged by RAGE activation, which clinically manifests as pathological epidermal hyperplasia[100]. A mouse skin glycation model induced by a high-fat diet and D-galactose showed that the epidermal thickness was 8.14 μm in the control group and137.41 μm in the glycation model[101]. Similarly, a guinea pig model of eczema-like skin lesions demonstrated that thickened epidermis, parakeratosis, as well as edema and inflammatory cell infiltration in the dermis, were attributed, at least partially to elevated AGE levels and the activation of AGE-RAGE-mediated inflammatory cascades[102].

RAGE also plays an important role in AGE-mediated melanogenesis. In both *ex vivo* skin organ cultures and *in vitro* melanocyte cultures, AGE administration resulted in increased melanin production[103]. However, this up-regulation of melanin synthesis was abolished by prior RAGE blockade, indicating that AGEs promoted melanogenesis via RAGE. Cyclic AMP response element-binding protein (CREB) and extracellular signal-regulated kinases (ERK) 1/2, downstream targets of RAGE signaling, were identified as crucial regulatory proteins in AGE/RAGE-induced melanogenesis.

In addition, AGEs exhibit positive feedback on up-regulation of RAGE expression. In human foreskin fibroblasts, administration of 50 mg/mL CML led to a marked increase in RAGE levels, with protein expression levels surging over 3 folds and mRNA levels rising by 1.5 folds, respectively[96]. This finding was corroborated by an *in vivo* study, which observed significantly elevated RAGE mRNA expression in murine skin following exposure to glycation[101]. Oligosaccharyl transferase-48 (OST-48, AGE-R1) is another AGE-binding receptor. A systematic review of clinical trials, encompassing data from 2935 adults and elderly participants with normal weight or overweight conditions, revealed that adherence to the Mediterranean diet for a minimum duration of 4 weeks resulted in reductions in serum AGE levels and skin autofluorescence intensity. Notably, the Mediterranean diet intervention was further associated with beneficial modulations in the gene expression patterns of AGE receptors, including RAGE and AGER1[104].

5. Intervention strategies to protect skin from RCS/AGEs-mediated carbonyl stress

Reducing excessive carbonyl stress benefits skin health and helps manage metabolic disease-related skin complication. Relevant intervention can be categorized into three strategies: (i) preventing the generation of carbonyl stress by inhibiting the RCS/AGE formation or by preventing the RCS/AGEs-induced damage to the

skin at the source; (ii) reducing carbonyl stress by catabolizing or removing the generated RCS/AGEs; and (iii) blocking the action of AGEs by breaking crosslinks and/or disrupting the AGE-RAGE signaling axis.

5.1 Inhibition pathways before carbonyl stress generation

In the last two decades, phytochemicals have gained increasing attention as potential inhibitors of glycation due to their superior ability to suppress AGE formation and related carbonyl stress, along with their low or minimal toxic effects. For example, pomegranate extract (50 μg/mL) and punicalagin (50 μM) have been shown to significantly alleviate MGO-induced carbonyl stress in HaCaT cells by reducing the formation of MGO-DNA adducts and tailed DNA by 60.2% and 49.7%, respectively[105]. Mechanistically, the protective effects of pomegranate extract and punicalagin on human keratinocytes against MGO-induced cytotoxicity were associated with decreased ROS levels, improved cell adhesion, migration, and wound healing capacities, and increased the cell viability[105]. Also, *Dunaliella salina* extract has been observed to reduce CML formation and RAGE expression levels, and improve the inflammatory condition in MGO-exposed human skin explants[106]. A subsequent double-blind, split-face, placebo-controlled clinical trial further confirmed the anti-glycation effect on skin of *Dunaliella salina* extract, as evidenced by a significant reduction in wrinkle counts and volume[106]. In a screening of glycation inhibitors, lemon balm leaf extract was identified from among 681 hot water plant extracts as exhibiting potential inhibitory activity against pentosidine formation[87]. A follow-up open-label, parallel-group comparative trial demonstrated that lemon balm leaf extract significantly reduced arterial stiffness and forearm skin yellowness in all subjects, and improved cheek skin elasticity in females[87]. Rosmarinic acid, a typical polyphenol in Lamiaceae plants, was found to be the key active constituent responsible for the protective effect of lemon balm extract against glycation-related damage in blood vessels and skin. Other natural exacts such as a polysaccharide fraction from pomegranate rind and a phenolic constituent from milk thistle flower, have also been found to inhibit AGE formation both *in vitro* and in human explants[107,108].

