Antiglycation an auspicious therapy for chronic diseases: glycation, glycation-induced pathologies, antiglycation strategies and drug delivery innovations

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Abstract

Background: Ageing is a major cause of multiple chronic diseases. Several mechanisms have been reported to contribute to the formation of these abnormalities including glycation, oxidative stress, the polyol pathway and osmotic stress. **Methods**: This study provides a recent and comprehensive review on possible causes, mechanisms, types, analytical techniques, diseases and treatments of the toxic glycation end products. Glycation, unlike glycosylation, is an irregular biochemical reaction to the formation of active advanced glycation end-products (AGEs), which are considered to be one of the causes of these chronic diseases. **Results**: Several mechanisms have found to play a role in generating hyperglycaemia-induced oxidative stress including an increase in the levels of reactive oxygen species (ROS), increase in the levels of AGEs, binding of AGEs and their receptors (RAGE) and the polyol pathway, and thus have been investigated as promising novel targets. **Conclusion**: Glycation is an example of what happens when the body's homeostasis is out of control; glucose can turn from a safe and vital molecule into a silent killer. This review focuses on the key mechanisms attributed to cumulative increases of glycation and pathological RAGE expression as a significant cause of multiple age-related diseases; and reporting on different aspects of anti-glycation therapy as a novel approach to manage/treat age-related diseases. Additionally, historical, current and possible future anti-glycation approaches will be presented focusing on novel drug delivery methods.

Keywords

Glycation, polyphenols, Maillard reaction, nanotechnology, flavonoids, drug repurposing

Introduction

Ageing is a very complicated process in which endogenous, environmental, and genetic elements have set roles; it happens in nearly all biological organisms and ultimately results in the dysfunction of cells, tissues and organs, which causes diseases and even death [1]. More than 300 different theories of the ageing process, including cellular senescence, mitochondrial DNA single mutations, free radicals and more have been trying to explain the changes involved in ageing and the occurrence of skin-ageing and different chronic diseases linked to ageing such as diabetes, Alzheimer's disease, cardiovascular diseases and cancer [2].

In recent years, several mechanisms have been discussed as having a major role in the occurrence of these age-related diseases including glycation, the polyol pathway and hyperglycaemia-induced oxidative stress mechanisms [1].

Anti-glycation has become one of the most recent approaches for the development of future novel pharmaceutical compounds [3]. This study extensively reviews reports on key mechanisms understood so far about cumulative increases of glycation and pathological RAGE expression as a significant cause of multiple age-related diseases as well as reporting on different aspects of anti-glycation therapy as a novel approach to manage/treat age-related diseases. Additionally, historical, current and possible future anti-glycation approaches and novel drug delivery strategies for treating chronic diseases and diabetic complications induced by accumulation of AGEs.

Glycosylation and glycation

Glycosylation is a necessary and essential enzymatic-regulated reaction that has a great biological significance. It is a physiological post-translational modification process in which proteins become active and functional. Protein glycosylation is cell or tissue-dependent and the glycosylation pattern is being encoded by the polypeptide itself [4]. Glycosylation is a complex process that involves approximately 13 monosaccharides, 8 amino acids and many enzymes. It forms around 40 different types of glycosidic bonds and 600 types of proteins [5]. It plays a vital role in the modification process of proteins since it helps create the right

protein folding and polymerisation; it protects proteins from proteolysis and degradation and thus improves their stability and prolongs their half-life in the plasma. It adjusts protein steric interactions and helps in differentiating human cell proteins from other pathogens, thus playing a significant role in innate immunity [6].

Glycation, the first phase of the **Maillard Reaction**, was initially reported in 1912 by Lois Camille Maillard as a reaction between amino acids and reducing sugars which led to the formation of CO_2 and the generation of a yellow-brown colour [7]. Nowadays, it is known as a non-enzymatic irregular reaction between the carbonyl compounds of reducing sugars and amino compounds of proteins, lipids and nucleic acids (most often between the ε-amino group of lysine and the guanidine group of arginine). Glycation is a spontaneous process that has the ability to damage many proteins in physiological systems. This process is built of three main stages which include biochemical reactions such as catalysation, dehydration and oxidation. It forms irreversible stable compounds known as Advanced Glycation End-products (AGEs). AGEs adducts can be assembled on long-lived proteins and affect their normal functions, can degrade to free AGEs and produce proteinase-resistant aggregates by forming cross-links between proteins [8].

AGEs accumulate in various body tissues, including the dermal layer, amyloid plaques, coronary atheroma, renal cortex, basement membrane, cartilage, cardiac muscle, lungs and the liver. Therefore, increasing AGEs levels in plasma has been associated with a broad range of diseases including diabetes, Alzheimer's disease, rheumatoid arthritis, atherosclerosis, etc [9]. Some exogenous sources have been identified as sources of AGEs including diet and smoking. Fried, baked or processed food can form AGEs during food processing which are then ingested into the human body [8]. Food with high contents of fat and protein including cheese, meat and eggs contain high levels of AGEs. Tobacco is another major source of AGEs; reactive glycation products found in tobacco smoke and extracts can react with proteins to form AGEs [10].

The signalling pathway in which AGEs enter into the cells was proposed to involve several cell surface receptors including macrophage scavenger receptors (MSR) type II, oligosaccharyl transferase-48 (OST-48), 80K-H phosphoprotein, galectin-3 (AGE-R3) and the receptor for AGEs (RAGE) [11]. RAGE has been found to be involved directly in the signal transduction and therefore, has become the most potential receptor for future blocking applications [12].

Hyperglycaemia-Induced Oxidative Stress and the Polyol Pathway

AGEs formation is not the only complication related to the Maillard reaction outcomes. **Hyperglycaemia-induced oxidative stress** is strongly connected to this mechanism since oxygen-free radicals are being formed in every step during this process [13]. These oxygen-free radicals are considered to be responsible for different undesirable reactions that can harmfully affect cellular functions including oxidation of DNA, lipids and proteins, generation of irregular cellular responses and activation of regulatory molecules [14]. Several mechanisms have been found to play a role in generating hyperglycaemia-induced oxidative stress including an increase in the levels of reactive oxygen species (ROS), increase in the levels of AGEs leading to binding of AGEs and RAGE, auto oxidation of glucose and the polyol pathway [15].

The polyol pathway is a biochemical reaction in which glucose converts into fructose with the help of 2 enzymes: aldose reductase (AR) and sorbitol dehydrogenase (SDH) [15]. AR plays a major role in the polyol pathway when it catalyses the reduction of glucose into sorbitol which is the rate-limiting step [16]. In the second stage of the polyol pathway, SDH transforms sorbitol to fructose by converting NAD+ into NADH [14]. In normal conditions, when the level of the glucose in the blood is normal, most of the free glucose is transformed into glucose 6-phosphate by hexokinase. Alternatively, a small amount of free glucose enters the polyol pathway which is another route of glucose metabolism. In this route, the glucose transforms initially into sorbitol and eventually to fructose. In hyperglycaemia, the hexokinase is saturated with glucose and the amount of glucose that enters the polyol pathway is about one-third of the total glucose turnover. It increases the formation of the polyol pathway products and reduces the amounts of the available NADPH and oxidized nicotinamide adenine dinucleotide

(NAD$^+$), which are the cofactors used in this pathway [16]. NADPH is a major co-factor that together with the enzyme glutathione reductase converts glutathione disulphide-oxidized form (GSSG) into glutathione thiol-reduced form (GSH). Since GSH plays a significant role in one of the major defence mechanisms against oxidative processes in vivo, its reduction will eventually cause oxidative stress [17]. Figure 1 summarises the correlation between hyperglycaemia, the Maillard reaction, AGEs, the polyol pathway, glutathione reduction and oxidative stress.

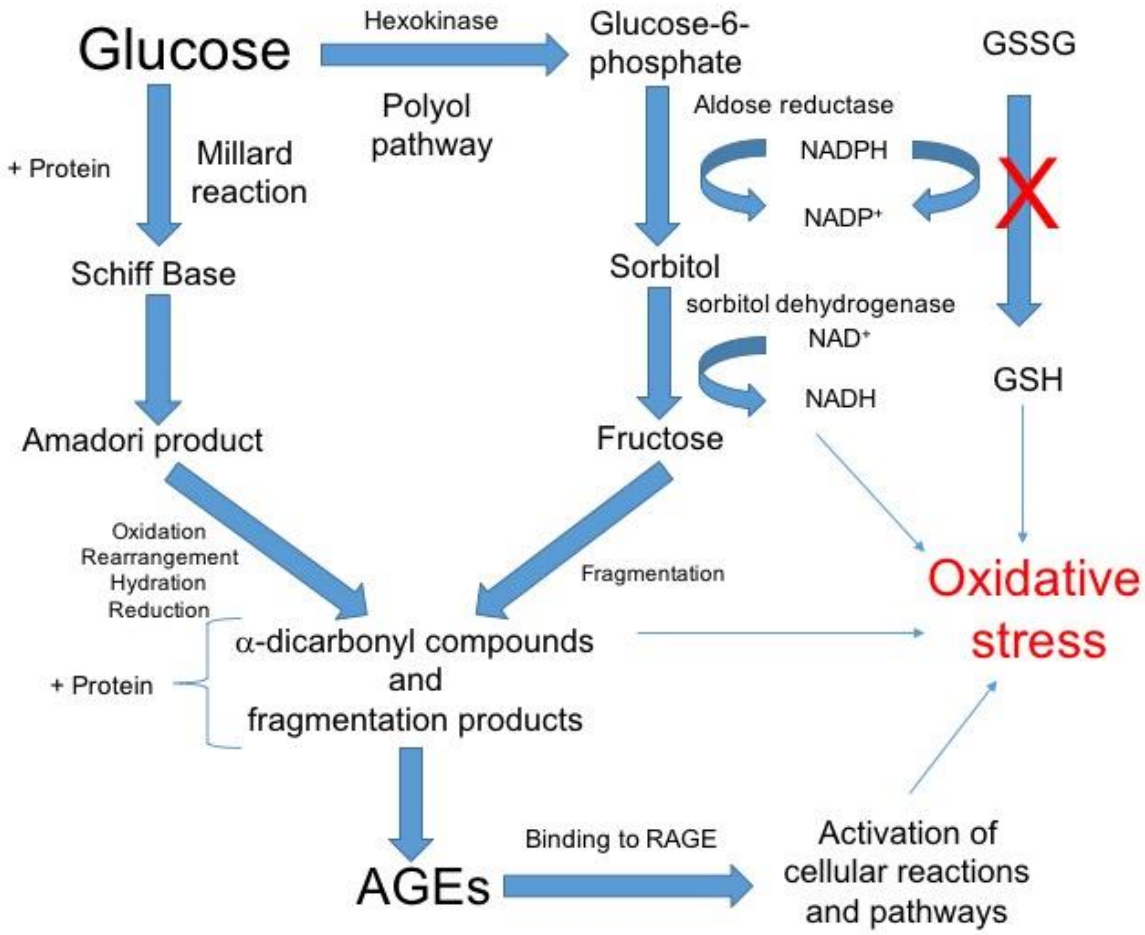

Figure 1. The relationship between glycation, the polyol pathway and hyperglycemia-induced oxidative stress mechanisms.

Maillard Reaction, Glycation and AGEs

Definition and General Mechanism

The Maillard reaction can be divided into 3 main stages: initiation, propagation and finally termination [7] (Figure 2 A-C). The initiation (Figure 2A) is a non-enzymatic reversible phase, which is also known as glycation. A Schiff base product is formed, followed by a spontaneous transformation to an Amadori product [3]. The Amadori product can either transform irreversibly into carboxymethylated lysine residues by going through an oxidative fragmentation or it can move straight to the propagation stage. Finally, in the termination stage, AGEs are formed irreversibly [7].

The initiation phase occurs over a period of several hours, even days, and thus it is reversible. Once it enters the propagation stage (Figure 2B), it turned down to be an irreversible process. The formation of the reactive irreversible compounds and the stable AGEs occurs over a period of week; thus, it affects long-living proteins [9]. It was found that the rate of glycation end product formation and reactivity are depended upon the amount of sugar available in an open-chain form. For example, both fructose and galactose are more available in open forms than glucose; therefore, the former two sugars have a greater glycation rates and reactivity than glucose [7].

