Chapter 10

Plant-Derived Agents with Anti-Glycation Activity

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Additional information is available at the end of the chapter

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1. Introduction

1.1. Glycation and consequences

Glycation or the Maillard reaction is the non-enzymatic adduct formation between amino groups (predominantly the ε-amino group of lysine and the guanidine group of arginine) [1, 2] and carbonyl groups of reducing sugars or other carbonyl compounds. This reaction is subdivided into three main stages: early, intermediate, and late. In the early stage, glucose (or other reducing sugars such as fructose, pentoses, galactose, mannose, xylulose) react with a free amino group of biological amines, to form an unstable aldimine compound, the Shiff base. Then through an acid-base catalysis, this labile compound undergoes a rearrangement to a more stable early glycation product known as Amadori product [3]. Because the Maillard reaction is non-enzymatic, the variables which regulate its velocity *in vivo* are the glucose and protein concentrations, the half-life of the protein, its reactivity in terms of free amino groups, and the cellular permeability to glucose.

In the intermediate stage, *via* dehydratation, oxidation and other chemical reactions, the Amadori product degrades to a variety of reactive dicarbonyl compounds such as glyoxal, methylglyoxal, and deoxyglucosones which, being much more reactive than the initial sugars, act as propagators of the reaction, again reacting with free amino groups of biomolecules. In the late stage of the glycation process through oxidation, dehydratation and cyclization reactions, irreversible compounds, called Advanced glycation end products (AGEs) are formed. The AGEs are yellow-brown, often fluorescent and insoluble adducts that accumulate on long-lived proteins thus compromising their physiological functions [4]. Glycation of proteins can interfere with their normal functions by disrupting molecular conformation, altering enzymatic activity, reducing degradation capacity, and interfering

with receptor recognition [5]. AGE-modified proteins lose their specific functions and undergo accelerated degradation to free AGEs such as 2-(2-furoyl)-4(5)-furanyl-1H-imidazole (FFI), imidazolone, N-ε-carboxy-methyl-lysine (CML), N-ε-carboxy-ethyl-lysine (CEL), glyoxal-lysine dimmer (GOLD), methyl-glyoxal-lysine dimer (MOLD), and others. Moreover, AGEs can also act as cross-linkers between proteins, resulting in the production of proteinase-resistant aggregates [6].

The formation of AGEs progressively increases with normal aging and age-dependent AGEs have been shown to accumulate in human cartilage, skin collagen and pericardial fluid [7]. Long-lived proteins such as lens crystallins and especially collagens contain numerous lysine, hydroxylysine and arginine residues, have a slow turn over, and are prone to age-related accumulation of glycation damage [8]. Besides accumulation during healthy aging, AGEs are formed at accelerated rates in diabetes [9]. They are markers and also important causative factors for the pathogenesis of diabetes [10], cataracts [11], atherosclerosis [12], diabetic nephropathy [13], and neurodegenerative diseases, including Alzheimer's disease [14]. Three routes have been proposed for AGEs formation: 1) autoxidative pathway in which sugars give rise to reactive products by autoxidation, 2) Amadori rearrangement, and 3) from the Shiff base. Reactive oxygen species (ROS) in the presence of trace levels of catalytic redox-active transition metal ions also contribute to AGEs formation. The process includes oxidative steps and is therefore called glycoxidation [15].

Except these endogenous AGEs, humans are also exposed to exogenous AGEs which are ingested with food. Some approaches for food processing promote the Maillard reaction and the development of browning products [16]. The formation of Maillard reaction products (MRPs) depends on the processing temperature and duration, and is greatly accelerated by long exposure to heat [17]. Food treatments such as frying or baking have a greater impact on the formation of MRPs than boiling [18]. MRPs are inherent to Western diet [19] and fructose intake was largely elevated in recent years because of an increased consumption of soft drinks and processed foods. Fructose and its metabolites, can initiate the non-enzymatic fructosylation of proteins. Moreover, among the various physiological sugars, fructose undergoes a more rapid oxidative degradation and is a more potent protein glycating agent than glucose [20]. During chronic hyperglycemia, excessive glucose uptake in tissues also affects the key enzyme aldose reductase (AR) in the polyol pathway. This leads to the reduction of various sugars to sugar alcohols, such as glucose to sorbitol, followed by nicotinamide adenine dinucleotide (NADH)-dependent sorbitol dehydrogenase-catalyzed fructose production. Increased fructose formation in turns leads to the production of reactive carbonyl species which are key factors in AGEs formation [21]. Furthermore, sorbitol and its metabolites accumulate in the nerves, retina, kidney, and lens due to poor penetration across membranes and inefficient metabolism, resulting in the development of diabetic complications [22]. Advanced glycation end products formed inside the body or ingested with food can also interact with specific receptors and/or binding proteins thus activating a series of intracellular signalling pathways, which are implicated in diabetic complications. Interaction of AGEs with receptors for advanced glycation end products (RAGE) can trigger signaling events through p38 MAP Kinase, nuclear factor kappa-B

(NF-κB), P21 Ras and Jak/STAT pathways. The cellular response can involve the overexpression of cell adhesion molecules such as vascular cell adhesion molecule-1(VCAM-1), and the production of cytokines (interleukin-2, interleukin-6 and tumor necrosis factor-α) and vascular endothelial growth factor (VEGF) [23-25]. Various studies have shown that diabetes mellitus is associated with an increased production of free radicals and also with a decrease in the antioxidant potential leading to oxidative stress. Thus, the disturbed balance between radical formation and radical neutralization leads to oxidative damage of cell components such as proteins, lipids, and nucleic acids [26]. During glycoxidative stress, NF-κB activates the production of TNF-α which in turn leads to enhanced ROS production. In such a way AGEs formation keeps the oxidative stress ongoing [27, 28].

ROS exert a multitude of effects. They are both harmful by-products and cellular messengers. As messengers, ROS are involved in a network of intracellular and intercellular communication pathways and that is why mitochondrial production of ROS plays a crucial role in the pathogenesis of type II diabetes, neurodegenerative and cardiovascular diseases [29]. It has been reported that direct exposure of endothelial cells to hyperglycaemic concentrations of glucose increases the formation of ROS. Activation of the enzyme NADPH oxidase is strongly implicated in this process [30]. NADPH oxidase may be activated through an increased diacylglycerol mediated activation of protein kinase C (PKC) [31]. High concentrations of glucose [32] and ROS [33] also have been reported to activate PKC. Since hyperglycaemia is responsible for a rise in the mitochondrial production of ROS, targeting antioxidants to mitochondria and increasing their overall antioxidant potential is expected to ameliorate diabetic symptoms [34]. In order to enhance the antioxidant capacity of the body, we must increase the exogenous intake of antioxidants or stimulate the endogenous synthesis of antioxidants such as superoxide dismutase and reduced glutathione. The inhibition of AR and advanced glycation end products formation is yet another mode for diabetes treatment, which is not dependent on the control of blood glucose, and would be useful in prevention of certain diabetic complications [35].

2. Therapeutic agents

Both synthetic compounds and natural products have been evaluated as inhibitors against the formation of advanced glycation end products (AGEs). The synthetic AGEs inhibitors so far discovered are divided into three classes: (a) carbonyl trapping agents which attenuate carbonyl stress; (b) metal ion chelators, which suppress glycoxidations; and (c) cross-link breakers that reverse AGE cross-links [9]. However, despite of their inhibitory capacities against the formation of AGEs, many synthetic inhibitors of AGEs formation were withdrawn from clinical trials due to relatively low efficacies, poor pharmacokinetics, and unsatisfactory safety [36, 37].

