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Advanced glycation end products and skin ageing - A Review

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ABSTRACT

Advanced glycation end products (AGEs) are compounds formed by non-enzymatic reaction between the carbonyl group of reducing sugars and amino group of proteins, nucleic acids, and lipids. They are formed in body tissues by both endogenous and exogenous ways. Elevated concentration of AGEs is a prominent feature observed in patients with diabetes mellitus, end-stage renal disease, and during ageing. Accumulation of various forms of AGEs are found in both intrinsic and extrinsic types of skin ageing. AGE-modified proteins interact with the receptor for AGE (RAGE) and increase the production of matrix metalloproteinases (MMPs), activate the transcription factor k-B (NFkB) and proinflammatory cytokines, reduce the production of dermal collagen and induce apoptosis of fibroblast *via* activation of a variety of signalling cascades. This brief review deals with the information on AGEs and the significance of glycation of dermal proteins in skin ageing. It also reviews anti-AGE strategies as a possible approach which may be beneficial in the management of skin ageing.

Figures : 03 References : 53 Table : 00
KEY WORDS : Advanced glycation end products (AGEs), Matrix metalloproteinases (MMPs), RAGE, Skin ageing

Introduction

The skin is the largest organ in the body, covering its entire external surface. It functions as a barrier against various factors like water loss, microbial infections, and dust. It also functions in maintaining skin homeostasis, thermoregulation, and sensory perceptions[8]. Like any other organ in the body, the skin also undergoes ageing process. Aged skin not only produces wrinkles but also impairs skin properties like permeability, wound healing, immune function, angiogenesis, synthesis of Vitamin D, and also it may be afflicted by various benign and malignant diseases[53]. Skin ageing is categorized into two types: intrinsic and extrinsic. Intrinsic type of ageing is the chronological ageing, whereas extrinsic ageing is influenced by various external factors like UV exposure, smoking, diet, stress, and pollution[4]. Amongst these factors, chronic exposure to UV rays of the sun is considered the major cause leading to premature skin-ageing. Both of the two types of skin ageing are instigated by oxidative stress induced by the reactive oxygen species (ROS). These are produced normally during the reaction processes involving the electron transport chain, NADPH oxidases, xanthine oxidoreductase, cyclooxygenase, peroxisomal oxidases, lipoxygenases and enzymes of the cytochrome P450 family[9,28]. In the skin, ROS is produced in the mitochondria of keratinocytes and fibroblasts. Its production is also increased by protein glycation and accumulation of AGEs. Recently, glycation has been considered as one of the underlying mechanisms of ageing[29]. It is a non-enzymatic reaction where reducing sugars react with the free amino groups of protein forming unstable Schiff base adducts which then form Amadori products because of the Maillard reaction, illustrated in Figure 1. These early glycation products further undergo complex changes to form the irreversible cross-linked compounds, advanced glycation end products AGEs. The effects of these AGEs are then expressed by binding with their specific receptors (RAGEs) and then activating different signalling pathways. Various roles of the AGEs with respect to skin ageing and strategies which can detoxify and degrade these harmful AGEs have been discussed

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in this review article. These anti-AGE strategies have been one of the keen research areas for developing anti skin-ageing compounds.