During the propagation phase, which occurs over a longer period of time than the initial phase, it depends on the Amadori products accumulation rate and oxidative stress levels. The tissue may be subjected to Amadori products that are subjected to different chemical reactions such as hydrations, oxidations and reductions. This can lead to the formation of the reactive and stable intermediate α-dicarbonyl compounds and fragmentation products such as 3-deoxyglucosone (3-DG), glyoxal (GO) and methylglyoxal (MGO) [18]. These compounds can accumulate in tissues and create “carbonyl stress” [19]. 3-deoxyglucosone (3-DG) can be also formed during the polyol pathway [9].

Throughout the termination phase (Figure 2C), which is the third and final phase of the Maillard reaction, the Amadori products can further react with amine groups in proteins to form intra- and inter-molecular crosslinks and protein-AGEs adducts that build up inside and outside the cells and obstruct protein normal function [20].

The rate of this stage is not dependent on the sugar levels, but on the hyperglycaemia continuation and the rate in which proteins are being formed [13]. Furthermore, redox active transition metals, oxygen levels, and reactive oxygen species increase AGEs production and accumulation [1].

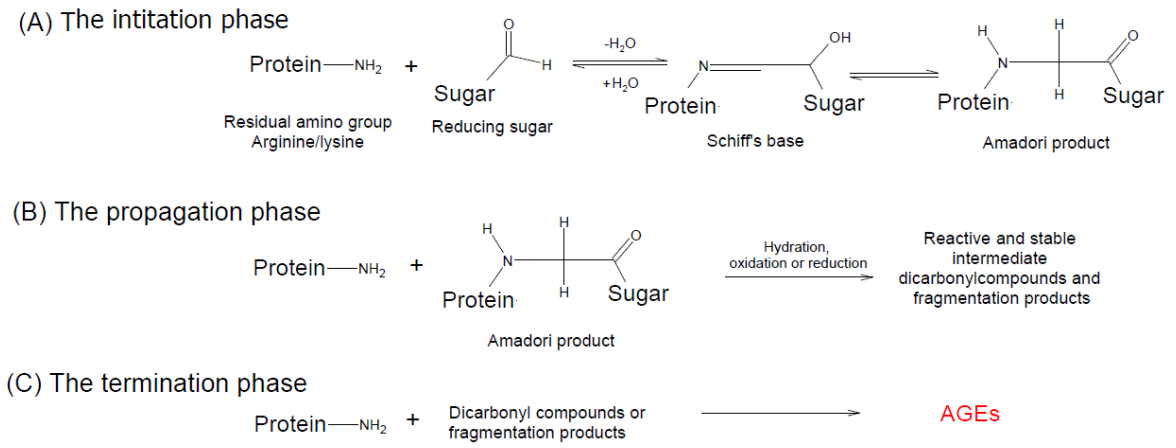

Figure 2. The Maillard reaction mechanism by phases; a) the initiation phase, b) the propagation phase, c) the termination phase, based on [7].

Recent studies suggest that genetic factors might also influence the levels of AGEs in the circulation system. Leaslie et al performed a classical study which included the participation of 39 monozygotic and 45 dizygotic normal twins aged 21 – 47 years. In this study, the serum CML levels were compared between both groups and were found to be higher in monozygotic twins than in dizygotic twins, indicating the high possibility of a genetic effect [21].

Types, Properties and Biological Effects of AGEs

AGEs are yellow and brown in colour and often fluorescent stable molecules [8] that stay permanently in the cells without being destroyed or secreted. They can neither be recognized or destroyed by proteasomes nor be released from the cells in which they accumulate [13].

More than 20 AGEs have been isolated including Nε-carboxymethyl lysine (CML), Nε-carboxyethyl lysine (CEL), pentosidine, glucosepane, hydroimidazolone, argpyrimidine, crossline, furoylfuranyl imidazole (FFI), 1-alkyl-2-formyl-3,4-

glycosyl-pyrrole [22], glyoxal-lysine dimer (GOLD), deoxyglucasone-lysine dimer (DOLD), methyl glyoxal-lysine dimer (MOLD) (Singh et al., 2001), N_{δ}-(5-hydro-4-imidazolon-2-yl)-ornithine (MG-H1) and N_{δ}-(5-hydro-5-(2,3,4-trihydroxybutyl)-4-imidazolon-2-yl)-ornithine (3DG-H) [23] (Figure 3). To date, CML and pentosidine are the most chemically and biologically investigated AGEs. For many years, glycated haemoglobin (HbA_{1c}) was considered to be a good AGE bio-marker. Concurrently, it is known as an Amadori product and is widely used as a marker for elevated glucose levels [9, 24, 25].

CML is a non-fluorescent AGE adduct that was discovered in 1985 by Ahmed et al during their studies on the chemical reactions between glucose and proteins. In their experiments, they discovered that CML was one of the oxidative degradation products of $N\alpha$-formyl-$N\varepsilon$-fructoselysine (fFL) and that it was also one of the products formed during glycation conditions in-vitro [26].

Presently, CML is being used as a bio-marker of glycoxidative, lipoxidative, oxidative and carbonyl stress and it is considered to be an important AGE and RAGE ligand. For this reason, it has the potential to serve as a bio-marker for several pathologies, including nephropathy, retinopathy, atherosclerosis and diabetes [27].

Pentosidine was discovered in 1989 by Sell and Monnier during their experiments that consisted of testing collagen samples from ageing and diabetic individuals and diabetic animals. They noticed the existence of an increased amount of Maillard-like fluorescence in these samples (excitation 370 nm, emission 440 nm), which left unchanged during hydrolysis in 6 N HCl for 24 h at 110°C. After performing structure elucidation, they discovered a pentose-mediated protein cross-link, which was named pentosidine [28]. It is now known that pentosidine is a lysine-arginine crosslink and its acidic stability and auto-fluorescence properties are being used to estimate its values in-vivo and to monitor AGEs accumulation in renal failure [27].

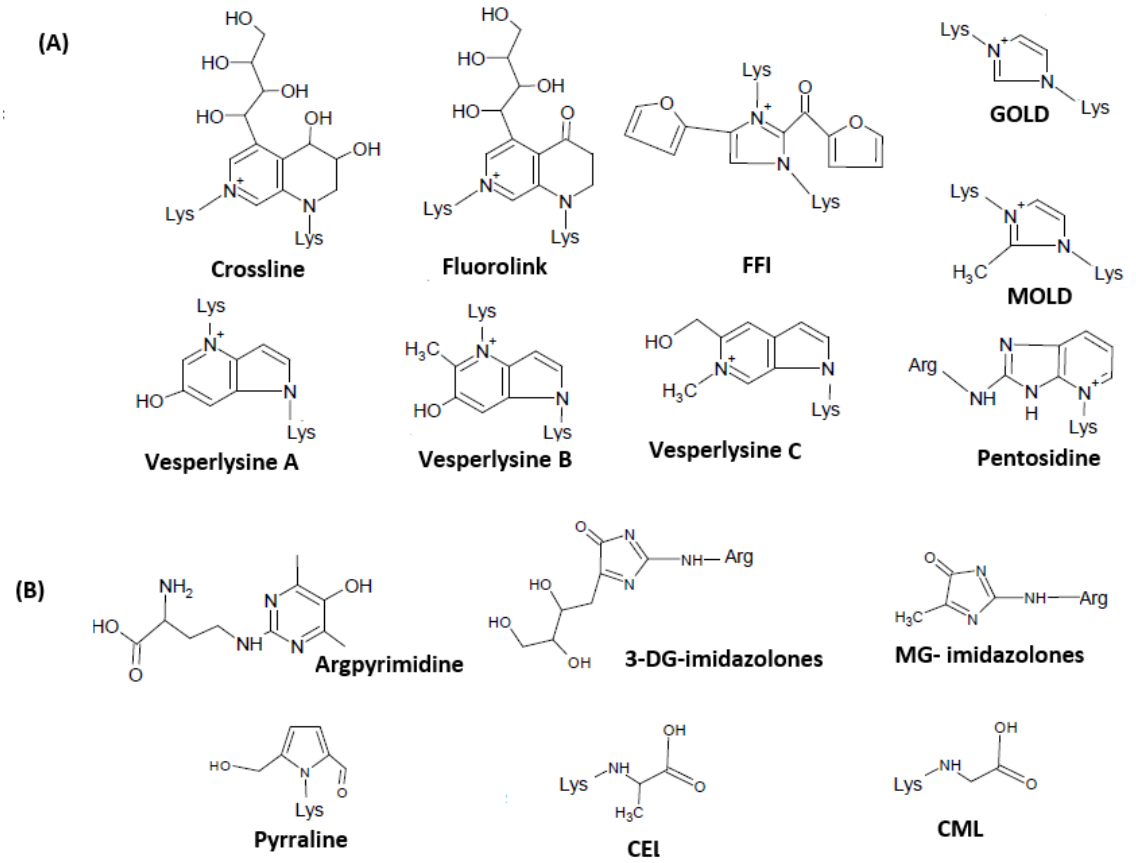

Figure 3. Chemical structures of some known AGEs. Fluorescence and crosslinking AGEs (A): crossline, fluorolink, FFI, GOLD, MOLD, vesperlysine A, B, and pentosidine; and non-fluorescence and non-crosslinking AGEs (B): argpyrimidine, CEL, CML, 3-DG-imidazolones, MG-imidazolones and pyrraline, adapted from [29].

AGEs have several characteristics in which they can cause damage. These characteristics will be discussed broadly in the pathology section. First of all, AGEs have the ability to covalently crosslink protein strands which can result in structure modification and therefore change their activity. Usually, it has an impact on long-lived proteins including collagen and lens proteins. These cross-links cause stiffness of the protein matrix, which reduces the elasticity of the vessels. It also creates a structure that cannot be removed by proteolic procedures, thus preventing the tissue from renewing itself [9]. Secondly, AGEs can bind to cell-surface AGE-binding receptors (RAGE) and thus trigger signalling events which can result in pro-oxidant or pro-inflammatory outcomes and modify gene expressions [3]. This binding action prompts activation of target genes and molecules including growth factors, adhesion molecules and pro-inflammatory cytokines.

Activation of NADPH was also reported as one of the outcomes of this binding, resulting in the elevation of ROS production. Finally, AGEs can bind to intracellular proteins and lipids. Thus, they influence cell functions. Glucose-6-phosphate, glyceraldehyde-3-phosphate, GO, MGO and 3-DG are examples of reactive intracellular sugars that have the ability to produce more intracellular AGEs than glucose. These AGEs bind to proteins in the electron transport chain system and effect the oxidative ATP synthesis process, can trigger intracellular mechanisms and they can alter function of intracellular enzymes such as GAPDH and glyoxalase-1 (GLO1) and can prompt post-translational modifications of regulatory and proteasome proteins [22]. GLO1 is an enzyme that detoxify dicarbonyl metabolites and the potent glycating agent methylglyoxal. GLO1 expression has been reported to improve metabolic and vascular health. GLO1 deficiency is linked to type 2-diabetes and obesity [30].

Dietary AGEs (d-AGEs)

Even though the main source of AGEs is endogenous, AGEs can also enter the body from diet and tobacco [3, 31]. Food with high contents of sugars, fat and protein such as sweetened foods, drinks, cheeses, meats, and eggs contains high levels of dietary AGEs [10]. Additionally, the Maillard reaction, which is being commonly utilized in the food industry and considered to enhance the taste, colour, aroma and quality of food, generates high levels of d-AGEs. Different food processing methods that use high temperatures over a short period of time (baking, frying, and sterilization) can trigger the Maillard reaction and therefore result in the formation of d-AGEs [32]. However, cooking in low temperatures over a longer period of time generates less d-AGEs and therefore, is considered to be healthier [32].