For exaple, aminoguanidine (AG), a nucleophilic hydrazine compound which prevents the formation of AGEs was withdrawn from the crucial phase III of clinical trials because of safety concerns and apparent lack of efficacy [38]. On the other hand natural products have been proven relatively safe for human consumption and many plant extracts have

been tested for their ability to prevent AGEs formation [39]. Moreover, a number of plant-derived products have been shown to possess hypoglycemic, hypolipidemic as well as antioxidant properties [40]. Some important compounds such as phenolics [41, 42], oligo- and polysaccharides [43, 44], carotenoids [45, 46], unsaturated fatty acids [45, 46] and many others have been reported to possess anti-glycating activity. Thus, the daily consumption of dietary components, mainly from plant sources which have an antioxidant effect, is considered to be of potential benefit for prevention of diabetes and diabetic complications [47]. For example ethanol fractions of *Melissa officinalis, L* (Lemon balm) were shown to possess high inhibitory effect on the formation of advanced glycation end products in the late stage of the glycation process [48]. Green tea consumption (drinking) also significantly reduced the advanced glycation, the accumulation of AGEs and the cross-linking of tail tendon collagen in diabetes [49]. Moreover, phenolics, particularly flavonoids, are responsible for the anti-glycation activity of herbal infusions [50]. Another beverage consumed worldwide, the coffee, is also rich in phenolic compounds, mainly caffeoylquinic, p-coumaroylquinic, feruoylquinic and dicaffeoylquinic acids which inhibit protein glycation and dicarbonyl compounds formation [51]. Except polyphenols which constitute a major group of plant-derived compounds with anti-glycation activity, some amino acids [52-54], triterpenes and saponins [55, 56], polysaccharides and oligosaccharides [43, 44, 57, 58] were shown to decrease the AGEs formation. Taurine, a sulfur amino acid, was shown to reduce acrylamide production in potato chip models suggesting its potential use in food processing to decrease acrylamide formation [53]. Another amino acid, arginine, was shown to have an immunomodulatory effect and to inhibit AGEs formation in *in vitro* studies [54].

3. Polyphenols

The anti-glycation capacity of numerous medicinal herbs and dietary plants was comparable with [59], or even stronger than that of aminoguanidine [42, 60, 61-63]. Several studies have demonstrated that the anti-glycation activity correlates significantly with the phenolic content of the tested plant extracts [5, 50, 59, 64, 65]. Polyphenols are the most abundant dietary antioxidants, being common constituents of fruits, vegetables, cereals, seeds, nuts, chocolate, and beverages, such as coffee, tea, and wine. They have been shown to lead to many health benefits, such as prevention of cancer [66], neurodegenerative diseases [67], cardiovascular diseases [68] and diabetes [69].

Although polyphenols are chemically characterized as compounds with phenolic structural features, this group of natural products is highly diverse and contains several sub-groups of phenolic compounds. The diversity and the wide distribution of polyphenols in plants have led to different ways of categorizing these naturally occurring compounds. Polyphenols have been classified by the source of origin, biological function, and chemical structure. Also, the majority of polyphenols in plants exist as glycosides with different sugar units and with sugars acylated at different positions of the polyphenol skeletons [70]. According to the chemical structure of the aglycones, polyphenols are subdivided into the following groups:

1. **Phenolic acids** are among the most important non-vitamin antioxidant phytochemicals naturally present in almost all vegetables and fruits. Their biological activity is related to their lipophilicity and is influenced by the presence of ring substituent hydroxyl groups and, in the case of polyhydroxylated phenolic esters, by the length of the ester moiety [71]. Phenolic acids are non-flavonoid polyphenolic compounds which can be divided into two main types, benzoic acid and cinnamic acid derivatives based on C1–C6 and C3–C6 backbones (Figure 1) [70].

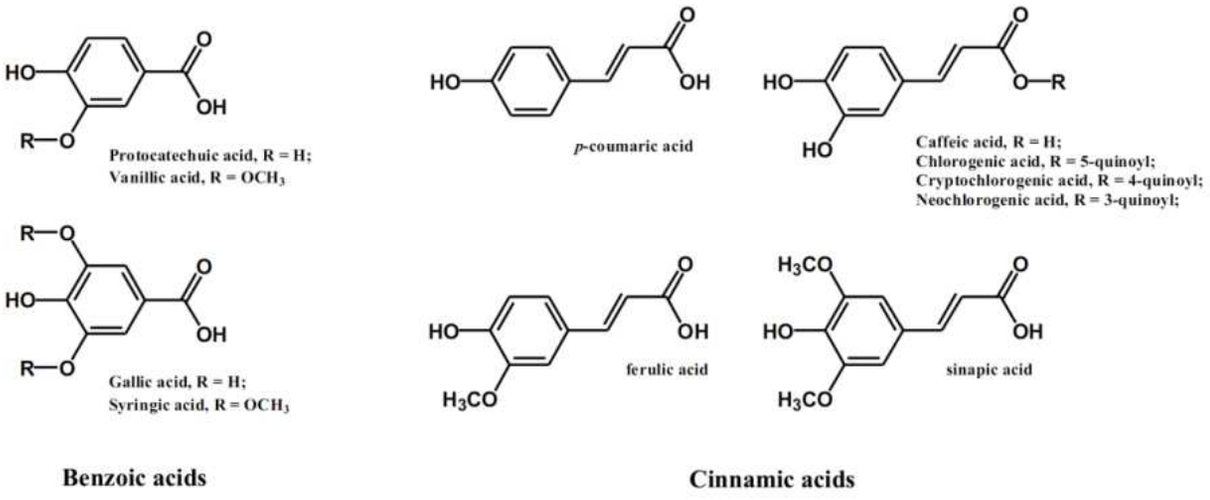

Figure 1. Phenolic acids: Left, Benzoic acids; right, Cinnamic acids. Tsao R (2010).

Cinnamic acids and derivatives

Caffeic acid is a naturally occurring cinnamic acid, found in many vegetables and herbs, e.g. coffee, pear, basil, oregano and apple [72]. In 2009 Gugliucci et al. demonstrated that caffeic acid in *Ilex paraguariensis* extracts inhibits the generation of fluorescent AGEs in *in vitro* experiments [65]. Moreover, extracts from two *Chrysanthemum* species (*C. morifolium* R. and *C. indicum* L.) demonstrated marked inhibition of the formation of AGEs and CML in *in vitro* model systems [42]. The plant extracts inhibited the formation of total AGEs after one week of incubation in BSA/glucose and BSA/fructose systems. Furthermore, the inhibitory effect of the *Chrysanthemum* extracts at a concentration of 5.0 $mg.ml^{-1}$ was stronger than that of AG at a concentration of 1 mM as a positive control. The active components in these plants were characterized by liquid chromatography-diode array detector-atmospheric pressure chemical ionization/mass spectrometry, which showed that *C. indicum* L. conatins large amounts of caffeic acic, as well as luteolin and kaemferol. The other *Chrysanthemum* species (*C. morifolium* R.) contains chlorogenic acid, flavonoid glucoside varieties, and apigenin [42]. **Chlorogenic acids**, esters formed between certain *trans* cinnamic acids and (-)-quinic acid, are the major phenolic compounds in coffee, strawberries, pineapple, apple, and sunflower. **5-caffeoylquinic acid (5-CQA)** is the only chlorogenic acid commercially available and has been extensively studied due to its antioxidant activity. Chlorogenic acids are free radical and metal scavengers, and along with other biological activities they may interfere with glucose absorption and have been shown to modulate gene expression of antioxidant

enzymes [73]. Coffee fractions, in which chlorogenic acids are the main compounds, have been shown to inhibit the formation of CML in a concentration-dependent manner. In addition polyphenols such as *caffeoylquinic, p-coumaroylquinic, feruloylquinic* and *dicaffeoylquinic* acids contributed to about 70% of the antioxidant capacity of the coffee fractions [51]. Notably, *Ilex paraguariensis*, like coffee, contains a high concentration of caffeic acid, mostly esterified as chlorogenic acids [65]. Large amounts of chlorogenic acid were identified also in *Chrysanthemum morifolium* R. [42].