Advanced glycation end products (AGEs) and their role in skin ageing

AGEs are introduced into the human body through two main routes: exogenous and endogenous. Exogenous AGEs are the ones which are consumed through the diet. The dietary AGEs are formed during the processing, cooking and storage of certain foods[33]. Processed foods and food rich in proteins and lipids such as nuts, meat, and animal products introduce the exogenous AGEs in our diet[26]. Foods cooked at high temperature, like baked-, grilled- and fried-food items, contain more AGEs as compared to the steamed or boiled foods[30]. Increased pH, high temperature and low water content during cooking are some factors that enhance the formation of AGEs in foodstuffs[20]. Sweetened beverages and sugar-rich snacks containing fructose participate in forming AGEs in food[49]. Microbes also produce these compounds significantly in fermented food and alcoholic drinks[48]. Whereas the endogenous AGEs are produced in the body in a multi-step reaction involving an initial glycation process. Reducing sugars react with the lysine or arginine residues in proteins and form a non-stable Schiff's base which undergoes Amadori rearrangement to form fructosamine or Amadori product[26]. Shciff's base and Amadori product are the early glycation products. Spontaneous oxidative degradation of glucose and Amadori products form á-oxoaldehydes, *viz.,* glyoxal (GO), methylglyoxal (MG) and 3-deoxyglucosone[1]. MG can also be synthesized from dihydroxyacetone phosphate (DHAP) by the enzyme methylglyoxal synthase and GO forms glycolaldehyde by autooxidation. These á-oxoaldehydes are dicarbonyl compounds which are electrophiles and therefore they are very reactive molecules. The dicarbonyl compounds and the early glycation products further undergo oxidative and non-oxidative reactions to form a wide range of stable heterogeneous fluorescent, yellow-brown products called advanced glycation end products (AGEs)[21]. N(6)-(carboxymethyl)lysine (CML), a GO-mediated AGE, is the most prevalent, non-fluorescent protein adduct or AGE[40]. Histone protein in humans forms the glycated protein CML due to the abundant presence of lysine in histones[3]. Pentosidine, an arginine and lysine residue cross-linked to pentose is a fluorescent protein-protein cross-link products also identified in ageing skin. N(6)-(Carboxyethyl)lysine (CEL), carboxymethyl hydrolysine, glyoxal-derived bis(lysyl)imidazolium crosslink (GOLD), methylglyoxal-derived bis(lysyl)- imidazolium crosslink (MOLD), MG-derived hydroimidazolones, 3-DG-derived bis(lysyl)- imidazolium crosslink (DOLD), pyrraline, glucosepane and fructose-lysine are some other AGEs[1].

Distinctive rise in the level of AGEs has been observed during the normal human dermal intrinsic ageing and it has been suggested that the associated glycation is also increased in photoaged skin[21]. Glycation is a physiological process which is often encountered by presence of protein having short half-life and high turnover rates. The turnover rate for proteins is an important criterion for the accumulation of AGE[47]. Glycation of the long-lived extracellular matrix proteins is the main reason for accumulation of AGEs in skin. Collagen, the most abundant protein of dermis has a turnover rate of about ten years. Collagen and other long-lived proteins of dermis like fibronectin are susceptible to glycation during intrinsic ageing process[13,21]. The intermediate filament protein, vimentin also suffers from glycation forming CML-modified vimentin. Accumulation of this protein in dermal fibroblast is found to disturb the key cellular and mechanical functions like wound healing, cell motility and chemotactic migration[22]. Accumulation of AGEs is found both in dermis and epidermis. Factors such as UV radiation, smoking and other unhealthy lifestyles can contribute to AGEs production[7]. Both the endogenously formed AGEs along with the absorbed

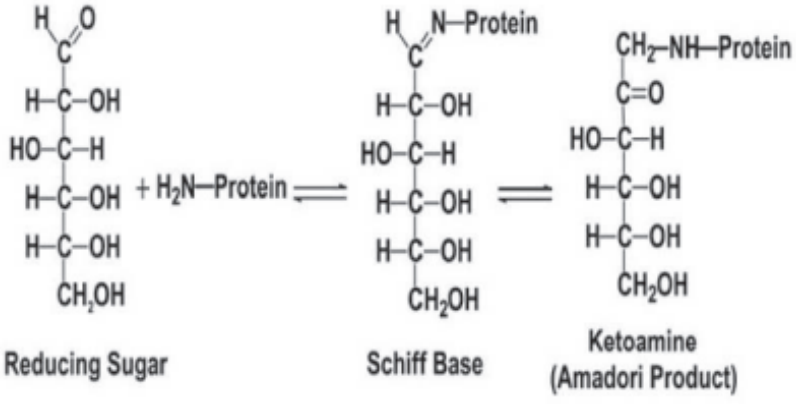

Fig.1 : The classic pathway of the Maillard reaction[45].

dietary AGEs contribute to the pool of AGEs in the body. AGEs are also found to have deleterious health effects, contributing to chronic renal diseases[5], neurodegenerative diseases like Parkinson's disease, multiple sclerosis, Alzheimer's disease[11], and diabetes mellitus[1].