An increase in the general intake of soft drinks and processed foods has led to an elevation in fructose uptake in tissues. Since fructose is considered to be more reactive than glucose, it has a greater chance to trigger the Maillard reaction and the glycation [8]. Studies have shown that approximately 7% of the d-AGEs intake in a single meal may remain in the body for up to 72 hours and thus promote AGEs

formation. Tobacco is another source of exogenous AGEs. During the curing process of the leaves, reducing sugars are being added in order to produce a unique smell and taste to the final product. Afterwards, the mixture goes through heating and drying cycles that can help the formation of AGEs, which can enter into the body via smoking and inhalation [33].

Analysis of various food items for their d-AGEs levels has generated a large database that is based on CML levels of 549 different food products. Chromatographic and immunoassay techniques have been used to detect different d-AGEs in many food products. Among the d-AGEs found were: CML, pyrraline, ornithinomidazolinone, pentosidine, GOLD, MOLD and DOLD [34]. It was discovered that the meat group had the highest d-AGEs levels, followed by cheeses, high-fat spreads and eggs. Cereals, legumes, breads, vegetables, fruits, and dairy products actually had the lowest amounts of d-AGEs [35] (Table 1).

Moreover, food is a good source of antioxidants that was proven to decrease the toxic effects of AGEs. Since antioxidants have chelation properties, they have ability to react with transition metal ions and inhibit the formation of both free-radicals and AGEs [36]. Cinnamon, garlic, rosemary, green tea, tomato paste, Chinese herbs extracts are among the dietary antioxidants to be rich in polyphenolic compounds, flavonoids and vitamins [8, 37]. The anti-glycation properties of natural products will be discussed broadly later in the anti-glycation strategies section in this review.

Table 1. MG and CML levels in selected food, adopted from [35]

Food product	Total MG nmol/100g	Total CML kU/100g
White bread	3,630	8.3
American cheese	16,790	8,677
Grilled chicken	14,400	4,848
Raw chicken	4,170	769
Fried egg	13,670	2,749
Margarine	10,790	6,229
Broiled salmon in olive oil	14,950	4,334
Raw salmon	6,820	527
Whole milk	620	4.9
Regular Pepsi	325	2
Pan-fried steak in olive oil	18,150	10,058
French fries	13,130	843

Quantification of AGEs

AGEs are structurally heterogeneous molecules; this makes it very difficult to quantify them and particularly to attribute the existence of one type of AGE to a specific pathology. It is also very challenging to compare the results between laboratories as there are no identified standards, methods or kits to quantify AGEs. Additionally, different techniques are being applied for the quantification; consequently, the accuracy and the reproducibility of the measurements are low [9].

To date, there are two types of analytical methods for the quantification of AGEs: chromatographic techniques including gas chromatography (GC) paired with mass spectrometer (MS) detector, HPLC paired with diode array (DAD), fluorescence or MS detectors and immunoassay techniques including ELISA [34]. Another analytical method, used mostly in clinical trials to quantify AGEs, is ‘total AGE fluorescence’. Because AGEs are yellow and brown in colour and often have a characteristic fluorescence pattern of excitation at 350-390 nm and emission at 440-

470 nm. This analytical approach can be used to quantify their levels in biological fluid such as urine, serum and different tissues [38].
In addition to some advantages, each technique also has major limitations (Table 2). The limitations of total AGE fluorescence analysis are:
(1) other fluorescent molecules (such as NADPH, glucose, or lipid-derived oxidation products and non-protein tissue components) can interfere with the analysis since they share the same fluorescence spectra as the fluorescent AGEs.
(2) Even though many AGEs have the desirable characteristic fluorescence pattern, there are many others that do not exhibit fluorescent characteristics, such as CML and pyrraline. Thus, they cannot be detected by this kind of analysis.
(3) As mentioned, and since it is considered to be easy to perform this analysis, most clinical trials use this approach to collect the clinical data. It requires the invasive collection of urine samples, serum and different tissues [38].

In 2005, Meerwaldt et al. published results of a simple, non-invasive experiment, which was performed with a new autofluorescence reader (AFR) instrument. Using this reader, they were able to analyse skin surface directly (normal, nonpigmented skin site, luck of scares, visible vessels or any other skin problems). The clinical evaluation was performed on both diabetic patients and control group and showed correlation between increase in skin auto-fluorescence and AGEs accumulation in the patients group. An age-related AGEs accumulation was also found to be correlated with the increase in the skin auto-fluorescence, both in the patients and the control group [39].

Immunoassay and immunohistochemistry techniques, such as ELISA are considered to be inexpensive, fast and more suitable for clinical use. AGEs that can be detected by this method are CML, CEL, Pentosidine and MG-derivatives [35, 40]. These techniques use antibodies against AGE to measure their level in serum samples. Common antibodies which are being used in Immunoassays are antibodies against keyhole limpet haemocyanine-bound AGE (AGE-KLH), bovine serum albumin (BSA-AGE), RNase-AGE [38], 6D12 [41] and ovalbumin AGE (AGE-OVA) [42].

Limitations of immunoassays are: (1) each antibody and AGE need to be identified and their structures need to be well elucidated; (2) it is necessary to validate method, since the chemical environment can affect the AGE-antibody binding; (3) it is difficult to compare results among various assays and laboratories since the results are expressed in the different units [34]; (4) some antibodies are not specific to one AGE. For example, 6D12 has affinity for both CML and CEL [41]; and last but not least, high background interferences and potential unspecific bindings due to the existence of other proteins and molecules in the sample could happen [23].

Chromatographic techniques are commonly used to quantify pyrraline, CML and pentosidine amounts in several food products. Despite of the fact that these techniques can detect AGEs specifically, they also have some limitations: (1) they are considered to be expensive and time consuming [38], (2) in order to be detected by UV or fluorescence detectors, the AGEs must exhibit matching properties, (3) detection by GC-MS, requires the existence of volatile derivatives of the AGEs, hence, an additional treatment of the samples needs to be carried out before performing the analysis. LC-MS/MS is considered to be the best chromatographic technique for AGEs analysis since it has better sensitivity and it does not require any additional steps prior to analysis [34]. Scheijen et al were able to validate a sensitive and precise UPLC-MS/MS for analysis of CML, CEL, MG-H1 in several dietary items [43].

Table 2. Summary of the analytical methods used for the determination of AGEs, advantages and limitations.

Analytical method	AGE detected	Advantages	Limitations	References
Total AGE fluorescence	- Crosslinks AGEs - Pentosidine	- Easy - Fast to perform	- Interference of other fluorescent molecules - Non-specific - Requires samples of tissues, urine and serum, invasive - Many AGEs do not exhibit the fluorescence pattern	- [34, 38]
Chromatographic techniques (e.g., HPLC, GC)	- Pyrraline - CML - Mostly CML	- Better sensitivity - More specific - Does not require additional steps	- Expensive - Time consuming - AGEs must exhibit matching properties to be detected. - Volatile derivatives of AGEs are required, Additional treatment. - GC needs no derivatisation - Multiple reaction monitoring by using MS/MS detector.	- [43, 44]
Immunoassays	- CML - CEL - Pentosidine - MG-derivatives	- Easy - Inexpensive - Suitable for clinical use.	- Non-specific - Antibodies and AGE need to be well identified and characterised	- [41, 42, 45]

			- Requires validation of validate each tested matrix. - Difficult to compare results between different assays and laboratories. - Some antibodies are non-specific	

Cell-Surface AGE-Binding Receptors and RAGE

Some cell-surface AGE-binding receptors have been discovered such as macrophage scavenger receptors (MSR) type II, oligosaccharyl transferase-48 (OST-48), 80K-H phosphoprotein, galectin-3 (AGE-R3) and the receptor for AGEs (RAGE) [11]. Most of the interactions between AGEs and their binding receptors were found to be involved in different tissue functions including the management of endocytosis, AGEs degradation and receptor-triggered gene expression modulation. However, RAGE was found to be involved directly in the signal transduction and therefore has become the most investigated potential receptor for future blocking applications [12].

RAGE was first discovered by Neeper and his colleagues in 1992 during their attempts to characterise surface receptors that were responsible for the interactions of AGEs with the cells [46]. RAGE is a 35,000 Da transmembrane receptor that belongs to the immunoglobulin superfamily. Its structure consists of five domains: a 332–amino acid 3 extracellular immunoglobulin-like positively charged domains (C, C’ and V), one transmembrane domain and one 43–amino acid cytoplasmic negatively charged tail. The extracellular V domain was found to have an important role in the binding process of the ligand and the cytoplasmic tail was found to play a crucial role in the intracellular activation [19, 22].

When conditions are normal, RAGE expression is low and regulated. In pathogenic conditions, when its ligands accumulate, it is over-expressed and over-activated. RAGE does not bind to specific amino acid sequences, but to a variety of tertiary structures of proteins. Therefore, it has the capability to recognize several molecules including amyloid components, S100/calgranulins, amphoterin (HMGB1) and AGEs, to include CML and hydroimidazolones. Various cell types express RAGE including endothelial cells (ECs), smooth muscle cells (SMCs), macrophages, monocytes, neurons, astrocytes, hepatocytes and podocytes [22, 47].

The binding of these molecules to RAGE may prompt signalling reactions and activation of several pathways such as MAP kinases, cdc42/rac, JAK/STAT, p21ras and p38. The binding also regulates the activation of NF-κB and influences the transcription of certain target genes, growth factors, adhesion molecules, and cytokines (IL-1, IL-6, TNF-α). It also induces the formation of ROS via NADPH oxidase activation [22]. Over-expression of RAGE is associated with a number of chronic pathologies, such as lung type-I pneumocytes, vascular disease, cancer, Alzheimer's disease and diabetes [36, 48-50]. Figure 4 summarises the effect of glycation, AGEs, RAGE activation and oxidative stress on cells.

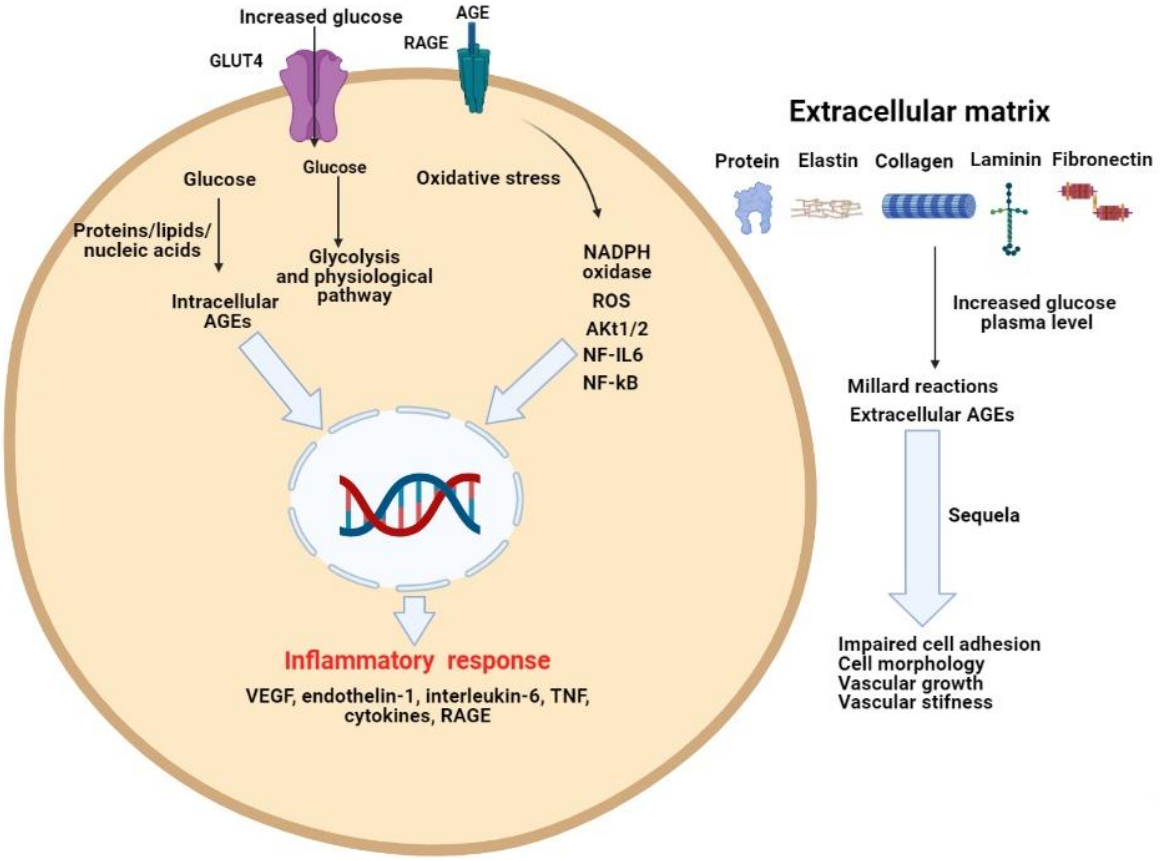

Figure 4. The effect of glycation, AGEs, RAGE activation and oxidative stress on the cells and extracellular matrix system