Recently, Jang et al. (2010) isolated three **quinic acid derivatives** from ethyl acetate soluble extract of the leaves and stems of *Erigeron annuus.* The structures of these compounds were identified as **3-caffeoylquinic acid, 3,5-di-O-caffeoylquinic acid methyl ester, and 3,5-di-O-caffeoyl-epi-quinic acid.** The last compound exhibited the most potent inhibitory activity against AGEs formation (IC_{50} value of 6.06 μM *vs.* 961 μM for AG) and prevented opacification of rat lenses, while **3-caffeoylquinic acid** (a **monocaffeoylquinic acid**) was not effective. **Two caffeoyl erigerosides and a sucrose ester** also were more effective AGEs inhibitors than AG. This is the first report on **3,5-di-O-caffeoyl-epi-quinic acid** as an inhibitor of RLAR (rat lens aldose reductase), AGEs formation, AGEs-BSA cross-linking, and cataractogenesis [62].

Ferulic acid (FA) is another cinnamic acid that occurs naturally and which is present in drinks and foods, e.g., rice, wheat, oats and some fruits and vegetables [58]. In 2002 Kikuzaki et al. reported that ferulic acid possesses free radical scavenging properties toward hydroxyl radicals, peroxynitrite and oxidized low-density lipoprotein *in vitro* [74]. It has been also shown that ferulic acid can bind human serum albumin (HSA) to form complexes [75]. This interaction led to a significant reduction of the HSA α-helix structure and caused structural changes to the protein providing unusual protective effects against protein oxidation. Silván et al. (2011) reported that the addition of ferulic acid reduces the formation of CML and fluorescent AGEs *in vitro* by nearly 90% [76]. It was shown that the presence of ferulic acid in samples containing proteins and fructose prevents the blocking of free amino groups by about 15% and 30% in soy glycinin and BSA glycation model systems, respectively. Based on previously published results, as well as on the latest findings regarding ferulic acid, Silván et al. (2011) concluded that FA might prevent AGE formation by some of the following ways: acting as an antioxidant, binding amino groups, and inhibiting sugar autoxidation and early Maillard Reaction Products (MRP) degradation [76]. However, the exact mechanism of anti-glycation by ferulic acid demands further investigations.

In 2011 Miroliaei et al. reported the presence of **rosmarinic acid,** a dimmer of caffeic acid, in *Melissa officinalis* L. extract. They demonstrated that treatment of BSA with this herb resulted in a profound prevention of structural changes caused by D-glucose keeping the protein molecule close to its native polar conformation. The extract has the potential to arrest changes in the α-conformers by concealing the glycation sites and lowering the extent of the solvent-accessible surface area, thereby producing barriers for cross β-structure formation. The behavior of the balm extract in this respect resembles that of molecular chaperones

which block the hydrophobic surfaces of substrate proteins. Moreover, when albumin molecules were treated with glucose in the presence of balm extract, a lower affinity of glycated BSA for RAGE receptors was observed. Based on the above experimental data, researchers concluded that the herb extract, possessing chaperone-like activity, would afford a protective effect against AGE-induced toxicity by suppression of receptor signaling pathways (e.g. RAGE antagonists) [48]. Also, Ma et al. (2011) reported that rosmarinic acid, isolated from *Salvia miltiorrhiza Bge,* has a more potent inhibitory effect against the formation of AGEs in α-glucosidase (IC_{50} 0.04 μM) than the positive control (AG with IC_{50} of 0.11 μM) [63].

Benzoic acid derivatives

Three derivatives of gallic acid: **ethyl gallate, pentagalloyl glucose,** and **protocatechuic acid** were isolated from ethyl acetate fraction of *Rhus verniciflua* extracts [77]. These gallic acid derivatives have been shown to inhibit recombinant human aldose reductase as well as the accumulation of advanced glycation endproducts in BSA-glucose model system.

In 2007 Ardestani et al. reported that the *Cyperus rotundus* extract (CRE) has a potent antioxidant activity and chelating properties. CRE inhibits high fructose-induced oxidative damage to protein in a dose-dependent manner by decreasing protein carbonyl (PCO) formation and preserving protein thiols from oxidation [59]. Recently, RP-HPLC analysis of *C. rotundus* revealed the presence of phenolic compounds such as **gallic acid**, **p-coumaric acid** (a typical cinnamic acid), and **epicatechin** (flavanol) [78]. Accordingly, the potent inhibitory activity of *C. rotundus* on AGEs formation and protein oxidation might be related to its polyphenolic content.

A new gallic acid-derivative, 7-*O*-galloyl-D-sedoheptulose (GS), was identified in *Cornus officinalis* (2007). This polyphenolic compound showed beneficial effect on the early stage of the diabetic kidney disease [79]. GS reduced renal glucose, AGE formation, and oxidative stress in diabetic rats. Moreover, GS did not show any toxicity at 20 and 100 mg, and reduced Maillard reaction-induced CML *via* the marked inhibition of mitochondrial lipid peroxidation. It also effectively ameliorates the increases in serum creatinine and urinary protein to nearly normal levels [80].

2. Flavonoids

Flavonoids have the C6–C3–C6 general structural backbone in which the two C6 units (Ring A and Ring B) are of phenolic nature (Figure 2)

Due to the hydroxylation pattern and variations in the chromane ring (Ring C), flavonoids can be further allocated to different sub-groups such as **anthocyanins, flavan-3-ols, flavones, flavanones and flavonols.** While the vast majority of the flavonoids have their Ring B attached to the C2 position of Ring C, in some flavonoids such as **isoflavones and neoflavonoids**, Ring B is connected at the C3 and C4 position of Ring C, respectively.

Since beans, particularly soybean, are a major constituent of the diet in many cultures, the role of isoflavones has, thus, great impact on human health [70]. Flavonoids are present in various kinds of vegetables, tea, and red wine [81]. Numerous flavonoids are well-known

antioxidants, effective in trapping free radicals, and in such a way participating in maintaining the overall plant cell redox homeostasis [82]. The primary structure of flavonoids (three benzene rings with one or more hydroxyl groups) is the key factor determining their antioxidation capacity. The antioxidation activity may involve the ability of flavonoids to scavenge free radicals, chelation of transition metal ions, sparing of LDL associated antioxidants, and binding to macromolecules or interaction with other kinds of antioxidants [83].