AGE has also been studied as one of the gerontotoxins. These are a group of toxins that causes cells to age by contributing to systemic inflammation[39]. Studies have shown the accumulation of pentosidine in collagen-rich tissues like skin, articular cartilage and lens capsule[47]. Accumulation of AGEs leads to a lack of elasticity and tissue stiffness[10]. AGE-modified chaperone protein Hsc70 (heat shock cognate 70) has been

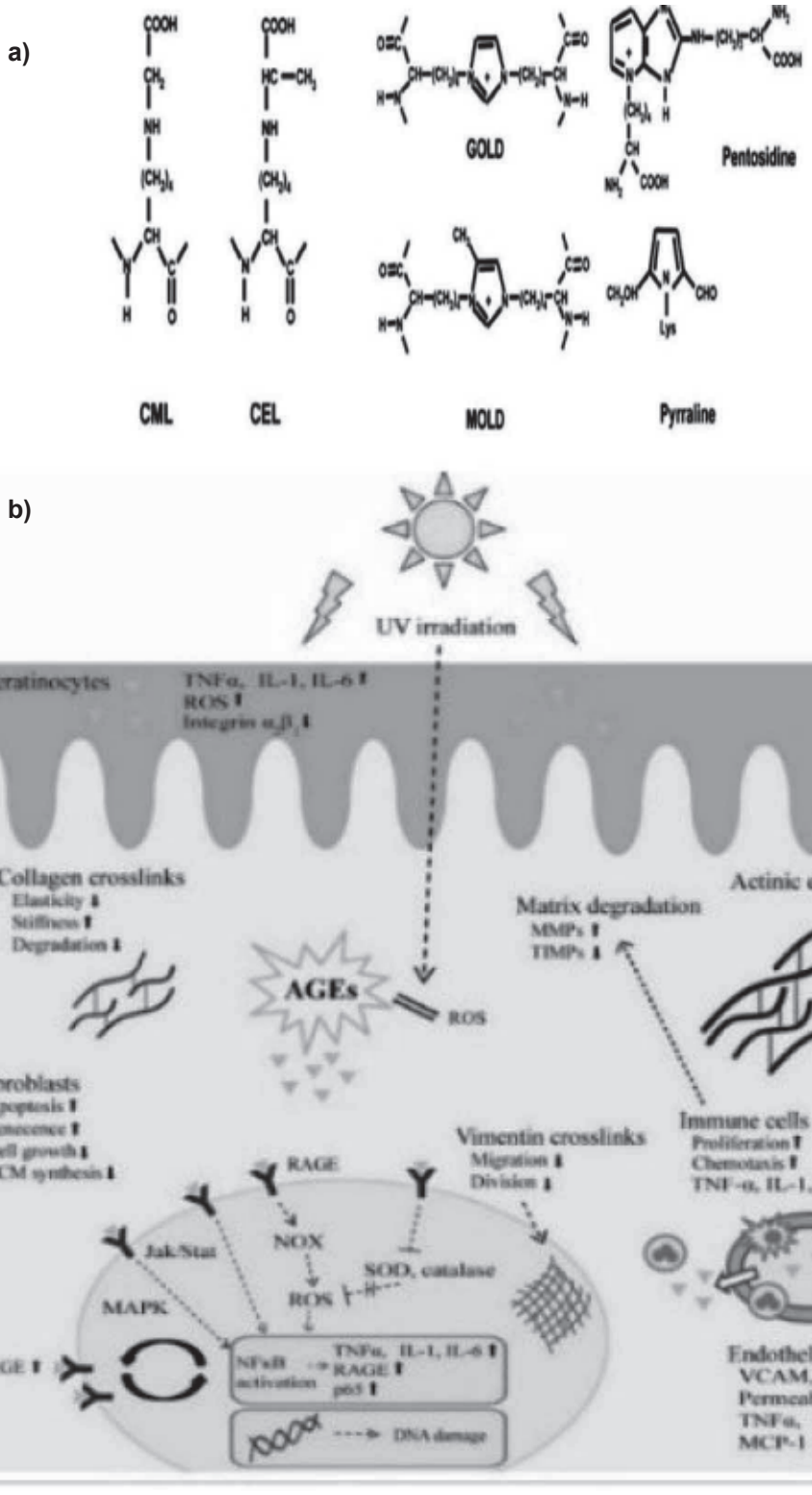

Fig. 2 : a. Schematic representation of the main AGEs produced in skin ageing[37]; b. Effect of AGEs on skin[17].

reported to be present in senescent dermal fibroblast of human[46]. The GO and MG-treated fibroblasts showed characteristic features similar to a senescent cell, like change in cell morphology, increased ROS, decrease in the antioxidant enzymes, irreversible growth arrest, increased senescence-associated â-galactosidase (SABG) activity, and increased levels of CML-modified protein[41]. The predominant AGEs produced during skin ageing and their effects on skin are summarised in Fig. 2.

The toxic effects of AGE are exhibited through many signal pathways, which get activated by the interaction of AGEs with its receptor (RAGE). RAGE belongs to the immunoglobulin superfamily of cell surface receptors. Ait is expressed in many cells like keratinocytes and fibroblasts of the dermis and epidermis of the skin[37] and its expression was found to increase in sun-exposed parts as compared to protected areas of skin[17]. RAGE is encoded by a gene that is located on chromosome 6 within the major