Oxidative stress

Several hypotheses have been trying to explain the correlation between oxidative stress and glycation. Oxidative stress takes place when the imbalance between the rate of the production of oxidants and the formation of antioxidants in vivo exists. This may be due to either the uncontrolled production of free-radicals, insufficient antioxidant defences or both [51]. Free-radicals are a reactive by-product of routine biochemical processes. Their reactivity derives from the presence of unpaired electrons, which make them unstable and lead them to react with other molecules in order to achieve a stable state. The reaction between free-radicals and non-radicals (lipids, proteins, nucleic acids and carbohydrates) prompts free-radical chain reactions that result in the formation of new reactive species including ROS, RCS and RNS [52]. ROS are found in every biological system. They vary in their site of origin, their physiological activity and their reactivity. ROS are produced from oxygen during cellular metabolism, when the mitochondria and P450 enzymes are considered to be the main production sites of the ROS. Three main ROS are

considered to be major players in the physiological systems: hydrogen peroxide (H_2O_2), reactive oxygen (O_2^-) and hydroxyl ($^{\bullet}OH$) species. Other oxygen-derived oxidants are peroxyl radicals ($ROO^{\bullet}$) and peroxynitrite ($ONOO^-$) [51].

There are also exogenous sources of oxidants; superoxide and nitric oxide are found in cigarette smoke. Smoking and the inhalation of smoke may result in the accumulation of neutrophils and macrophages, and hence expend the oxidant damage. Exposure to the ozone can trigger the peroxidation of lipids, release inflammatory mediators, and decrease pulmonary functions. Hyperoxia (high oxygen levels in the lungs or tissues) accelerates the formation of ROS and RNS. Ionizing radiation in an oxygen environment produces hydrogen peroxide and organic hydroperoxides, which further react with active metal ions through Fenton's reaction and produce more ROS [53].

Reactive species are considered to play a major role in routine cellular signalling pathways. ROS and RNS act as second messengers that are responsible for important cellular events. In pathological conditions, these routine physiological functions may be affected and result in major outcomes, including modification of biomolecules, interruption to intracellular signalling pathways, gene expressions and even cells apoptosis that can lead to pathological conditions, such as cancer, neurological disorders, hypertension, diabetes and more [13].

1.1 Glycation-Induced Oxidative Stress

Several hypotheses have tried to explain the correlation between glycation and oxidative stress [13]. These hypotheses include: (1) every step of the Maillard reaction generates oxygen-free radicals; (2) glycated proteins are likely to lose their native structures and original functions; the outcomes could be an increase in ROS formation and oxidative stress (3) the binding of AGEs to RAGE leads to cellular reactions and activation of p38 MAP Kinase, NF-κB, P21 Ras and Jak/STAT pathways. The activation of these pathways may prompt the production of TNF-α which results in ROS formation. Finally, the fourth hypothesis suggests that oxidative stress may damage the mitochondria and as a result, glucose, amino acids, and lipids will not be used. Instead, they will assemble outside the

mitochondria and will be subjected to further glycation processes. Fujii et al. have found that mutated Cu-Zn superoxide dismutase (Cu-Zn-SOD) incubated with glucose, produced more hydroxyl radicals than the wild type enzyme. This suggests that modulation of Cu-Zn-SOD by AGEs may result in ROS production [54].

Trinei et al., reported that the activation of the p53-p66Shc pathway resulted in increased intracellular levels of ROS and cells apoptosis [55]. Alikhani et al., investigated the mechanism of an apoptosis induced by CML-collagen in fibroblasts. They found that this AGE-adduct activated FOXO1 which is a pro-apoptotic transcription factor ($P < 0.05$). CML-collagen also upregulated the p38 and JNK 1/2 activities ($P < 0.05$). Their individual inhibition lowered the apoptosis rate by 48% and 57%, respectively, and both of them (in combination) by 89%. Also, inhibition of ROS and NO formations reduced the stimulation of these pathways. These findings support the hypothesis that correlates between AGEs and the formation of oxidative stress [56].

Hyperglycaemia-Induced Oxidative Stress and the Polyol Pathway

Under normoglycaemia, when the glucose levels are normal (3.8-6.1 mmol/L), blood sugar is phosphorylated by hexokinase to glucose-6-phosphate and its metabolism takes place mostly in the glycolytic pathway. Only about 3% of the un-phosphorylated glucose moves into the polyol pathway, which is the second pathway in which glucose can be metabolised [57]. Two enzymes play a role in the glucose metabolism through the polyol pathway: AR and SDH. AR is a small 36 kDa enzyme and consists of 316 amino acids. It is a nicotinamide adenine dinucleotide phosphate (NADPH) dependent oxidoreductase protein which belongs to the aldo-keto reductase superfamily. During the first and rate-limiting step of the polyol pathway, AR transforms glucose to sorbitol by converting the co-factor NADPH into $NADP^+$ [15]. AR is located in the cytoplasm of most cells and is found in various human and animal tissues, including the eyes, liver, placenta, ovaries, kidneys, erythrocytes, cardiac muscles, skeletal muscles and the brain [57]. SDH is a zinc-dependent tetramer enzyme that consists of one zinc ion per subunit [58]. SDH belongs to the dehydrogenase / reductase protein family; it is found in most mammalian tissues. During the second step of the polyol pathway, SDH transforms

sorbitol to fructose by converting the co-factor nicotinamide adenine dinucleotide (NAD^+) into NADH [14].

Under hyperglycaemia conditions (above 7 mmol/L), hexokinase is saturated with glucose and as a result 30% of the un-phosphorylated glucose enters into the polyol pathway [57]; this increases the accumulation of the polyol pathway products and reduces the amounts of the available co-factors NADPH and NAD^+ in the tissues. Sorbitol is a molecule that does not have the ability to diffuse across cells and may therefore be assembled inside the tissues and lead to osmotic stress [16].

The acceleration of the polyol pathway and the utilization of the co-factors NADPH and NAD+ create metabolic imbalances and alter the redox state. This acceleration also directly affects other interrelated metabolic processes, some of which are responsible for the detoxification of oxidants [16]. NADPH is a major co-factor that together with the enzyme glutathione reductase play a role in the one of the major defence mechanisms against oxidative processes in vivo.

AGEs-Related Pathology

AGEs accumulation has been proven to be associated with ageing, since most of their accumulation is taking place in long-lived proteins, such as collagen and lens proteins (crystallins). AGEs cross-linking causes stiffness of tissues and blood vessels by forming stable proteins [59]. In regards to ageing, this process occurs over a period of time in healthy ageing people. In diabetic individuals, the glycation processes occur more rapidly, and therefore, the accumulation rate of the AGEs increases [60]. Additionally, glycation can influence almost every tissue in the human body including kidneys, eyes, liver, arteries, muscle, placenta, skeletal, brain and reproductive tissues. Glycation processes in these tissues have been linked to various metabolic disorders and age-related pathologies, such as diabetes, cataract, Alzheimer's disease (AD) and liver diseases, inflammations, cardiovascular diseases, renal failure and rheumatoid arthritis [9, 61]. More recently, accumulation of AGEs could be a potential risk factor for increased COVID-19-linked fatalities in elderly patients [49]. RAGE expressed by

type 2 epithelial cells in the alveolar sac has been reported to be associated with lung inflammation caused by COVID-19 [50, 62].

There is a growing body of knowledge that highlights the negative effects of glycation and chronic diseases-linked to accumulation of plasma AGEs. Unfortunately, it is impossible to put everything in writing. The emphasis of this work was primarily on the negative effects of glycation as it relates to ageing, diabetes, cataract, and AD and the treatments related to these illnesses [59]. Figure 5 summarises the pathological responses of AGEs on some human organs discussed in this review.

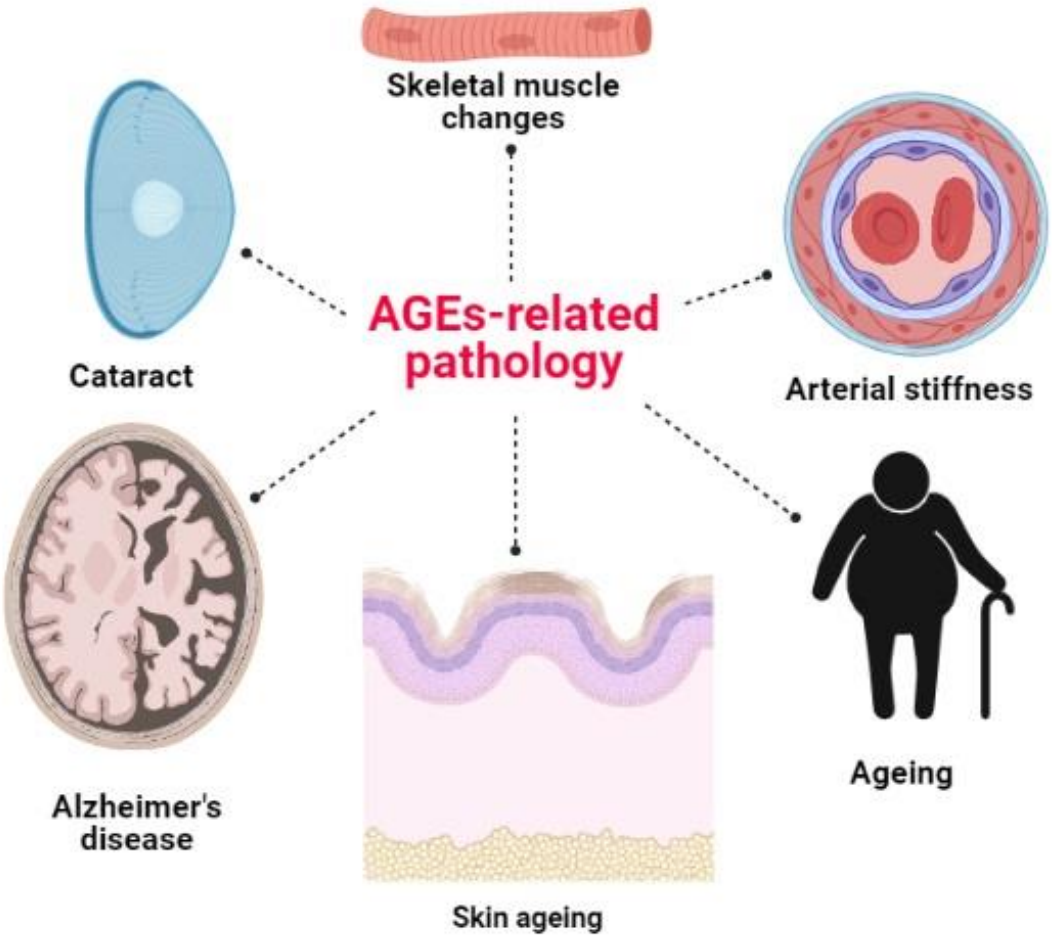

Figure 5. Pathologies related to Advanced Glycation End Products (AGEs)

Glycation and Ageing

In regards to glycation, ageing has been associated with the existence of high levels of glycation intermediates and AGEs in the body tissues; hence, they have been

used as bio-markers of ageing in-vivo. Ageing is a complicated process controlled by genetic, endogenous and exogenous factors. During this process, a series of biochemical changes accumulate with time and lead to cellular, tissue and organ damage that may result in the occurrences of some chronic age-related illnesses and eventually death [1].