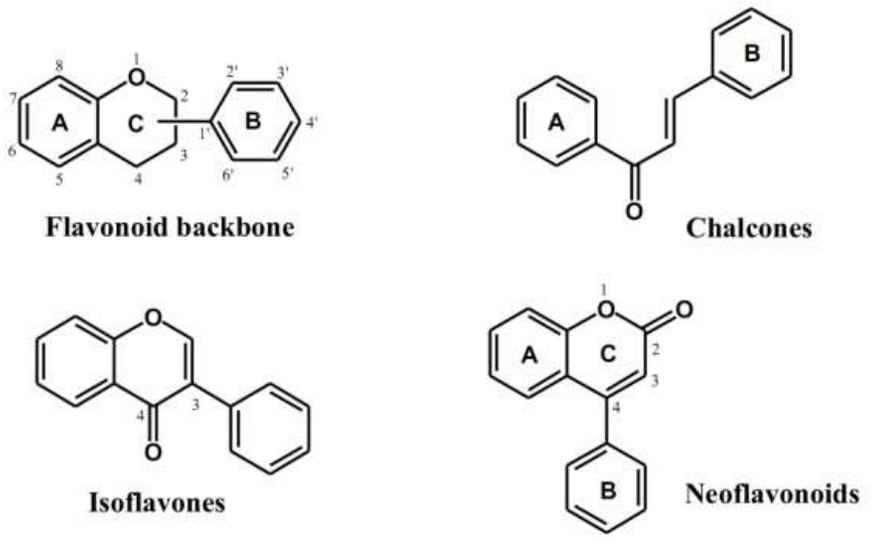

Figure 2. Flavonoid structures. Tsao R (2010).

The antioxidant activity of flavonoids has been demonstrated in many lipid systems. Therefore, they are speculated to have potential in atherosclerosis prevention [81]. The antioxidant capacity of flavonoids depends on both their structure and glycosylation pattern. *Cuminum cyminum* (CC), commonly known as Jeera, was found to contain 51.87% w/w **flavonoids**, which were proposed to be responsible for its antiglycation property. Researchers have shown that treatment of streptozotocin-diabetic rats with CC reduced the renal oxidative stress and AGEs accumulation by increasing the antioxidant defense and reducing the free radical induced lipid peroxidation. The antioxidant activity of superoxide dismutase, catalase and reduced glutathione, increased upon CC treatment. Further experiment revealed that the antihyperglycemic effect of CC may be due to protection of surviving pancreatic β cells, and increase in insulin secretion and glycogen storage [84].

Flavonoids are also abundant in honeys, and honeys rich in flavonoids, such as buckwheat honey, exhibited higher antioxidant activity than flavonoid-poorer honeys such as acacia honey [85]. Raw Millefiori honey, for example, is packed full of antioxidants [86-88]. In addition to the direct contribution to the radical scavenging activity, the polyphenolic content also influences the honey color. Conjugated systems of double bonds, such as those present in flavonoids, terpenes, isoprene units and long chain phenolic acids present in honey, constitute chromophores that absorb photons of visible light giving rise to colors

ranging from yellow to brown. Several reports point out the positive and highly significant correlation between honey color, phenolic content and antioxidant activity [85, 87, 88].

Chalcones, though lacking the heterocyclic Ring C, are still categorized as members of the flavonoid family [70]. The chalcone **butein** isolated from ethyl acetate fraction of *Rhus verniciflua* proved to be a potent inhibitor of Recombinant Human ALR2 (rhALR2) with an IC_{50} value of 0.7 μM. Butein also strongly inhibits the advanced glycation end products accumulation *in vitro*. It has been reported that the hydroxyl groups at the 3′-, 4′-, 5-, and 7-positions of flavones increase their AGE inhibitory activities, whereas the methylation or glycosylation of the 3′- or 4′-hydroxyl group reduces this activity [89]. In agreement with this report, the open ring form of 3-, 4-, 2′-, and 4′-tetrahydroxylated flavone, butein, has an increased AGE inhibitory activity. From these results the conclusion could be drawn that the inhibitory effect of *Rhus verniciflua*, and especially of the ethyl acetate fraction on rhALR2, is possibly exerted by butein acting as an active component.

In apple trees (*Malus domestica*), the major sub-family of flavonoids is represented by **dihydrochalcones**, which are found in large amounts (up to 5% of dry weight) in leaves and in immature fruits [90]. Among the known dihydrochalcones, **phloridzin** and its aglycone, **phloretin**, are simple forms [91] and their biosynthesis in Malus has been recently described [92]. Bernonville et al. (2010), demonstrated the presence of **phloridzin** alone or in combination with two additional dihydrochalcones, identified as **sieboldin** and **trilobatin** [60]. **Phloridzin** was shown to inhibit glucose intestinal absorption and renal resorption, resulting in normalization of blood glucose and overall diminution of glycaemia in animal models [93]. Based on the results of the antioxidant assays and the fact that **sieboldin** was several folds more efficient than **phloridzin** in inhibiting AGE formation (10-fold lower IC_{50} than phloridzin and 40-fold lower IC_{50} (0.2 mM) than AG), a role for **sieboldin** in inhibiting the formation of intermediate glycation products is suggestive [60].

Isoflavones

Isoflanones have their ring B attached to the C3 position of ring C. They are mostly found in the leguminous family of plants [70]. Soy products and soybeans are particularly abundant sources of **isoflavones** which have both antioxidant and phytoesterogenic activities that may contribute to their potential anticarcinogenic and cardioprotective effects [94-96]. High soybean consumption has been implicated in the longevity of the Japanese [97]. Genistein and daidzein are the two main isoflavones in soy along with glycetein, biochanin A and formononetin [98]. In 2009 Hsieh et al. reported that soy isoflavones supplementation significantly and dose-dependently decreased the concentration of protein carbonyls in the liver, kidney and brain in D-galactose treated mice. Soy isoflavones administration effectively attenuate oxidative damage and improve parameters related to aging and Alzheimer's disease [99].

Puerarin (daidzein-8-C-glucoside) is an isoflavone glycoside isolated from the root of *Pueraria lobata* and has various pharmacological effects, including anti-hyperglycemic and anti-allergic properties [100-102]. Additionally, puerarin has been reported to effectively

inhibit advanced glycation end products formation which is one of the typical risk factors for diabetic complications [103]. In 2010 Kim et al. reported that puerarin administration to mouse mesanglial cells increased heme oxygenase-1(HO-1) protein levels in a dose-dependent manner [104]. This enzyme participates in conversion of heme to biliverdin, which is rapidly metabolized to bilirubin, a potent antioxidant [105]. Moreover, puerarin treatment was able to enhance the phosphorylation of protein kinase C δ-subunit which primarily regulates the expression of HO-1, which in turn inhibited AGE-induced inflammation in mouse mesanglial cells.

Flavones, Flavonols, Flavanones and Flavanonoles

These flavonoid subgroups are the most common and almost ubiquitous throughout the plant kingdom. (Figure 3)

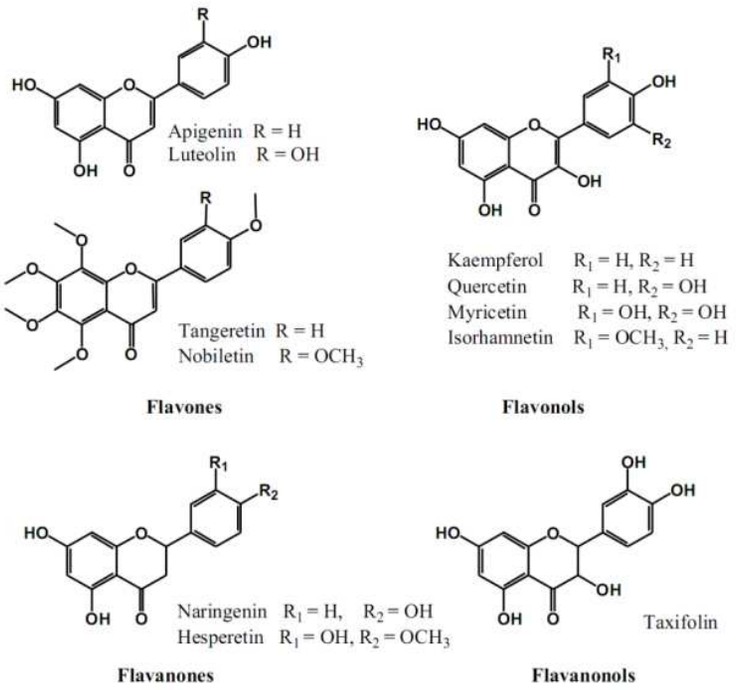

Figure 3. Flavones, Flavonols, Flavanones and Flavanonoles. Tsao R (2010).