histocompatibility complex (MHC class III region). As the skin continues ageing, the localization of the receptor is found to vary. It is localized in the upper and middle layers of the epidermis in young skin but localized in the middle and basal layers in aged skin. Melanoma cells also increase the expression of RAGE as compared to normal cells[24]. Engagement of RAGE with AGE stimulates various signalling cascades by activating mitogen-activated protein kinases (MAPK), extracellular signal-regulated kinases (ERK) 1 and 2, Ki-Ras, phosphatidyl-inositol 3 kinase, stress-activated protein kinase and the janus kinases[14]. These pathways altogether lead to activation of the transcription factor like nuclear factor ê-B (NFêB) and expression of many proinflammatory genes[6]. The binding of AGE-modified proteins with RAGE in HaCaT keratinocytes leads to subsequent activation of various signaling pathways like MAPK (Mitogen Activating Protein Kinase), NF-êB (nuclear factor êB) pathways which ultimately increases the production of MMP-9[52]. AGE CML-collagen induces apoptosis of fibroblasts by activation of caspase-3, which involves both caspase-8 and-9 pathways[2]. Binding of AGE to its receptor RAGE on dermal fibroblast reduces the production of matrix protein collagen[32]. AGEs also activate enzymes like nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase (NOX) and reduce the activity of various antioxidant defence systems like catalase, superoxide dismutase (SOD), GSH, and ascorbic acid. This further causes increased production of ROS and oxidative stress[25].