Several mechanisms have been suggested as being responsible for the contribution of glycation to the ageing process; binding of AGEs to RAGE activates intracellular signaling pathways that may result in oxidative stress and inflammatory processes. Additionally, AGEs binding to proteins may change their structures and functions. It was also suggested that even though structural proteins remain for a longer time in the body and are more subjected to AGEs modifications, soluble proteins may also be affected by these modifications and affect related signaling pathways. AGEs accumulation with time is also dependent on the balance between the endogenous formation, the exogenous intake of AGEs, the renal excretion, and the enzymatic clearance rates. It was suggested that ageing and some other pathological disorders are characterized by an imbalance between these processes [63].

Arterial Stiffening

Glycation and accumulation of AGEs appear to be major players in age-related arterial stiffening. The arterial wall consists of two main proteins: collagen and elastin, which are considered to be potential targets for glycation mechanisms or AGEs binding. Formation of cross-linked collagen-AGE results in the hardening of the vessel wall, the loss of elasticity, and stiffening [64]. In comparison to collagen, elastin has a low content of lysine residues. Therefore, it is not being subjected directly to the glycation mechanism, but to other modifications such as binding to CML and being subjected to the Fenton's reaction. AGEs precursors also have the ability to induce arterial stiffening. MGO and GO may form some minor collagen-AGE cross links, such as MOLD and GOLD. GO is also a precursor for the formation of CML, which, as aforementioned, can alter elastin [65].

The formation of AGEs increased in diabetic patients and it has been associated with diabetes-induced vascular stiffness. Further, it has been reported that

concentrations of AGEs in the plasma of hypertensive patients (7.8 ± 1 μg/ml) are statistically higher than normotensive subjects (3 ± 1 μg/ml). There is a significant correlation between plasma AGEs levels and aortic stiffness [66]. Interestingly, treatment with AGE breakers such as thiazolium derivatives (e.g. alagebrium) could reverse stiffness of large artery [67].

Alteration in Mass and Function of the Skeletal Muscles

It has been observed that AGEs are involved in age-related changes in mass and function of the skeletal muscles. Different studies have suggested that myosin structure and the interaction between actin and myosin may be altered by AGEs-induced post-translational modifications [68]. For example, a study consisting of 20 young (22-28 years old) and 22 old (72-84 years old) inactive subjects was performed in order to study the main reasons for the age-related changes in the skeletal muscle mass and function. It was found that the concentrations of endomysial collagen were 9.6 and 10.2 μg/mg muscle wet weight in young and old, respectively; enzymatically regulated crossed-linked collagen was found to be 395 for old versus 351 mmol HP/mol collagen in young subjects; myosin was 46 and 54 μg/mg muscle wet wt in young and old, respectively. Actin (young: 21, old: 17 μg/mg muscle wet wt) did not change with ageing ($P > 0.05$), while the concentration of the pentosidine increased by 200% with ageing (young: 5.2, old: 15.9 mmol pentosidine/mol collagen, $P < 0.05$). These findings show that the concentrations of myosin, actin, collagen and enzymatically regulated cross-linked collagen are being regulated during ageing and that the accumulation of AGEs with time has a role in altering the skeletal muscle mass and function [69].

Skin Ageing

The glycation process begins in an early stage of life, but it is well established before reaching the age of 30. The accumulation rate of glycated collagen is estimated to be about 3.7% per year, when life style, exposure to UV light and diet affect this percentage [70].

Glycation has a major impact on skin ageing, yet the specific biochemical mechanisms involved in skin ageing have not been identified. The skin is the largest organ in the human body and it serves as the first line of defense, creating a barrier between the body and the environment. As a result, it is prone to both internal ageing processes and external influences. Aged skin influenced by internal processes tends to be less elastic, wrinkled, thin, dry and yellow in colour. These characteristics tend to be accelerated by external influences (a process named photo-ageing) including exposure to ultraviolet irradiation (UV-A and UV-B), infrared light from the sun, tobacco, chemicals, and pollution [1].

Photo-ageing is characterized by the appearance of wrinkles, uneven skin tone (lentigo seniles), small dark spots on the back of the hands and even tumors. Few glycation-related mechanisms have been suggested as responsible for accelerating skin ageing processes; pentosidine can cause inflammatory skin changes by the activation of NF-κB and the induction of cytokines formation [71]. Glycation of keratin, which is a structural protein found in the horny layer of the skin, may prompt changes in the optical properties of the skin and alter its transparency [72]. Keratinocytes differentiation (the process in which a cell is being changed into a different type) from the basal layer to the horny layer is monitored by the protein K10. Glycation processes can affect this protein and therefore influence the differentiation process. Yellowing of the skin might be due to AGE accumulation in the dermis. In addition to the reduction of elasticity, glycation of collagen may result in the formation of wrinkles; however, this has not been confirmed yet [72]. As for external influences, it has been suggested that prolonged exposure to sunlight may result in the expedited formation of CML, which can result in the accumulation of abnormal elastin in the dermis (actinic elastosis). Using 6D12 antibodies, Mizutari et al. have shown that skin samples of sun-exposed areas contained higher levels of CML than skin samples that were not exposed to sun [73]. It was also suggested that UV-A can accelerate the negative effects of AGE on the skin by inducing the formation of free radicals [74].

Glycation and Diabetes

Several hyperglycaemia-related mechanisms have been suggested as the main causes for diabetic complications when glycation, oxidative stress and enhanced polyol pathway are considered to be major contributors.

Diabetes is a common condition, associated not only with ageing, but also with genetics, diet and obesity [75]. Diabetes is characterized by the elevation of plasma glucose due to insulin deficiency or resistance resulting in both direct and indirect effects on cellular and tissue functions. Consequently, it may result in serious outcomes including chronic complications such as cataract, blindness, neuropathies, macrovascular and microvascular diseases and even mortality [76]. Additionally, studies have shown that cells in which the glucose uptake is not being controlled by insulin (heart, lenses, kidneys and the nervous system) are prone to be highly affected by hyperglycaemia [77, 78].

The accelerated glycation processes and the accumulation of AGEs in diabetic patients may affect several cell functions including: ligand bindings, modifications of proteins and enzymes, change in the immunogenicity, and the oxidation of lipids and nucleic acids. Over-expression of RAGE is also associated with diabetes; binding of AGEs to RAGE may activate the NF-κB. The p21-ras, and the MAP kinase signalling pathways influence transcriptions of genes and growth factors. This may induce production of inflammatory cytokines [77, 79]. For example, the Vascular endothelial growth factor (VEGF) is essential for the proper development of the retina and the iris. Studies on rat and rabbit retinas demonstrated that AGEs accumulation in the retina resulted in over-expression of VEGF, while treatment with Anti-VEGF and antioxidants prevented VEGF production and endothelial cell proliferation [80].

It was also suggested that the modification of extracellular matrix (ECM) proteins such as collagen, laminin, and fibronectin by AGEs may be an important factor in the formation of diabetic complications including fibrosis and retinopathy [81, 82]. Cardiovascular diseases are other complications that may be induced in diabetic patients. The formation of cross-links between AGEs with collagen may result in arterial stiffening, changes in ventricular compliance and cardiac dysfunction [83].

Different studies have examined the correlation between high levels of AGEs and resistance to insulin. The exact mechanisms are not yet elucidated, different studies have found few possible mechanisms in which AGEs can cause insulin resistance. It was suggested that binding of AGEs directly to insulin results in its alteration, which eventually leads to the biochemical dysfunctions observed in diabetic patients, such as poor glucose uptake, reduced clearance of insulin, or enhanced secretion of insulin. Additionally, binding of AGEs to RAGE may affect insulin resistance by changing signalling pathways, such as tumour necrosis factor (TNFα) and protein kinase C (PKCα) and hence prompt inflammation [84].

Glycation and Cataract

Glycation can also result in accumulation of AGEs and the activation of RAGE in the cells and the tissues of the vision systems. Therefore, it has a major contribution to many eye disorders, such as cataract, age-related macular degeneration (AMD), and diabetic retinopathy (DR) [22].

Cataract, which is the cloudiness of the lens, results in blurry vision in one or both eyes. During cataract formation, the clear lens changes its colour to a yellow-brown colour, which may also result in brown shade vision. With time, as the cloudiness expends, the vision gets worse, as bright lights can become more difficult to look at, the patients may experience double vision and may have poor night vision. Known risk factors for cataractogenesis include diabetes, ageing, smoking, alcohol consumption and continuous exposure to UV (the National Institutes of Health, 2016).

Age-Related Cataract

The correlation between glycation and age-related cataract is not completely understood. One interesting study, conducted by Duhaiman, investigated the glycation process in both diabetic and non-diabetic cataract patients. High levels of glycation products were found in both non-diabetic and diabetic cataract patients, with higher levels in the diabetic patients group [85]. These findings imply that glycation might have a role in the general formation of cataract and that hypoglycaemia conditions induce its formation.

With time, the lens goes through morphological and biochemical modifications which are associated with the formation of age-related cataracts; growth in the weight and the thickness of the lens progressively disrupt the supply of nutrients and antioxidants from the lens epithelium and cortex. Lens crystallins are long-lived proteins which have almost no turnover, hence, they are more subjected to post-translational modifications, such as glycation, phosphorylation, oxidation and cross-linking. Additionally, enzymatic modifications (low GSH, high levels of GSSG, and low levels of NADPH), colourization of the lens, and oxidation also contribute to the cataract formation [86]. Glycation and the accumulation of AGE adducts in ocular tissues during ageing may prompt protein cross-linking, alter proteins' structure, inactivate enzymes, activate intracellular signalling pathway via binding to RAGE, and weaken receptors recognition [22]. AGES has been recently reported to accumulate in human lens capsules. This results in potentiating transforming growth factor-β2 which suggests that play a role in increasing the incidence of posterior capsular opacification after cataract surgeries [44].

Diabetic-Related Cataract

Cataract is considered to be one of the earliest outcomes of diabetes mellitus. Since glucose diffusion into the lens is not insulin-dependent, the lens is one of the most likely organs to be influenced by hyperglycemia. It is presumably that diabetic patients have 2-5 times higher risk in developing cataract than non-diabetic patients. Diabetic-related cataract occurs in an earlier age than an age-related cataract [86, 87]. Different studies examined the correlation between diabetes and the development of cataract; Janghorbani and Amini examined the occurrences of cataract development in early type II diabetic patients. The results have shown that after 3.6 years of follow-up, patients that were free of cataract in the early stages, developed the disease in a rate of 33.1 per 1000 individuals per year [88].

Li et al. have presented results of meta-analysis study that was performed on diabetics and non-diabetics subjects. In their study, they have shown that the risk of cataract in type II diabetic patients was two times higher than in the non-diabetic control group [89]. The accumulation of glycation products, the accelerated polyol

pathway, the activation of protein kinase C and oxidative stress have all been suggested as contributors to diabetic-related cataract, but the exact mechanism is not fully understood yet [90].

Glycation and Alzheimer's Disease

The correlation between AGEs and Alzheimer's disease (AD) has been widely investigated. AD is the most common type of dementia that impacts more than one out of every twenty adults aged over 65 [91]. Dementia influences the patient's daily performances and basic abilities, since it affects the memory and the overall thinking abilities. Neurons, which are nerve cells in the brain, can be damaged and eventually destroyed, leading to unclear memory, thinking, and behavior. In AD, the first neurons to be affected are the ones responsible for receiving new information and creating new memories. Therefore, one of the first symptoms of AD is decrease in the ability to recall and process new details and information. With time, when the disease spreads to different areas of the brain, other complications start to arise, and common behaviors such as movement and feeding can be forgotten. Soon, the patients become bedridden and require care until they pass away due to these complications, not from the disease itself (Alzheimer's Association, 2014). Several risk factors have been associated with AD including genetics, age, head traumas, hypertension, diabetes and high cholesterol [92].

AD is considered to be an incurable disease, and no effective treatments or preventive measures have been found for this condition yet. Several molecular mechanisms have been found to be involved in the disease's progression, and intensive efforts to develop pharmaceutical treatments have been going on for years [93]. The correlation between glycation and AD have been studied broadly; analysis of AD brains for the presence of AGEs showed that AGEs were found to be accumulated in senile plaques, neurofibrillary tangles (NFTs), and cerebral amyloid angiopathy. Glycation and hyper-phosphorylation of MAP-tau and Aβ resulted in the formation of paired helical filaments in vitro. It was suggested that the accumulation

of free radicals and reactive carbonyl compounds and the formation of proteins cross-links may have a role in AD complications [94, 95].