Flavones and their 3-hydroxy derivatives flavonols, including their glycosides, methoxides, and other acylated products, make this the largest subgroup among all polyphenols [70]. The most common flavonol aglicones, *quercetin and kaemferol*, alone have at least 279 and 347 different combinations, respectively [106-108].

Kaempferol is a well known anti-oxidant flavonol aglycone that possesses anti-inflammatory properties resulting from its ability to diminish the formation of reactive species (RS) [109]. **Kaempferol** was detected in plant extracts of two *Chrysanthemum* species [42] and *Erigeron annuus* [110]. *Kaempferol* causes the inhibition of the inducible nitric oxide synthase and cyclooxygenase-2 and the down-regulation of NF-κB pathway [111]. In 2010 Kim et al. demonstrated that the short-term feeding of aged rats with kaempferol modulated

both AGE accumulation and RAGE expression which are dependent on NF-κB transcriptional activity. Furthermore, kaempferol suppressed age-related NF-κB activation and its pro-inflammatory genes through the suppression of AGE-induced NADPH oxidase activation [112]. **Quercetin** is another example of flavonol aglycone found in citrus fruit, buckwheat and onions. Many researchers examined the ability of *quercitrin* to protect against protein damage (AGEs formation) using *in vitro* model systems [77, 113]. Both *quercetin* and *kaempferol* together with *kaempferol-3-O-rutinoside* were reported as the main polyphenols present in crude extracts of aerial parts of *Cassia auriculata*. Ethyl acetate fraction of this medicinal plant showed radical scavenging activity and inhibition of lipid peroxidation. The guava leaves extracts also are a very good source of phenolic compounds such as *gallic acid, ferrulic acid, quercetin and quercetin derived glycosides*. The phenolic compounds of guava leaf extracts significantly decreased fasting blood glucose levels in streptozotocin-induced diabetic rats, decreased glycation products, lipid peroxidation and improved the antioxidant status in a dose-dependent manner [114]. Thus, the effect of guava leaves on glycation may be due to the different composition of the phenolic compounds. The latter also showed strong inhibitory effects on the glycation of albumin, especially quercetin exhibited over 95% inhibitory effect at a concentration of 100μg.ml^{-1}. The anti-glycation activity of the aqueous extracts of guava was higher than that of AG and green tea polyphenols [115]. More interestingly, flavonoids with the 3′,4′-dihydroxy group (i.e., **quercetin** and **quercitrin**) demonstrated the highest inhibitory activity against AGEs formation after incubation at 37°C for 14 days, with IC_{50} values much lower than that of AG [111]. Besides *quercetin*, the flavonoid glycosides *isoquercitrin* (quercetin-3-β-glucopyranoside) and *hyperin* (quercetin-3-D-galactoside) are well-known antioxidants [116-118]. *Isoquercitrin* showed outstanding antioxidant activity in yeast cells by increasing the activity of superoxide dismutase (SOD) [118]. It also demonstrated free radical scavenging properties [119]. Marzouk et al. (2006) reported that hyperin strongly inhibited the formation of 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radicals [117] and lipid peroxidation, as well as the hydroxyl radical and superoxide anion generation [120]. Also, hyperin inhibits lipopolysaccharide (LPS)-induced nitric oxide (NO) production [120]. It is worth mentioning that *isoquercitrin* and *hyperin* showed a dose-dependent inhibitory activity against the formation of AGEs which was stronger than that of the AG positive control. Thereby, hyperin demonstrated a greater effect by inhibiting AGEs formation by 92% as compared to isoquercitrin, which inhibited the accumulation of AGEs by 89.6%.

In 2011 Manaharan et al. reported the presence of **quercetin-3-O-β-D-galactopyranoside** in ethanolic extracts of *Peltophorum pterocarpum* leaves as the major bioactive compound. *Peltophorum pterocarpum* leaf and bark extracts were shown to inhibit aldose reductase far better than the pure compound quercetin [121]. The plant leaf and bark extracts were found to be about 28-fold and 56-fold more effective than quercetin, respectively in inhibiting aldose reductase which points to their potential use in hyperglycemia treatment. Also, the HPLC profiles of the active ethyl acetate fraction from *Nelumbo nucifera* leaves indicated the presence of **quercetin 3-O-b-D-glucopyranoside** and **quercetin 3-O-b-D-**

glucuronopyranoside. In terms of *N. nucifera's* antioxidant effect, the leaf extract exhibited potent antioxidant capacities in the DPPH and total ROS assay. The leaf extracts also showed remarkable inhibitory activities on RLAR and AGE formation [35].

Quercetin-3-O-rutinoside (Rutin), a common dietary flavonoid is an established antioxidant. It is found in fruits, vegetables and plant-derived beverages such as tea and wine [122]. Gut microflora in the large intestine metabolize rutin to a variety of compounds that include *quercetin* and phenol derivatives such as 3,4-dihydroxyphenylacetic acid (DHPAA), 3,4-dihydroxytoluene (DHT), 3-hydroxyphenylacetic acid (HPAA), and 4-hydroxy-3-methoxyphenylacetic acid (homovanillic acid, HVA) [122-124]. Rutin metabolites, particularly those that include vicinal hydroxyl groups in their structure such as 3,4-dihydroxyphenylacetic acid (DHPAA) and 3,4-dihydroxytoluene (DHT), are powerful inhibitors of the formation of CML and fluorescent derivatives (370-440 nm and 335-385 nm) in histone H1 caused by ADP-ribose. The plasma concentrations of these rutin metabolites are expected to effectively neutralize the reported plasma concentrations of glyoxal and methylglyoxal [125]. Rutin was also found to inhibit the formation of glycation products in collagen type I induced by glucose *in vitro* [126] and to be an effective inhibitor of lipoprotein glycation by increasing the resistance of LDL to HG/Cu (II)-mediated oxidation [127].

In 2009 Tsuji-Naito et al. reported that **apigenin** (*4',5, 7-trihydroxyflavone*) in *C. indicum* L. is a minor flavonoid aglycone, although *apigenin* in *C. morifolium* R. is the main component of the plant extract which inhibits AGEs accumulation. Large amounts of another flavone – **luteolin** (*2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-chromenone)* were found in *C. indicum* L [42]. A**pigenin**, **luteolin**, **apigenin-7-O- β -D-glucuronide methyl ester** and **apigenin-7-O- β -D-glucuronide** were indentified in the ethyl acetate-soluble extract of flowers of *Erigeron annuus* [110]. This is the first report on apigenin-7-*O*-*β*-D-glucuronide and apigenin-7-*O*-*β*-D-glucuronide methyl ester having significant inhibitory activity towards aldose reductase and AGEs formation, which makes it worth to further study their potential for treatment of diabetic complications. The presence of *luteolin* together with *maysin* was also reported in the silk of *Zea mays*. These flavonoids are abundant in corn silk and *in vitro* glycation studies demonstrated their role in inhibiting AGE formation with **luteolin** being exceptionally active [61].