Elimination of AGEs and its importance during skin ageing

Nature has given the human body specific enzyme systems to detoxify the highly reactive dicarbonyl compound and prevent proteins from getting glycated. Many detoxifying enzyme systems against glycation and

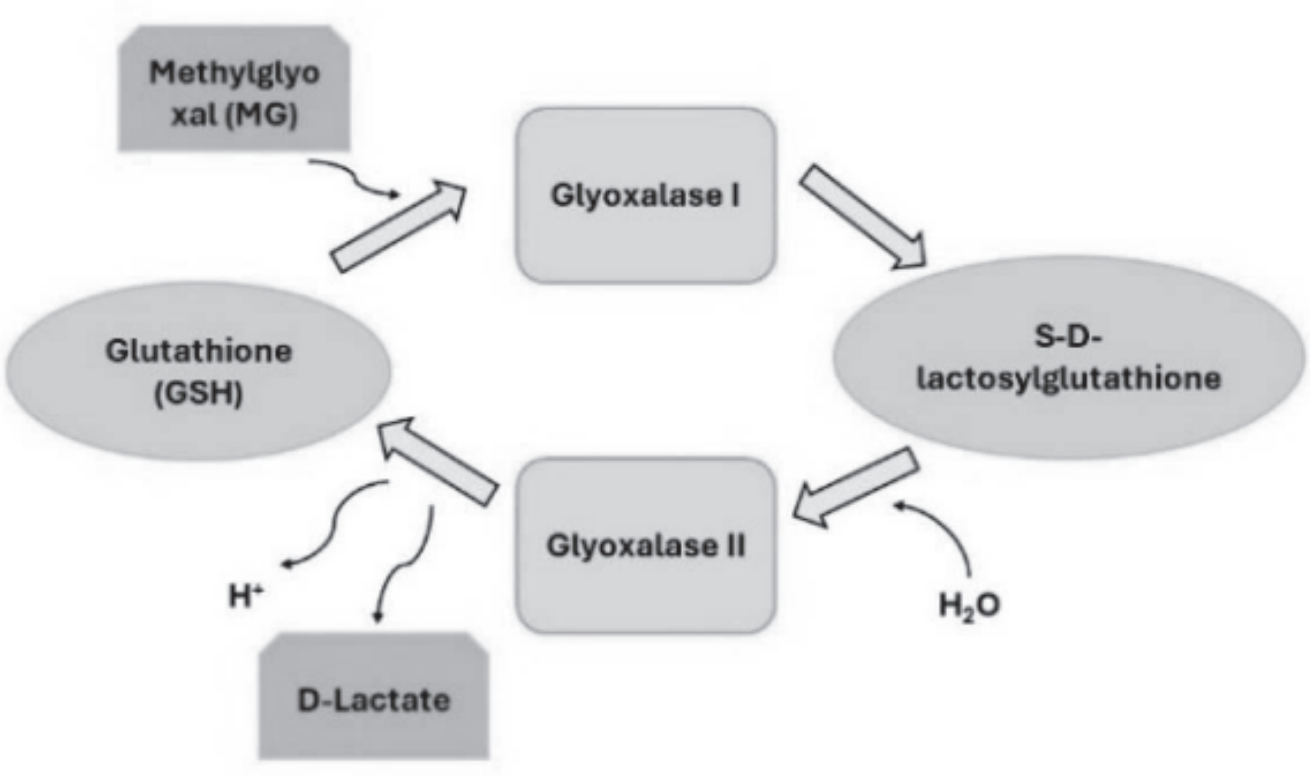

Fig. 3: The glyoxalase system

accumulation of AGEs are present in the biological system[44]. Among these, the glyoxalase system is the most prevalent one. Aldose reductase and aldehyde dehydrogenase are the pathways which eliminate the reactive precursors of AGE like methylglyoxal (MG)[27,36]. Aldose reductase eliminates the AGE precursors in the endothelial and cardiac tissues. However, glyoxalase is more relevant concerning ageing as it removes MG and GO without producing ROS in contrary to the aldose reductase system[37]. The glyoxalase system is comprised of glyoxalase (Glo) I and II which require glutathione (GSH) as a cofactor[51]. It converts the reactive GO, MG and other á-oxoaldehydes to lesser active á-hydroxyacids. Glo I catalyses the isomerization of hemithioacetal, formed in the reaction between the glutathionyl group of the reduced form of glutathione (GSH) and á-oxoaldehydes, to S-2-hydroxyacylglutathione derivatives. Glo II catalyses the hydrolysis of *S*-2-hydroxyacylglutathione derivatives to produce hydroxyacids and regenerate GSH[44] (Figure 3). Glo I is primarily located in the actively dividing basal layers (stratum basale) whereas Glo II is found in the upper layer of epidermis[38]. Age-associated decreased transcription, expression and activity of Glo I in mice skin fibroblasts elevates MG level contributing to delayed wound healing[15]. Another enzymatic system which can prevent AGE formation includes fructosamine-3-kinases (FN3K) which phosphorylates the fructosamine that is formed during the glycation process. This modification of fructosamine leads to rearrangement and breakdown of the Amadori products. In intrinsically aged skin, there is more production of glyoxalase enzymes, and thus low glycated proteins are found. However, it is seen that Glo II production is reduced due to photo exposure in both young and aged skin[38]. With increased oxidative stress due to glycation, there is a depletion of GSH, the cofactor required by the glyoxalase system. This further decreases the activity of Glo I, thereby increasing the concentration of the reactive AGE precursors like MG and GO[51].