Anti-Glycation Strategies

As the damaging effects of glycation have become better understood, there has been a growing concern to counter the negative effects of glycation, either through using preventative measures or through finding new therapeutic opportunities. Life style changes, such as proper diet and exercise, abstaining from alcohol and tobacco, using healthier cooking methods and limit the direct exposure to a sunlight, can help in controlling the AGEs levels in the tissues [1, 8].

Therapeutic strategies involve either natural products or synthetic agents and their influence can vary according to their targeted structure, the mechanism of action, and the Maillard reaction step in which they can have their effect. The design of anti-glycation drugs is considered to be challenging but promising; as discussed earlier, AGEs are heterogeneous molecules and their production involves the formation of several intermediates and is carried out by several stages in which they are being formed. Since the Maillard reaction can be broken down into three main stages: initiation, propagation, and termination, each one of these stages may be a potential treatment target. Consequently, anti-glycation agents must react stoichiometrically with AGES that have various chemical structures. Potential antiglycation agents may produce their effects, either by preventing the formation of reactive carbonyl intermediates at an early stage of the Maillard reaction and/ or by inhibiting the toxic effects of AGEs after their formation (Figure 6).

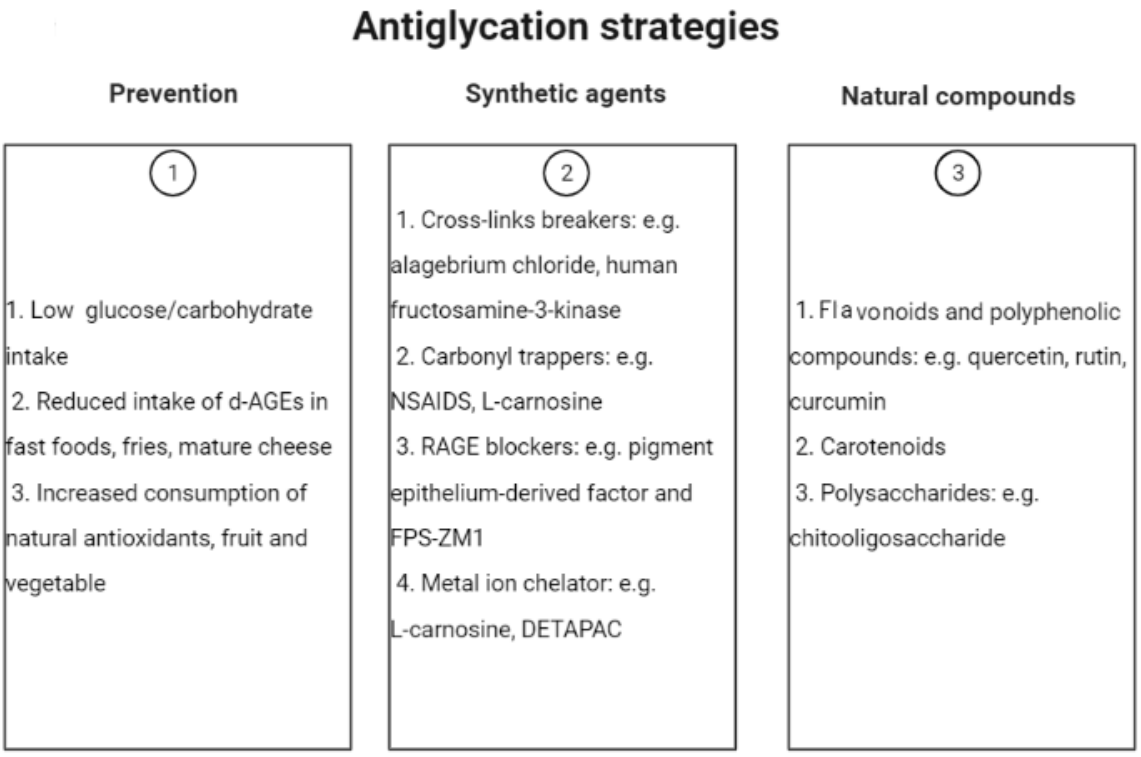

Figure 6. Summary of the anti-glycation strategies of formation prevention (bracket 1) and inhibition of toxic effects (brackets 2 and 3)

Prevention of glycation

Since glycation is mainly dependent on the sugar concentration in the circulation and the tissues, the best strategy is to control the sugar levels in the blood, and the sooner, the better. Additionally, and as discussed earlier, diet is a significant source of dietary AGEs (d-AGEs) that have the ability to increase the accumulation of AGEs and to affect intracellular and extracellular components. Cooking methods have a major impact on the AGEs levels in the food, and therefore, healthier cooking approaches should be used; cooking methods that use high temperatures, such as roasting, grilling, frying, and baking tend to form more AGEs than cooking methods that use low heat and high humidity, such as stewing, boiling, and poaching. Prepackaged foods, processed foods, fast foods and soft drinks also contain high levels of AGEs and therefore their intake should also be controlled [33].

One of the main concerns and issues regarding the processed food and the fast food is that the Maillard reaction is known to have a positive effect on many important characteristics of food proteins, such as solubility, water retention, gelling capacity, smell and taste, without adding any chemicals or using extreme

conditions. For this reason, it is being widely used in the food industry and widely consumed as part of the western diet.

Synthetic Anti-Glycation Agents

In general, synthetic anti-glycation agents can be divided into different categories, according to their characteristics and mechanism of action. The main categories include cross-link breakers, redox metal ions chelators, free radical scavengers, carbonyl trappers, RAGE blockers, antioxidants, enzymes and aldose reductase inhibitors [1, 8].

Cross-links Breakers

AGEs cross-link breakers have been investigated as potential therapeutic anti-glycation agents. They are characterized by the ability to break the existing AGE-protein cross-links, and thus, reverse their harmful effect [60]. Several AGEs cross-links have been investigated as potential targets for the cross-links breakers including pentosidine, GODIC, MODIC, DOGDIC, glucosepane, GOLD, MOLD, DOLD, crosslines, vesperlysine and GOLA [60].

Alagebrium (previously known as ALT-711) is a small molecule that belongs to the thiazoles derivatives family and was considered as the first potential AGE-breaker to be discovered. Studies on animal models have proven the effectiveness of alagebrium in reducing large artery stiffness and have shown its positive cardiovascular and renal effects in aged spontaneously hypertensive rats [96].
A study, that was trying to evaluate the effectives of ALT-711 on myocardial stiffness, was conducted on aged dogs with normal systolic function and resulted in a 40% reduction in age-related left ventricular stiffness and improvement in cardiac function [97]. In addition to its cross-link breaking properties, ALT-711 has been suggested to act as an inhibitor of protein kinase (PKC) expression in diabetic kidneys. In 2004, Thallas-Bonke et al. studied the effect of ALT-711 on vascular smooth muscle cells that were taken from diabetic male rats. They have found that treatment with ALT-711 reduced the expression of VEGF and the extracellular matrix proteins, fibronectin and laminin. Therefore, they concluded that ALT-711 has the ability to inhibit the expression of PKC in diabetic kidneys [98]. After some successful animal model studies, a series of clinical trials tried to determine the

efficacy and safety of ALT-711 on humans. It was found that ALT-711 has the ability to improve arterial compliance in ageing patients with vascular stiffening. Additionally, ALT-711 was able to improve cardiac function and systolic blood pressure in patients with severe heart failure and hypertension [99]. After few promising phase I and phase II clinical trials, Alteon corporation, the company which purchased the ALT-711 commercial development rights, stopped its development because of financial complications [100]. Due to this reason, unfortunately, additional research and clinical data is needed to bring ALT-711 into a commercial use.

Enzymes have the ability to react specifically with substrates without causing severe side effects. Several enzymes have been found to be major players in the protection of tissues against glycation and accumulation of AGEs [101]. For example, the glyoxalase system (GLO) is located in the cytosol of every cell and it consists of glyoxylase I (GLO1), glyoxylase II (GLO2) and GSH. This system has been found to play a significant role in the enzymatic defense against glycation, since it catalyzes the conversion of α-oxoaldehydes (such as GO, MGO) into α-hydroxyacids, which are non-reactive molecules [102]. Recent studies have found that the GLO system could be used as a target for intervention in diabetic neuropathy [103], Alzheimer's disease [104], vascular complications, and obesity [105].

Human fructosamine-3-kinase (FN3K) is another example of a possible anti-glycation enzyme. Fructosamines are Amadori products that are formed during the glycation process of glucose [106]. FN3K is a 309 amino acid monomeric enzyme that belongs to the protein kinases group and is found in mammals and birds. It was found to be active in almost every tissue in the mice and rats, especially in their kidneys, brains and red blood cells (mainly erythrocytes) [107]. FN3K has the ability to inhibit the glycation process at an early stage, since it disconnects fructosamines residues from glycated proteins by phosphorylating them into fructoselysine-3-phosphate (FL3P), making them unstable and eventually causing them to decompose spontaneously [108]. Studies on FN3K have suggested a possible correlation between FN3K diabetic complications [109] and colorectal carcinoma [110].

As aforementioned, aldose reductase is an enzyme that is responsible for the production of sorbitol from glucose during the first stage of the polyol pathway. In hyperglycemia, higher amounts of free glucose enter the polyol pathway, which eventually may result in metabolic imbalance and oxidative stress. Many studies have tried to evaluate the correlation between AR and chronic diseases, such as diabetic, heart diseases, renal failure, inflammations, neurological disorders, and even cancer. One interesting therapeutic approach that researchers have been investigated for several years, is the development of aldose reductase inhibitors (ARIs). ARIs can be classified into five different groups: ARIs that contain five-membered cyclic imides (spirohydantoins), ARIs that derived from carboxylic acid (alrestatin), ARIs from natural sources, ARIs from dietary sources and ARIs that are structurally diverse [111].

Early attempts to investigate the therapeutic effects of the ARIs sorbinil, ponalrestat and tolrestat in clinical trials, resulted in poor efficacy and therefore, were terminated early on in the trials [16]. Later approaches suggested that combining the ARIs and the antioxidants therapy strategies together may have better outcomes, since in chronic diseases, the effect of the ARIs may be weakened by the oxidative stress that can be generated from other mechanisms [112].
To date, this enzymatic approach is still more hypothetical than practical and further investigations are still required to understand the various mechanisms of action and the future possible pharmaceutical opportunities.

Carbonyl trappers/sacrificing antiglycation

The formation of carbonyl intermediates such as MGO, GO and 3-DG is a crucial step in the Maillard reaction, since it is considered to be irreversible and it leads to the formation of AGEs. Anti-glycation agents that have the ability to trap these compounds and therefore inhibit their formation, may prevent the development of further complications.
Aminoguanidine (AG) is a nucleophilic hydrazine that was initially considered to become a prototype anti-glycation agent. In 1986, its potential as a possible inhibitor for the formation of AGEs was discovered. AG reacts with carbonyl intermediates

such as MGO, GO and 3-DG, forms 3-amino-1,2,4-triazine derivatives and therefore, prevents their transformation to AGEs [113]. It was widely investigated in pre-clinical and clinical trials and was proven to be efficient in different age-related and diabetes complications [1] including cataract [114], diabetes, renal insufficiency [115], arterial wall protein cross-linking [76], diabetic retinopathy [116], reactive oxygen species formation, lipid peroxidation, oxidant-induced apoptosis [117] and cardiac hypertrophy [118]. However, further interest was stopped when a phase III clinical trial resulted in low efficiency and raised some safety concerns, due to its high toxicity and major side effects when AG was administrated in high doses (gastrointestinal and liver function abnormalities, vasculitis and even kidney tumours) [119].