Hispidulin is a flavone compound from *Artemisia campestris ssp*. glutinosa [128], while **vitexin** (*apigenin-8-C-glucoside*) and **isovitexin (***apigenin-6-C-glucoside*) are flavone C-glucosides, which have been identified in mung bean extract. The use of *A. campestris* has been recommended in Tunisian folk medicine for their antivenom [129], anti-inflammatory, antirheumatic and antimicrobial activities [130]. Recent studies provide for the first time data on the effect of an ethyl-acetate fraction from *A. capillaries* on the oxidative stress and antioxidant enzymes in high-fat diet induced obese and type 2 diabetic mice [131]. In 2010 Sefi et al. demonstrated that administration of an aqueous extract of *A. campestris* to diabetic rats increased significantly serum insulin levels, reduced serum glucose level by 60% ($p < 0.001$) and tended to bring the glucose value to near normal after 21 days. The ability of *A. campestris* extracts to reduce the blood glucose level could be attributed to a stimulation of

langerhans islets, to an improvement of the peripheral sensitivity to remnant insulin, and to the strong antioxidant properties of the plant compounds [132].

Vitexin and isovitexin have been identified in other plants, such as bamboo leaves [133] and pigeonpea leaves [134]. Their anti-glycation activity could be attributed to their free radical scavenging and/or metal ion trapping activities, as they failed to directly trap reactive carbonyl species, such as methylglyoxal [64].

The number of **flavanones**, and their **3-hydroxy derivatives (flavanonols, which are also referred to as dihydroflavonols)** identified in the last 15 years has significantly increased. Some **flavanones** have unique substitution patterns, e.g., prenylated flavanones, furanoflavanones, pyranoflavanones, benzylated flavanones, giving a large number of substituted derivatives of this subgroup [135]. A new compound that was designated as **4`-O-[β -D-apiosyl (1→2)] - β -D-glucopyranosyl] - 5-hydroxyl-7-O-sinapylflavanone** was isolated from *Viscum album* (European Mistletoe). This compound together with previously identified compounds in *V. album*, **5,7-dimethoxy-4`-O-β -D-glucopyranoside flavanone, 4`,5-dimethoxy-7-hydroxy flavanone** and **5,7-dimethoxy-4`-hydroxy flavanone**, showed a potent anti-glycation activity, *i.e.* 72.5% (IC_{50} = 199.85 ± 0.067 mM) as well as superoxide anion scavenging capacity. The antioxidant potential of **4`,5-dimethoxy-7-hydroxy flavanone** (IC_{50} = 58.36 ± 2.9m M) was determined to be greater than that of *rutin* used as a standard [41]. Recently, Jang et al. (2010) isolated from the flowers of *E. annuus* a novel **2,3-dioxygenated flavanone**, **erigeroflavanone**, which was also shown to possess a strong anti–AGE activity [110]. In addition, the presence of **fustin** (2-(3, 4-dihydroxyphenyl)-3,7-dihydroxy-2,3-dihydrochromen-4-one), a flavanonol together with quercetin, morin (flavonol), and butein was reported in an ethyl-acetate fraction of *Rhus verniciflua*. All these flavonoids, especially those with hydroxyl groups at the 3′-,4′-,5′-, and 7-positions have shown a significant inhibitory activity against AGE in *in vitro* experiments [77].

In 2007 two **dihydroflavonol glycoside, engeletin** and **astilbin**, were isolated from an ethyl acetate extract of the leaves of *Stelechocarpus cauliflorus* R.E. Fr. The inhibitory activity of **engeletin** against a recombinant human aldose reductase (IC_{50} value = 1.16 μM) was twice that of **quercetin** used as a positive control (2.48 μM), and 23 times greater than that of **astilbin** (26.7 μM). **Engeletin** was shown to inhibit the aldose reductase uncompetitively. On the other hand, in contrast to its inhibitory activity against AR, **astilbin** was more potent than **engeletin** in suppressing AGE formation. Moreover**, astilbin** was almost as potent as the positive control, quercetin, in inhibiting advanced glycation end-products accumulation. Interestingly, the only structural difference between **engeletin** and **astilbin** is the number of hydroxyl groups in the B ring. Of both compounds only **astilbin** has the catechol orientation. Both **astilbin** and **taxifolin (2, 3-dihydro quercetin)**, its aglycone, have been demonstrated to protect against oxidative damage [136]. Therefore, the antioxidant flavonoids such as **engeletin** and **astilbin** are potentially useful for therapeutic prevention of diabetic complications resulting from AGEs accumulation [137].

Flavanols and procyanidins

Flavanols or flavan-3-ols are often called catechins (Figure 4). They differ from most flavonoids in that they do not have a double bond between C2 and C3, and there is no C4 carbonyl in ring C [70]

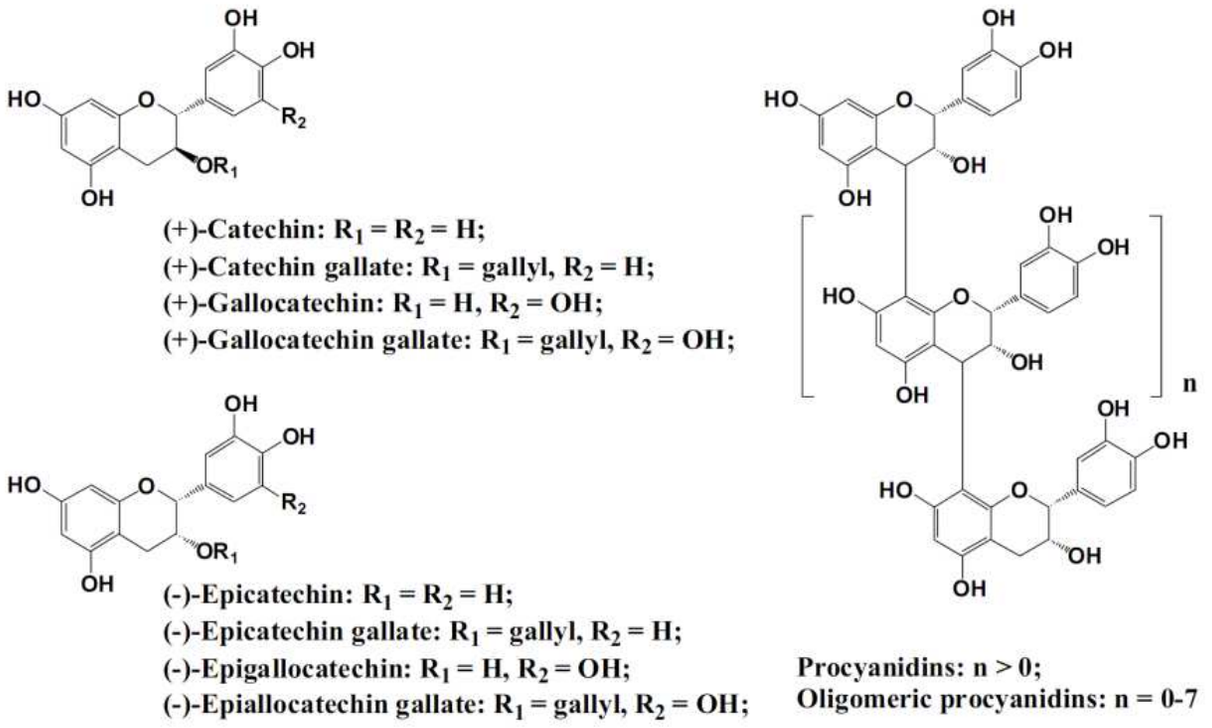

Figure 4. Flavanols and procyanidins. Tsao R (2010).