Exacerbated oxidative stress may act as a contributing factor in the glycation process, which accelerates skin ageing by promoting the formation of wrinkles and atypical pigmentation[109]. An *in vivo* study found that applying squalene monohydroperoxide to the skin of hairless mice induced skin roughness and even disrupted the skin barrier function[110]. In a screening of glycation inhibitors against skin ageing, a plant extract rich in antioxidant molecules was identified as the most promising candidate as it significantly protected human skin from different forms of carbonyl stress[111]. These results suggest that therapeutic interventions targeting ROS through neutralization, inhibition, or scavenging mechanisms may represent a viable approach to suppress glycation reactions and slow down skin ageing. Polyphenols, well-known for their strong antioxidant properties, are representative examples of effective anti-glycation phytochemicals[112,113]. The underlying mechanism may involve antioxidants reducing oxidative stress, thereby preserving protein structures and inhibiting RCS formation during sugar chain degradation or lipid peroxidation[114,115]. For instance, A proprietary red maple leaf extract (Maplifa™) and its major phenolic constituent, ginnalin A exhibited both antioxidant and anti-glycation activities, protecting human keratinocytes from MGO- and hydrogen peroxide

(H_2O_2)-induced cytotoxicity[116]. Specifically, pretreatment with Maplifa™ (50 μg/mL) and garlic acid (50 μmol/L) increased the viability of H_2O_2- and MGO-treated HaCaT cells by 22.0% and 15.5%, respectively. They also reduced apoptosis by 8.0% and 7.2%, decreased the levels of apoptosis-related enzymes including caspases-3/7 and -8 by 49.5% and 19.0%, and reduced ROS level by 84.1% and 56.8%, respectively[116].

Although polyphenols exhibit promising anti-glycation properties, their clinical application remains constrained by poor oral bioavailability. Due to limited membrane permeability and particularly the extensive metabolism *in vivo*, less than 5% of ingested polyphenols is absorbed intact to the systemic circulation through the intestinal barrier and liver detoxification[117]. As such, recent advances in understanding the *in vivo* metabolic transformation and bioavailability patterns of polyphenols have shifted research focus toward their bioactive metabolites, especially those generated through intestinal gut microbiota-mediated biotransformation. Emerging evidence suggests that gut microbiota plays an underexplored role in mediating the post-ingestion bioactivity of polyphenols and their subsequent health benefits. A case in point is the demonstrated efficacy of lotus seedpod-derived procyanidin oligomers, which exhibited potent inhibition of AGE formation and significant MGO scavenging capacity[118]. Following oral administration of lotus seedpod extract, HPLC-MS/MS analysis identified (+)-catechin and seven aromatic acids as the predominant procyanidin metabolites in rat urine within 24 h. The major gut microbiota-derived metabolites, including 3-hydroxyphenylacetic acid, 3-hydroxyphenylpropionic acid, ferulic acid, and 3-hydroxybenzoic acid, represented approximately 87% of the total detected metabolites. Of note, these microbial metabolites were capable of suppressing AGEs and scavenging MGO[118]. Moreover, certain microbial metabolites of polyphenols demonstrate superior pharmacokinetic profiles compared to their parent counterparts, exhibiting both enhanced stability and significantly higher circulating concentrations that reach biologically active levels[119,120]. For example, a human study revealed that polyphenols-rich apple consumption elevated fasting serum levels of phenolic acid metabolites to (5-40) μmol/L, a concentration approaching those of endogenous antioxidants like ascorbate (30-100) μmol/L[121]. These findings indicated that the gut microbiota may represent a promising research frontier to help clarify the longstanding paradox between the low bioavailability of dietary polyphenols and their multiple bioactivities, including anti-glycation effects and skin protection benefits. Moreover, topical application may be an effective delivery way for natural phytochemicals to bypass mucosal and hepatic first-pass metabolism while providing localized protection for skin against glycation and related carbonyl stress. Clinical evidence from an 8-week trial showed that regular use of facial cream containing 0.5% Akebia quinata fruit extract significantly diminished periorbital wrinkle depth[122]. The observed anti-ageing effects were attributed to the alleviation of MGO-induced cellular senescence, inhibition of glycation, reduction of CML expression, and stimulation of fibrillin-1 expression[122].