Pyridoxamine (PM) is a small molecule isoform of vitamin B_6 that can inhibit the formation of AGEs by trapping carbonyl intermediate compounds and ROS [120]. PM is also considered to react as a post Amadori inhibitor (Amadorin), since it has the ability to inhibit the formation of AGEs from Amadori-modified protein [121]. The inhibition of the post Amadori modified proteins may also result in the reduction in ROS formation, since ROS are being formed during the post- Amadori oxidative reactions [120]. PM efficiency as an anti-glycation agent has been broadly studied and was found to be efficient in numerous pathologies including diabetes-induced retinal vascular lesions [122], renal disease, dyslipidaemia [123], age-related aortic stiffening and vascular resistance [124]. Even though PM is considered to become a promising anti-glycation agent, additional future clinical studies are needed in order to evaluate its safety profile. Recently, sulfonated ester derivatives of piroxicam (one of non-steroidal anti-inflammatory drugs) demonstrated potent in vitro antiglycation activities. These results might hold a promise for ameliorating diabetic complications [125]. Other 18 widely used pharmacological active compounds have been investigated for repurposing as antiglycating agents. The in vitro antiglycation assays (bovine serum-glucose and bovine serum glyoxal models) demonstrated that some non-steroidal anti-inflammatory drug like nimesulide, meloxicam, piroxicam; and other therapeutically active compounds such as penicillin G and D-penicillamine had potent antiglycation activities (up to 90% inhibition) comparable to the reference antigylcating agent (rutin with 86% inhibition) [126]. L-carnosine is a dipeptide (β-alanyl-L-histidine) drug has been

reported to show potent antiglycation mechanism in vitro and in ex vivo cataract models. The antiglycating effects were attributed to having a unique terminal amino group in β-position that is able to sacrifice it and spare residual amino groups of proteins and crystallins an inhibit cataractogenesis [127, 128]. An additional antiglycating mechanism attributed to L-carnosine is metal chelation [128].
Similarly, vitamins and nutrients such as vitamin C (ascorbic acid), vitamin E (tocopherol), sodium selenite and selenium yeast showed that a market inhibition of glycation using the in vitro glycation assay [78, 129]. Serum glycated proteins of 17 volunteers was decreased by approximately 47% when the volunteers were on a diet containing 1 g of vitamin C daily for 4 weeks [129].

RAGE blockers

As discussed earlier, RAGE was found to be a multi-binding receptor for many compounds including AGEs. RAGE is expressed in various cells and over-expression of RAGE was found to have a role in a number of chronic pathologies, since its activation may prompt signalling reactions and activation of several pathways, ROS formation and inflammatory responses. Therefore, a growing body of studies have suggested that the blockade of RAGE may be a good therapeutic approach [63, 130, 131].

Pigment epithelium-derived factor (PEDF), a 50 kDa protein, belongs to the serpin group was found to be a good potent neurotrophic factor that has a role in cell differentiation, cell survival and the inhibition of angiogenesis [132]. These findings have led researchers to investigate the possible role of PEDF as a RAGE blocker; animal models have also shown that PEDF prevented the formation of retinal leukostasis in diabetic rats by inhibiting the AGE-induced ICAM-1 expression [133]. Another study, conducted by Ishibashi et al. on mice cultured podocytes, suggested that PEDF may have a role in preventing the AGE-induced apoptosis of podocytes in diabetic nephropathy by blocking RAGE expression and thus, preventing ROS formation [134].

FPS-ZM1 is a new potent RAGE-blocker for the treatment of Alzheimer's disease (AD). RAGE expression can be found in microglia, cerebral endothelial cells, and neurons and it was suggested that there is a strong correlation between increased expression of RAGE and AD. Anti-glycation studies for AD management are considered to be challenging, because of the existence of the blood brain barrier (BBB). Several studies that used RAGE-antibodies have failed, since only the peripheral RAGE was blocked, not the central RAGE [135]. Deane et al. developed and identified the FPS-ZM1 as a high affinity RAGE-specific inhibitor and showed that it was able to cross the BBB, to bind to the V-domain of RAGE, and to reduce Aβ-induced cellular stress in the brain without having any toxic effects on the mice cells [136].

In another AGEs-RAGE-activated rat model study that investigated the effects of FPS-ZM1 on Aβ production and AGEs-induced oxidative stress and inflammation, the intraperitoneal administration of FPS-ZM1 minimised Aβ formation, inflammation and oxidative stress levels, and improved cognitive behaviours [135]. FPS-ZM1 was also found to have an effect on BBB damage, brain oedema, motor dysfunction and nerve-fibre injury following intracerebral haemorrhage [137]. Even though FPS-ZM1 seems to be a potential anti-glycation agent for AD treatment, it is still being pre-clinically investigated and additional animal models and clinical trials must be conducted in order to evaluate its efficacy and toxicity.

Metal Ions Chelators

Transition metal ions play a role in the Maillard reaction and in several mechanisms that lead to oxidative stress. Therefore, metal chelators and antioxidants have been suggested as a possible anti-glycation therapeutic approach that chelate Cu, Zn and Fe-induced Fenton's reactions. Sajithlal et al. performed a study that investigated the potential role of the antioxidants mannitol, sodium benzoate and diethylene triamine penta acetic acid (DETAPAC) on the inhibition of AGEs formation. They found that the addition of metal ions to the studied medium increased the formation rate of the AGEs. On the other hand, mannitol, sodium benzoate and DETAPAC actually slowed down their formation [138]. Lalezari-Rahbar (LR) compounds, including LR-9, LR-20, LR-59, LR-74, LR-90 and

edaravone derivatives (TM-2002) have been investigated as potential chelating compounds. Even the administration of low dosage (5% of the aminoguanidine dose) resulted in the inhibition of the formation of AGEs in rats and mice models [45]. Evidence from these different studies has suggested that LR-90 and LR-74 reduced the formation of CML in the kidneys, blocked the cross-linking of collagen-AGE in the tissues and prevented oxidative stress [101]. Another potential metal chelator that was studied is trientine and it was suggested that trientine might have a role in preventing diabetic-related cardiac pathology. A study performed by Baynes and Murray showed that treatment with trientine improved the systolic and diastolic pressure and changed the structure of diabetic rats' hearts [139]. Although this approach seems to be a promising one, additional research and further studies need to be carried out in order to understand the exact mechanisms related to the chelation processes. Finally, only a small number of phase I clinical trials were conducted and resulted in inefficient results that need to be further examined [140].

Natural products

The interest in natural products has been growing during the last decade [141, 142]. There is strong evidence that natural products have the ability to prevent the occurrences of lifestyle-related and chronic illness, such as diabetes, cataract, hypertension, cardiovascular diseases, renal complications and cancer.

Natural products and plant-based drugs are considered to be promising approaches for anti-glycation therapeutics (Figure 7), since they are more available, relatively safer to use, and have fewer side effects. Furthermore, several studies have proven that natural products containing terpenoids (e.g. limonene, labdadiene and Oleanolic acid), polyphenols and flavonoids have antioxidant (Figure 7 (A)), antiglycation and hypoglycaemic characteristics, hence they may reduce the glycation-related oxidative stress [8, 37]. For example, one of the preventative measurements of hyperglycaemia-induced cataract, is to control the glucose levels in the blood, and to add greater intakes of vitamins, fruits and vegetables to the diet. These products contain different compounds, such as minerals, phenols, and carotenoids that may have anti-oxidative protective properties and therefore can be used as anti-glycation agents. Green tea, coffee, wine, nuts, vegetables, herbs, rice, and wheat are just a few of these dietary products that are considered to have anti-

oxidant effects [8]. Green tea is widely consumed and is a great source of gallic acid, caffeic acid, catechins and quercetin. Numerous studies have suggested that green tea may play a role in controlling cardiovascular diseases, diabetic-related nephropathy, arterial pressure, inflammation, and cancer [143].
Polyphenols are found in every fruit and vegetable. The most common polyphenols include phenolic acid, flavonoids. Phenolic acids; such as caffeic acid, ferulic acid, chlorogenic acid and gallic acid; can be found in almost all fruits and vegetables. Flavonoids can be further divided into anthocyanins, flavones, flavonols, flavan-3-ols and flavanones; they can be found in various different types of vegetables and beverages [8]. Polyphenols are considered to be potential anti-glycation agents since they were proven to be able to inhibit the formation of CML and EML by chelating ion metals and by trapping dicarbonyl compounds [144]. The basic structure of flavonoids has many hydroxyl groups; therefore, it may have antiglycating and MG trapping functions; different positions of the carboxylic group has been reported to produce different effects [145]. Combination of two or more of flavonoid products demonstrate better antiglycation activities than using a single flavonoid compound [145]. The use of hesperidin (120mg) ad resveratrol (90 mg) in combination significantly increased reduced GSH, activation of GLO1 by 22% and reduced plasma MG level by 37% after 8 weeks of supplementation in overweight and obese diabetic patients [30].

Carotenoids are a vast group natural pigments that encompass over 700 compounds. Carotenoids in food such as carrots are classified into two main groups that give yellow and red colors: carotene (e.g., β-carotene and lycopene) and the oxygenated carotenoids xanthophylls (e.g., lutein). These are among the most commonly catenoids that have medicinal application. The basic chemical structure of carotenoids is made of a polyisoprenoid carbon chain with a series of conjugated double bonds localized in the central part of the molecule [146] (Figure 7 (B)). Carotenoids are found to have anti-glycation characteristics by inhibiting the glycation of haemoglobin [147], having anti-inflammatory and anti-neoplastic properties and regulating gene expression [148]. The carotenoids zeaxanthin, astaxanthin, lycopene and lutein were found to play a role in the management of diabetic microvascular complications [149]. It was also found that carotenoids from

peach-derived products suppressed the expression of RAGE and hence inhibited oxidative stress and liver damage [150]. The development of natural anti-glycation agents may delay and prevent premature ageing and diabetic complications. Anti-glycation mechanisms to be investigated are: antioxidation, chelating of metal ion, trapping of carbonyl groups, breaking of AGE crosslinks, and blocking RAGE and therefore unwanted cellular pathways.

Natural polysaccharides have recently gained popularity as antioxidant, antiglycation and metal chelator properties [151]. Polysaccharides like chitooligosaccharide (Figure 7 (C)) prepared from chitosan has been recently reported to show in vitro antiglycation activities and has been able to inhibit serum CML levels in mice with a daily oral dose of 2.4 g of the polysaccharide [40].

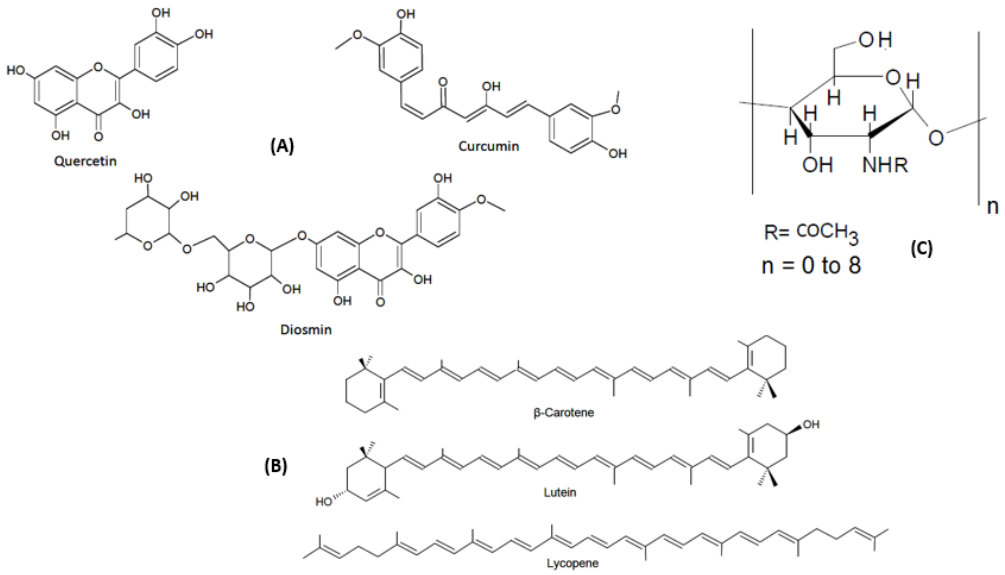

Figure 7. Chemical structures of commonly natural active constituents: flavonoids (A), carotenoids (B) and chitooligosaccharide (C) for breaking AGEs