Catechin is the isomer with *trans* configuration and **epicatechin** is the one with *cis* configuration. Each of these two configurations has two steroisomers, *i.e.*, **(+)-catechin, (–)-catechin, (+)-epicatechin and (–)-epicatechin. (+)-Catechin and (–)-epicatechin** are the two isomers often found in food plants. Catechin and epicatechin can form polymers, which are often referred to as **proanthocyanidins** because an acid-catalyzed cleavage of the polymeric chains produces **anthocyanidins** [70]. The presence of **catechins** was reported in green tea, which is an excellent source of many polyphenol antioxidants [49]. The most important catechins of green tea are **(-)-epicatechin (EC), (-)-epicatechin- 3-gallate (ECG), (-)-epigallocatechin (EGC) and (-)-epigallocatechin-3-gallate (EGCG)** [138]. Nearly 80% of the extract of green tea is a mixture of **catechins** namely **epigallocatechin** (**EGC), epicatechin (EC), epigallocatechin-3-gallate (EGCG)** and **epicatechin-3-gallate (ECG)**. The sum of **EGC** and **EGCG** weighed more than 70% of the catechin mixture in the green tea extract [49]. It was shown that green tea treatment of diabetic rats significantly reduced the blood glucose level. This antihyperglycemic effect may be linked to enhanced basal and insulin-stimulated glucose uptake in rat adipocytes [139], inhibition of the intestinal glucose transporter [140], and decreased expression of genes that control gluconeogenesis [141]. Green tea supplementation also reduced the accumulation of AGEs in diabetic rats as indicated by

decreased collagen linked fluorescence [49]. In 2009 Rasheed et al. reported that EGCG significantly decreased AGE-stimulated gene expression and the production of TNFα and matrix metalloproteinase-13 (MMP-13) in human chondrocytes. The inhibitory effect of EGCG on the AGE-BSA-induced expression of TNFα and MMP-13 was mediated at least in part *via* suppression of p38-MAPK and activation of JNK. In addition, EGCG inhibited the phosphorylating activity of IKKβ kinase in an *in vitro* assay and also the AGE-mediated activation and DNA binding activity of NF-κB by suppressing the degradation of its inhibitory protein IκBα in the cytoplasm [142]. EGCG has also been shown to prevent intracellular AGEs formation and the production of proinflammatory cytokines in monocytes under hyperglycemic conditions [143]. EGCG is capable of trapping reactive dicarbonyl species, such as methylglyoxal and glyoxal, as demonstrated by Ho and coworkers in 2007 [144]. Data from HPLC-DAD demonstrated that EGCG was able to bind lipoproteins and to enhance the antioxidant and antiglycation properties of LDL [145].

Proanthocyanidins are traditionally considered to be condensed tannins and depending on the interflavanic linkages, oligomeric proanthocyanidins can have A-type structure in which monomers are linked through C2–*O*–C7 or C2–*O*–C5 bonding, or B-type in which C4–C6 or C4–C8 bonds are common (Figure 4) [70]. *Catechin and epicatechin procyanidin B2 (a dimer-type proanthocyanidin*) isolated from cinnamon bark extract have been shown to possess a significant MGO trapping activitiy, with *procyanidin B2* demonstrating the strongest inhibition of AGE formation among *proanthocyanidins* isolated from cinnamon bark [146]. All these flavonoids potently inhibited (more than 50%) the formation of pentosidine and CML [147] with *procyanidin B2* showing the highest inhibition capacity (almost 80%) on the CML formation. **Proanthocyanidins** could further abate the MGO mediated formation of cross-links in creatine kinase in a dose-dependent manner. They also exerted various protective effects on glucose consumption impaired by high MGO concentrations through potential interaction with proteins involved in insulin signaling pathways [147]. **Proanthocyanidin B-4** and two more **nitrogen containing flavonoids** were identified for the first time in *Actinidia arguta* [148]. The N-containing flavonoids comprise a very small class of natural products, which have been only rarely isolated from natural sources. The ^{1}H- and ^{13}C-NMR spectral data revealed that these newly isolated compounds are **6- and 8-(2- pyrrolidinone-5-yl)-(-)-epicatechins,** which may be produced by condensation between (-)-epicatechin and 5-hydroxypyrrolidin-2-one under acidic conditions. **Proanthocyanidin B-4** and the two novel compounds showed a significant activity against AGEs formation with IC_{50} values for **proanthocyanidin B-4** of 10.1 μM, which is lower than that of the well known glycation inhibitor AG [148].

Geraniin, an **ellagitannin**, is the major **tannin** in *Geranium thunbergii*. It was also identified as the major bioactive compound in an ethanolic *Nephelium lappaceum* L. rind extract [149]. Previous studies have shown that *N. lappaceum* rind extract exhibits high anti-oxidant activity [150]. In 2011 Palanisamy et al. reported the ability of *geraniin* to scavenge free radicals and to possess *in vitro* hypoglycemic activity [149]. *Geraniin* is also an excellent inhibitor of carbohydrate hydrolysing enzymes (α-glucosidase and α-amylase) – superior to

the positive control acarbose (carbohydrate hydrolysis inhibitor). It was far more effective in preventing polyol and advanced glycation endproducts formation as compared to the positive controls quercetin and green tea which reveals geraniin as an ideal candidate for the management of hyperglycemia in diabetic individuals [149].

4. Other phenolic compounds

A stilbene glucoside - *2,3,5,4'-tetrahydroxystilbene 2-O-β-D-glucoside (THSG*) is a natural compound with strong antioxidative and anti-inflammatory properties, which has been reported as the major bioactive compound from *Polygonum multiflorum* Thunb., a traditional Chinese herbal tea [151,152]. It was shown to efficiently inhibit the formation of AGEs in a dose-dependent manner by trapping reactive MGO under physiological conditions (pH 7.4, 37°C) [153]. More than 60% of MGO was trapped by THSG within 24 hours and THSG was much more effective than resveratrol and its methylated derivative pterostilbene (two major bioactive stilbenes) [153]. In 2011 **Chompoo et al.** isolated two previously described compounds from *Alpinia zerumbet*, namely **5,6-dehydrokawain (DK)** and **dihydro-5,6-dehydrokawain (DDK)** which are kawalactones. DK and DDK were present in all six different parts of the plant but rhizomes had higher inhibitory activity against AGEs formation than the other parts [154]. A previous study also provided data about the antioxidant acitivities of DDK present in leaves and rhizomes of *A. zerumbet* [155]. Among the compounds isolated from *Alpinia zerumbet* rhizomes, DK had the strongest inhibitory activity against BSA glycation with IC_{50} value of 15.9 μM. DK has been also shown to inhibit human platelet aggregation and to possess anti-inflamatory and cancer chemoprotective therapeutic properties [156].

5. Terpenes, carotenoids and polyunsaturated fatty acids

A terpene, 8(17),12-Labdadiene-15,16-dial (labdadiene) was isolated for the first time from the rhizome of *Alpinia zerumbet* together with **5,6-dehydrokawain (DK)** and **dihydro-5,6-dehydrokawain (DDK**) [154]. In contrast to DK which strongly inhibited AGEs formation in BSA **labdadiene** markedly suppressed the fructosamine adduct formation with IC_{50} = 51.1 μg/mL. **Labdadiene** was also more efficient than DK in inhibiting glycation-induced protein oxidation and the formation of α-dicarbonyl compounds, at first place preventing glyoxal accumulation. It is possible that the aldehyde groups of labdadiene have a significant role in inhibiting AGEs formation. These aldehyde groups may compete with sugars for Schiff's bases formation and/or limit the amount of amines available for glucose attachment. The fructosamine assay revealed that **labdadiene** has strong activity when compared to **rutin** and **quercetin** used as positive controls, although the inhibitory mechanism of **labdadiene** is likely to differ from that of **rutin** and **quercetin** [154].