Dietary intake constitutes a major exogenous source of AGEs in humans, with emerging evidence suggesting that adopting a low-AGE dietary pattern may reduce AGE exposure and provide potential health benefits[123]. The fundamental principle of low-AGE dietary intervention lies not in altering macronutrient

composition, but in modifying food preparation techniques, as the cooking process predominantly determines final AGE content[124]. This is exemplified by the dramatic increase in AGE levels observed in beef subjected to different cooking conditions: raw (707 kU/100 g), water-boiled at 100℃ (212 ℉) for 7 min (7484 kU/100 g), and broiled at 232.2℃ (450 ℉) for 5 min (11270 kU/100 g)[125]. A randomized crossover trial involving 62 healthy participants demonstrated that high-AGE diets, characterized by high-temperature cooking methods, significantly increased circulating AGE levels and upregulated metabolic biomarkers associated with T2DM and cardiovascular disease risk[126]. Fortunately, two databases encompassing AGE content for over 500 commonly consumed foods are now available. These resources provide a basis for precise estimation of dietary AGE intake, and facilitate the design of customized meal plans with controlled AGE content[125,127]. However, the databases have certain limitations. The present data relies on measurements of CML and MG, while many other AGEs present in food remain unquantified, albeit of unknown significance. Furthermore, the foods included were selected from diets typical of a northeastern U.S. metropolitan area, meaning they may not reflect global dietary averages. Ongoing research is necessary to further expand the dietary AGE database and explore more efficient methods for AGE determination. Also, future studies should continue to investigate the health effects of various AGEs and refine recommendations for safe dietary intakes.

5.2 Degradation pathways after RCS/AGEs formation

As the principal precursors of AGEs, RCS play a pivotal role in regulating endogenous formation of AGEs. Overwhelming evidence supports that RCS sequestration is an effective approach for inhibiting or mitigating carbonyl stress-related pathologies. Aminoguanidine, as a prototypical AGE inhibitor, has been shown to effectively scavenge α-DCs and suppress AGE formation through its nucleophilic trapping mechanism[128]. Currently, this compound is undergoing Phase III clinical trials to evaluate its therapeutic potential for diabetic nephropathy. While aminoguanidine has demonstrated efficacious effects in AGE inhibition, its dermal applications present more complex challenges. An *in vivo* study showed that within collagen-rich tissues, aminoguanidine exhibited only marginal effectiveness in blocking cross-links and AGE formation[129]. Current evidence regarding the potential of aminoguanidine to confer cutaneous protection through AGE inhibition is notably limited and warrants further investigations to fully delineate its dermato-pharmacological properties. Regarding the phytochemicals, emerging evidence highlights tea as a rich source of bioactive RCS scavengers. Epigallocatechin-3-gallate (EGCG), a major tea polyphenol, exhibited remarkable RCS trapping capacity, capturing over 90% of MGO within 10 min under physiological conditions (pH 7.4, 37 ℃)[130]. The MGO-capturing ability of EGCG surpassed that of amino acids[131]. Theanine, another tea component, could quench RCS by forming imine adducts. Intriguingly, despite its lower content compared to catechins that include EGCG, epicatechin gallate, epigallocatechin, and epicatechin, theanine was found to produce more RCS adducts in both green and black tea. This may due to the stronger nucleophilicity of free amino groups in theanine molecules[132]. In addition, some endogenous nutrient molecules including carnosine, amino acids, and thiamine (vitamin B_1), have also been reported to capture RCS and inhibit AGE formation[133-135]. However, it is important to note that, while excessive RCS is

implicated in ageing process and may promote pathological progression, a low tolerance level of RCS is indispensable for their biological functions participated in cellular signal transduction, gene expression regulation, and immune response modulation[1]. Consequently, the therapeutic objective should not focus on complete RCS elimination, but rather on restoring and maintaining their natural physiological levels.