Novel Drug Delivery Systems - A Look for The Future

Because many trials resulted in insufficient results, poor efficacy and high toxicity, future treatment approaches must include specific targeting of the anti-glycation agents to the defective tissue (Figure 8). Furthermore, current treatment strategies only treat the symptoms of the previously discussed diseases without treating the disease itself. In cataract, for example, the only corrective treatment is surgery. Although surgery is considered to be safe in 95% of patients, it still has its

limitations: it is invasive, it is followed by discomfort and a difficult period of recovery, and serious complications may follow. Notwithstanding, these problems only occur in a small number of cases; the most common one is the rupture of the posterior lens capsule [152]. Diabetic patients are advised to take some preventative measures in order to prevent hyperglycaemia-induced cataract. These include controlling the glucose levels in the blood and adding a daily intake of vitamins, fruits and vegetables to their diet, since they contain minerals and phytochemicals that may have anti-oxidative protective properties [153]. Over the past few decades, researchers have been trying to find new ways to treat both ageing and diabetic related cataract. Local ocular drug delivery routes are considered to be the safest and most acceptable among patients, but the physical structure of the eye has still remained one of the greatest obstacles to overcome; the anatomical and physiological natural defence barriers of the eye halt the delivery of drugs into the eye, resulting in less than 5% bioavailability of the drug. A variety of synthetic drugs, including N-acetyl carnosine (NAC), aspirin, aspirin-like analogues, NSAIDS, bendazac and sorbinol were studied as potential therapeutic agents, but several limitations, such as high doses, systematic side effects and small grouped clinical trials prevented them from being marketed [86]. Recently, L-carnosine has been reported to show antiglycation, metal chelation and antioxidant potential [128]. L-carnosine was prepared in nano-lipid complexes with phospholipid. These nano-lipid carriers had the capacity to enhance corneal penetration of the hydrophilic drug with high ocular tolerability and in vitro anticataract efficacy using diabetic cataract models of excised pig lenses [127].

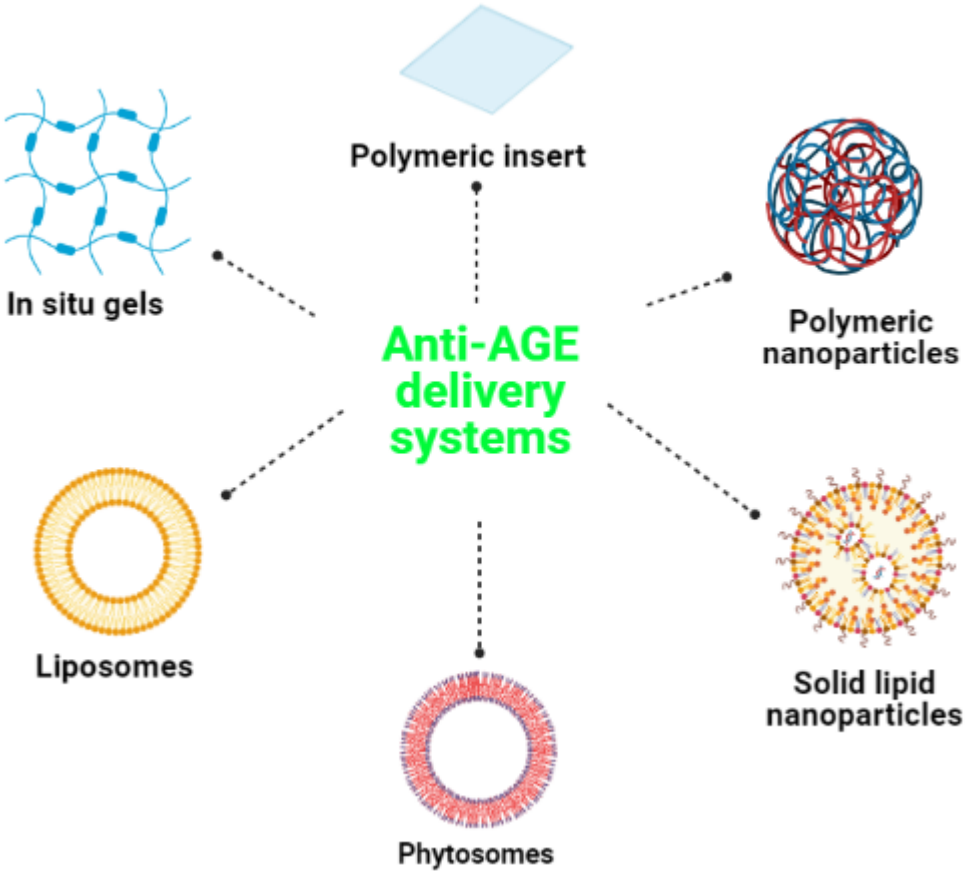

Figure 8. Outline of drug delivery strategies for antiglycating agents

As previously discussed, natural products and plant-based drugs are considered to be promising approaches for anti-glycation therapeutics, with a specific emphasis on antioxidants, such as carotenoids, flavonoids, phenolic compounds, and vitamins. These anti-oxidants prevent the formation of free-radicals by stopping the free-radical chain reactions [153]. Even though several anti-oxidants studies on animal models resulted in promising outcomes, human epidemiological studies results were inconsistent and additional studies are needed [154]. On the downside, extremely poor solubility and permeability for such natural products flavonoids have hampered its utilization as potential antiglycation for therapeutic purposes. Both solubility and dissolution rate of quercetin and rutin (a standard antiglycating agent) were significantly enhanced [155] using a simple and reproducible technique by co-grinding the flavonoid with L-lysine [155]. These favourable properties attributed for L-lysine have been ascribed to the increasing ionization of the flavonoid drugs and formation of drug-lysine ion pair complexes.

Future approaches that include the specific targeting with maximum efficacy and minimum toxicity and intervention, are being investigated and developed every day. Nano-encapsulation, microemulsions, liposomes, and solid lipid nanoparticles are only a few examples for these new kinds of technologies that have been investigated as promising drug-delivery approaches for quercetin, curcumin and resveratrol for treatment of Alzheimer's disease and diabetic complications [156-158]. Table 3 presents some examples of anti-cataract ongoing strategies using advanced drug delivery systems.

Table 3. Representative antiglycating agents loaded onto advanced drug delivery systems for combating chronic age-related diseases

Delivery system	Anti-glycating agent	Antiglycation Mechanism	Therapeutic application	Reference
In situ thermal gels	Tiopronin	Metal chelation/antioxidant	Anti-cataract	[159]
In situ pH-sensitive gels	Baicalin	ARI, metal chelator and antioxidant	Anti-cataract, age-related diseases	[160]
Chitosan-coated liposomes	Coenzyme Q_{10}	Antioxidant	Anti-cataract and cardiac diseases	[161]
Self-emulsifying phospholipid suspension (SEPS)	Lutein	Antioxidant	Anti-cataract	[162]
Nanostructured lipid carriers (NSCs)	Genistein	Antioxidant, metal chelator and ARI	Anti-cataract and age-related diseases	[163]
Polymeric nanoparticles (PLGA)	Quercetin	Antioxidant and metal chelator	Breast cancer	[164]
Liposomes	Curcumin	Antioxidant, metal chelator and ARI	Alzheimer	[165]
Polymeric nanoparticles	Cerium (III) acetate	Antioxidant	Alzheimer	[166]
Phytosomes-hyaluronic acid	L-carnosine	Antioxidant, sacrificing antiglycating agent	Anti-cataract	[127]

Amino acid complexes	Quercetin Rutin	Antioxidant, metal chelator and ARI	Alzheimer, skin ageing and anticataract	[155]
Zein-sodium caseinate nanoparticles	Rutin	Standard antiglycating agent, antioxidant, metal chelator and ARI	Diabetic complications and age-related diseases	[167]
In situ polymeric inserts	Curcumin	Antioxidant, antiglycating agent	Diabetic ocular diseases	[168]

Conclusions

Glycation is an evident example of what possibly happens when the body's homeostasis gets out of control; glucose can turn from a safe and vital molecule into a silent killer. The purpose of this review was to gather all the relevant information and knowledge about the Maillard reaction, AGEs, hyperglycaemia-induced oxidative stress, and the pathologies related to them. Glycation is an example of "too much of something good, can be bad". It is what happens when the body's homeostasis is out of control; glucose can turn from a safe and vital molecule into a silent killer causing extensive damage to vital organs such as heart, kidney and the eye. A growing number of studies and evidence have found a correlation between glycation and its complications to age-related and chronic complications, such as ageing, diabetes, cataract, AD, cardiovascular diseases, renal diseases and even cancer. An important strategy to be further investigated is whether or not it is feasible that one of the risk factors to AD could be diabetes. Since this correlation between AD and hyperglycaemia has been demonstrated in several recent studies. It could be possible that diabetic patients may be prone to diabetic-induced AD.

While the investigation of anti-glycation synthetic agents and natural products using mostly animal models have produced promising results, clinical trials have failed to demonstrate the same effects in humans. These trials were terminated early due to poor efficacy, administration of high dosages, high levels of toxicity, and severe side effects. There is no single safe and effective strategy to inhibit or control glycation complications; dietary restrictions of excessive consumption of carbohydrate and fat combined with antiglycation and natural antioxidants could be safe and effective targeting diabetic complications and other glycation-induced chronic diseases.
Reversal of diabetic complications and arterial stiffness are possible by using AGEs breakers. Despite the evidences connecting glycation to many chronic diseases, further studies are needed to elucidate the exact mechanisms and the therapeutic opportunities of anti-glycation treatments. Several natural compounds such as polyphenols and flavonoids are yet to be commercially available in pharmaceutical products treating glycation-associated complications because of inherent poor solubility and permeability. Future anti-glycation strategies include combining

investigated antiglycation agents into new drug delivery systems in order to enhance their therapeutic effects or to reduce their toxicity. Reversal of glycation-induced complications (arterial stiffness and cataract) by natural products should be a potential line of research to be assessed and evaluated.

List of Abbreviations

AGEs: advanced glycation end-products

CEL: Nℨ-carboxyethyl lysine

CML: Nℨ-carboxymethyl lysine

DETAPAC: diethylene triamine penta acetic acid

DOLD: deoxyglucasone-lysine dimer

FFI: furoylfuranyl imidazole

FPS-ZM1: N-Benzyl-4-chloro-N-cyclohexylbenzamide

GLO1: glyoxalase 1

GOLD: glyoxal-lysine dimer

HbA1c: glycated haemoglobin (HbA1c)

MOLD: methyl glyoxal-lysine dimer

MG-H1: N-(5-hydro-4-imidazolon-2-yl)-ornithine

PEDF: Pigment epithelium-derived factor

RAGE: receptors of AGEs

ROS: reactive oxygen species

VEGF: vascular endothelium growth factor

3DG-H: N-(5-hydro-5-(2,3,4-trihydroxybutyl)-4-imidazolon-2-yl)-ornithine

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Figure Legend

Figure 1 The relationship between glycation, the polyol pathway and hyperglycemia-induced oxidative stress mechanisms

Figure 2 The Maillard reaction mechanism by phases; a) the initiation phase, b) the propagation phase, c) the termination phase, based on [7].

Figure 3 Chemical structures of some known AGEs. Fluorescence and crosslinking AGEs (A): crossline, fluorolink, FFI, GOLD, MOLD, vesperlysine A, B, and pentosidine; and non-fluorescence and non-crosslinking AGEs (B): argpyrimidine, CEL, CML, 3-DG-imidazolones, MG-imidazolones and pyrraline, as modified from [29].

Figure 4 The effect of glycation, AGEs, RAGE activation, and oxidative stress on the cells and extracellular matrix system

Figure 5 Pathologies related to Advanced Glycation End Products (AGEs)

Figure 6 Summary of the anti-glycation strategies of formation prevention (bracket 1) and inhibition of toxic effects (brackets 2 and 3)

Figure 7 Outline of drug delivery strategies for antiglycating agents

Table legend

Table 1 MG and CML levels in selected food (adopted and modified from [35]

Table 2 Summary of the analytical methods used for the determination of AGEs, advantages and limitations.

Table 3 Examples of antiglycating agents with current drug delivery strategies using advanced drug delivery systems.