Along with the presence of enzyme systems that prevent the formation of AGEs from their precursors, another mechanism, like intracellular degradation of AGE, also makes an important contribution in detoxifying the AGEs from the biological system (a clearance mechanism). AGEs are internalised for endocytosis by a scavenger receptor-mediated pathway[23] and removed by proteasomes or lysosomal protease cathepsin D, B and L[19]. Surface receptors like AGE-R1 (OST-48), AGE-R2 (80 K-H) and AGE-R3 (Gal-3) mediate endocytosis and breakdown of AGEs[16]. Macrophage scavenger receptor, types I and II (SR-A)[27] also have role in removal or scavenging the AGEs. CD36, a scavenger receptor class B, also binds AGE-modified protein which is then internalized and removed by endocytosis. It is found to be increased in keratinocytes when cultured with glycated collagens I and II[16]. Recent studies have shown that cathepsin D is found to have a vital role in the intracellular degradation of AGEs and is more effective in degrading AGE-modified proteins as compared to cathepsin B[18]. The expression and activity of cathepsin D in human dermal fibroblasts (HDF) were significantly compromised in photoaged compared to non-photoaged HDF. Photoaged fibroblasts show decreased expression of cathepsin D which further causes more accumulation of AGEs[50]. An increase in oxidatively modified proteins such as carbonylated proteins, HNE (4-hydroxynoneal)- and AGE-mediated proteins, together with a decrease in proteasome activity and content, were found in keratinocytes from old donors compared with young donors[35].

Several studies on a potential relationship between diet and skin health, including skin ageing are continuously emerging. A diet with low AGE content reduces inflammation and improves wound healing and diabetes-related consequences in mice models[34]. Water-based cooking and a low-sugar diet can limit the intake of dietary AGEs[31]. The extract of *Akebia quinata* fruit protects the human dermal fibroblast cells from oxidative stress and reduces the expression of carboxymethyl-lysine (CML) and stimulates fibrillin-1 expression[42]. Many herbs and spices including cinnamon, oregano, and cloves are found to inhibit the AGE formation in the body[12]. As ROS accelerates the glycation process, antioxidants are considered effective in limiting the formation of AGEs and reducing AGE-induced tissue damage or inflammation. Several natural products like ginger, flavonoids, pyridoxal, zinc, manganese, riboflavin, carnitine, α-lipoic acid, and garlic, are found to inhibit formation of AGEs[12].

Conclusion

Skin ageing has been a keen area of research in recent decades. The formation of advanced glycation end products with the dermal and epidermal matrix proteins is a concern with skin ageing owing to the fact that long-lived proteins of skin are highly vulnerable to glycation. There are adequate experimental evidences that support the role of AGEs in skin ageing. Therefore, strategies for developing potential anti-AGE substances might be a promising future research in the area of cosmetics.

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