An alternative approach to mitigate carbonyl stress involves enhancing the body's natural occurring detoxification pathways for RCS and AGEs. The glyoxalase system, functionally active in epidermal keratinocytes and dermal fibroblasts, serves as a primary metabolic pathway to detoxify α-DCs and counteract glycation reactions in the skin[136]. In human umbilical vein endothelial cells, pterostilbene has been shown to activate the glyoxalase defense system by up-regulating GLO1 expression and increasing GSH levels, helping relieve MGO overload[137]. Moreover, *Musa balbisiana* seeds and gromwell root have been found to protect the skin from glycation damage and carbonyl stress. This protective effect of the two extracts was partly attributed to the enhancement of glyoxalase activity and subsequent RCS detoxification[138,139]. However, targeting the glyoxalase system presents significant challenges due to its intracellular localization and the current lack of efficient delivery systems for therapeutic agents. Moreover, accumulating evidence indicates that GLO1 overexpression are associated with tumor progression and metastasis[140], complicating potential therapeutic strategies aimed at mitigating carbonyl stress through GLO1 activation.

Despite extensive evaluation of multiple anti-RCS/AGE compounds and natural products, no effective candidates have been identified, at least to date, and approved for glycation-associated carbonyl stress indications. Several factors may contribute to this, but notably, one key reason is that solely targeting AGEs fails to address the diverse pathobiological effects mediated by other distinct RAGE ligands. This mechanistic limitation provides compelling rationale for the current shift in therapeutic strategy toward direct RAGE targeting approaches.

5.3 Blocking the action of AGEs

RAGE and its downstream signaling pathways have emerged as promising therapeutic targets for counteracting skin damage caused by AGE-mediated carbonyl stress. In this regard, Han *et al*. constructed a novel echinacoside-zinc nanomaterial (PPZn) and evaluated its skin protective effects against glycation-induced skin damage using a murine model combining high-fat diet and *D*-galactose administration[101]. Their findings demonstrated that PPZn treatment effectively attenuated multiple hallmarks of skin aging, including inflammatory epidermal hyperplasia, collagen fiber degradation, and cellular apoptosis. At the molecular level, PPZn was shown to inhibit RAGE transcriptional activation by disrupting the formation of the MDM2/STAT2 (mouse double minute 2/signal transducer and activator of transcription 2) transcriptional complex, thereby elucidating its anti-glycation mechanism. Complementing these findings, another study performed in guinea pig models with eczema-like lesions revealed that ointment made from Huanglian (*Coptis chinensis* Franch) could ameliorate cutaneous inflammation and restore barrier function through regulation of c-Jun and JunB expression and inhibition of AGE-RAGE signaling pathway[102]. Additionally, rutin has been reported to exert anti-psoriatic effects in murine models, potentially through

similar downregulation of the AGE-RAGE axis, highlighting the pathway's broad therapeutic potential across various dermatological conditions[141]. Several RAGE inhibitors are currently under clinical investigation, including Azeliragon (TTP488) which is undergoing Phase III trials for mild Alzheimer's disease (AD) and Phase II studies for glioblastoma, along with FPS-ZM1 in Phase I trials for diabetic retinopathy. However, their potential dermatological benefits through RAGE inhibition remain poorly characterized.

Breaking crosslinks between AGEs and proteins, especially long-lived proteins such as collagen and elastin, is an alternative strategy to block the action of AGEs and further mitigate AGE-mediated carbonyl stress. Such effects theoretically enable functional restoration of tissues and organs compromised by AGE-induced structural modifications and loss of elasticity. Alagebrium, or ALT7-11, is the most studied AGE-crosslink breaker with capacity of reversing already formed AGE-crosslinks. In Phase II clinical trials, Alagebrium has demonstrated relevant clinical activity against heart failure, as well as in animal models of heart failure and nephropathy, diabetes, hypertension, vascular sclerotic pathologies, and similar processes[142]. Dermatological applications also show promises in preclinical trials, with murine studies indicating significant improvements in aged skin elasticity and accelerated diabetic foot ulcer healing[142,143]. These effects are mechanistically linked to downregulation of RAGE expression and reduced AGE-collagen crosslink deposition in skin[144]. Nevertheless, the anti-glycation and skin-protective properties of Alagebrium await definitive clinical validation. Additionally, multiple phytochemicals have been reported as AGE-crosslink breaker. Oral administration of curcumin to diabetic rats was found to reduce the levels of AGEs, as well as the crosslinking and browning of collagen in tail tendons and skin[145]. Similarly, polyphenols from cranberry juice inhibited skin collagen glycation and crosslinking in the skin, while also breaking the existing crosslinks[146]. The breaking effects on crosslinks of collagen-AGEs was also observed with *Cirsium japonicum* flower extract[147]. Several translational challenges need to be addressed when developing therapeutic strategies to mitigate carbonyl stress by blocking the action of AGEs[148,149]. For nanomaterial-based approaches (e.g. PPZn), comprehensive assessment of long-term biosafety parameters is essential, particularly regarding the necessity of surface modifications to minimize off-target interactions. Similarly, natural crosslink-breakers may encounter limitations in bioavailability and stability under physiological conditions, and inherent variability in extract compositions.

Although some progress has been achieved in developing interventions to mitigate RCS/AGEs-induced carbonyl stress, the therapeutic efficacy of these strategies in combating carbonyl stress-mediated skin ageing and damage still requires further confirmation, particularly through well-designed clinical trials and mechanistic studies.

6. Concluding remarks

Growing evidence suggests that chronic exposure to excessive RCS and their resultant AGEs induces a pathological state termed carbonyl stress. This biochemical disturbance has been mechanistically linked to both intrinsic and extrinsic skin ageing, as well as the exacerbation of various dermatological disorders. The pathophysiological consequences manifest across three principle dimensions: (i) structural deterioration,

characterized by CE defects, ECM modification, and aberrant protein crosslinking - such as collagen fragmentation and elastin degradation; (ii) functional impairments, including disrupted epidermal differentiation, proliferative arrest, and the induction of senescence and apoptosis; and (iii) clinical manifestations, encompassing (a) chronological ageing phenotypes, such as wrinkles, yellowing, dryness, pigmentation, and elasticity reduction; (b) metabolic dermatopathies, such as diabetic dermopathy; and (c) inflammatory or chronic skin issues, including atopic dermatitis and plaque psoriasis. Over the past two decades, there has been a marked surge in pharmacological research targeting carbonyl stress mitigation, with particular emphasis on anti-AGE therapeutic strategies. Although several synthetic compounds, such as the AGE formation inhibitor aminoguanidine, RAGE antagonist azeliragon, and AGE-crosslink breaker alagebrium, have progressed through various phases of clinical trials, their efficacy in cutaneous applications remains largely limited to preclinical studies, with clinical evidence being particularly scarce. Notably, no therapeutic agent has yet received regulatory approval specifically for anti-carbonyl stress indications. This translational gap is further compounded by the absence of standardized criteria for recognizing "anti-carbonyl stress" as a discrete therapeutic category within global drug evaluation frameworks, as well as the lack of consensus regarding appropriate clinical endpoints for assessing anti-carbonyl stress efficacy.

Beyond pharmacological interventions, dietary regimen emerges as a clinically promising strategy to mitigate RCS/AGEs-mediated carbonyl stress. One solution is to minimize dietary exposure to glycotoxins. Modern food processing methods, especially thermal treatments involving dry heat，such as grilling, baking, frying, roasting, dramatically elevate AGE formation. The ultimate dietary AGE load depends on cooking methodology, industrial processing intensity, but also intrinsic food composition. Notably, the establishment of AGE content database lays a foundation for accurate estimation of dietary AGE intake and promotes the development of personalized low-AGE dietary regimens. Augmenting consumption of bioactive phytochemicals with demonstrated anti-carbonyl stress properties is another solution. Polyphenols and other bioactives exhibit potential to mitigate RCS/AGEs-induced carbonyl stress through multimodal mechanisms of action, and particularly they have superior safety profiles compared to synthetic alternatives. Nevertheless, rigorous preclinical validation and randomized controlled human trial study are imperative to establish their clinical efficacy in mitigating carbonyl stress-induced cutaneous aging and pathology. Additionally, considering the complex composition of bioactive-containing foods, future research should focus on: (i) isolating and characterizing specific bioactive constituents with anti-carbonyl stress activity; (ii) elucidating the underlying action mechanisms; (iii) prioritizing well-designed clinical trials (e.g., longitudinal studies) to validate the anti-skin-aging efficacy; and (iv) developing evidence-based dietary guidelines for anti-carbonyl stress modulation to optimize both systemic and dermatological health outcomes.

We hope this review will inspire further research to better define the role of RCS/AGEs-mediated carbonyl stress in skin ageing and associated impairments. Additionally, we aim to encourage the discovery of RCS and/or AGE inhibitory agents and bioactives with potent therapeutic potential to mitigate carbonyl stress, ultimately improving skin health and slowing the progression of skin ageing.

Conflicts of Interest

All authors declare that there are no conflicts of interest.

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