The ability of microalgal extracts to inhibit AGEs formation differs from that of many other plant species and is not promoted by phenolic compounds. There is a weak correlation between the antiglycative activity and the total phenolic content of several microalgae as

demonstrated by the very small correlation coefficient. For example, in total AGEs inhibition, the value of R^2 was 0.035 for ethyl acetate fractions of green microalgae *Chlorella* [45]. In microalgae, a wide range of antioxidants can be produced such as **carotenoids, polyunsaturated fatty acids** and **polysaccharides** [157]. HPLC and gas chromatography (GC) analysis revealed that **carotenoids,** especially **lutein** in *Chlorella* and **unsaturated fatty acids**, mainly of **linoleic acid, arachidonic acid** and **eicosapentaenoic acid** in *Nitzschia laevis* contributed to the strong antiglycative capacities of these species [45]. The green microalga *Chlorella zofingiensis* accumulates primary carotenoids such as **lutein** and **β-carotene** to protect the cells from oxidative damage [158]. Results showed that **lutein** and some **unsaturated fatty acids** effectively inhibited the formation of both total AGEs and specific AGEs *in vitro* in a dose-dependent manner. For **lutein**, at the concentration of 0.8 $mg.ml^{-1}$, the inhibitory efficacy was comparable to or even higher than the effect of 1 mM AG solution [45]. It is noteworthy that if the amount of primary carotenoids is not enough, secondary carotenoids (i.e. **astaxanthin, canthaxanthin and adonixanthin**) are generated to diminish the excessive oxidative stress. The green microalga *Chlorella zofingiensis* is known as a natural source of **astaxanthin,** a red ketocarotenoid that is a potent anti-oxidant. It acts as the major secondary carotenoid and over 90% of the **astaxanthin** is in the form of mono- and di-esters [158]. The antioxidant activity of **astaxanthin** is an order of magnitude higher than that of other carotenoids such as zeaxanthin, **lutein**, canthaxanthin and β-carotene, and 100 times higher than the antioxidant activity of a-tocopherol [159]. It was shown that under heterotrophic conditions the colour of *C. zofingiensis* gradually changed from green to red, indicating the accumulation of astaxanthin within algal cells. *C. zofingiensis* extracts and especially the red one are suggested to scavenge hydroxyl radicals and/or to chelate transition metals. Seven major fractions were obtained from astaxanthin-rich extract of *C. zofingiensis*. HPLC results revealed that they are astaxanthin diester, astaxanthin monoester, adonixanthin ester, free astaxanthin, free adonixanthin, lutein and zeaxanthin, and neoxanthin. The **astaxanthin diester** was found to be the most potent antiglycative compound among all fractions [46].

Several unsaturated fatty acids showed inhibitory activity against AGEs formation. Although palmitoleic and oleic acid were involved in the inhibition of pentosidine formation, the main contributors were linoleic acid, arachidonic acid, and eicosapentaenoic acid [45].

Hydrophobic compounds which also display antioxidant and hypoglycemic activities, such as oleanolic and ursolic acid, were observed in non-polar extracts from medicinal herbs [160]. Ursolic acid and its isomer, oleanolic acid, are triterpenoid compounds found across the vegetal kingdom that have anti-inflammatory, anti-arthritic, cytostatic, antiproliferative, and hepato-protective effects in mice, as well as membrane stabilizing properties [161-163]. One of the major components of yerba maté (*Ilex paraguariensis*) is oleanolic acid (OA) [65]. It has been reported that oleanolic acid has hypoglycemic and hypolipidemic effects in diabetic rats [164]. Oleanolic acid or ursolic acid (UA) intake at 0.1 or 0.2% increased the content of both acids in the kidney, dose-dependently decreased plasma glucose, HbA1c, renal N^{ε}-(carboxymethyl)lysine, urinary glycated albumin and urinary albumin levels. OA

or UA intake significantly reduced renal pentosidine and decreased AR activity. The triterpens have been shown also to elevate plasma insulin levels and renal creatinine clearance as well as to decrease renal sorbitol and fructose concentrations [55].

Arjunolic acid (2,3,23-trihydroxyolean-12-en-28-oic acid, AA), a natural pentacyclic triterpenoid saponin isolated from the bark of *Terminalia arjuna*, is well known to display various biological functions, including antioxidative [165], antifungal [166], hepatoprotective [167], and antibacterial activities [168]. AA plays a protective role against hepatotoxicity induced by environmental toxins such as drugs and chemicals. AA was shown to be effective in preventing the formation of reactive oxygen species (ROS), reactive nitrogen species (RNS), HbA1c, AGEs, and oxidative stress signaling cascades. AA also has been reported to protect against poly (ADP-ribose) polymerase (PARP)-mediated DNA fragmentation. Treatment with AA both before and after diabetes, on the other hand, prevented the NO signaling pathways and thereby brought the affected organs back to their physiological state. AA treatment was effective in preventing the phosphorylation of IκBα and NF-κB p65. Aslo, treatment with AA could prevent the hyperglycemia-induced phosphorylation of extracellular signal-regulated kinase (ERK) and p38. It was observed that the antidiabetic as well as antioxidant properties of AA were comparable to those of insulin [56].

6. Polysaccharides

In recent years a lot of attention has been paid to **polysaccharides** because of their unique biological activities [169]. Yang et al. (2009) have confirmed the presence of high quantity of polysaccharides in longan pericarp tissues (*Dimocarpus longan* Lour.) Polysaccharides of longan fruit pericarp (PLFP) have been found to be strong radical scavengers [170]. It is hypothesized that there is a link between the antioxidant and anti-glycative properties of PLFP. On the other hand, polysaccharides are composed of monosaccharides, which can compete with glucose for binding free amino groups in proteins thus lowering the effective concentration of glycation targets in proteins. This might be another pathway in which PLFP inhibits the formation of advanced glycation end products [44]. Moreover, it has been found that the molecular weight of the polysaccharide chain and the antioxidant activity of PLFP can be modified by ultrasonic treatment [44].

In 2009 Chen et al. reported on the ability of *Ganoderma lucidum* **polysaccharides** (GLP) to reduce lipid peroxidation and blood glucose levels in diabetic rats [171]. Administration of middle or high doses of GLP in diabetic mice significantly decreased blood glucose and HbA_{1c} [43]. Blood cholesterol and triglyceride levels were also improved which could be ascribed to the reduced blood glucose levels [172]. GLP administration to diabetic rats further influenced the myocardial hydroxyproline as well as the soluble and insoluble myocardial collagen. After 16-week treatment of diabetic mice with GLP, the cross-linked and non-cross-linked collagens tended to decrease. The AGEs formation was also significantly reduced upon GLP treatment. In addition, the activities of antioxidant enzymes such as SOD, GSH-Px, and CAT from streptozotocin-treated diabetic rats were significantly enhanced after GLP administration [43]. Another study showed that all **polysaccharides from pumpkin** *(Cucurbita moschata)* (PPs)

inhibited the formation of dicarbonyl compounds. Two of the ethanolic fractions isolated from *pumpkin*, PPIII and PPII, were proposed to be stronger inhibitors than AG. PPIII was shown to have 65% inhibitory effect at a concentration of 50μM. PPs also inhibited the aldose reductase in a dose-dependent manner [57]. Least but not last, the anti-glycative activity of PPs increased with a decrease in their molecular weight.

7. Other anti-glycative compouds

The major biochemical constituents of *Withania somnifera* roots are steroidal alkaloids and steroidal lactones from the class called **withanolides** [173]. To date, up to 19 **withanolide derivatives** have been isolated from *Withania* roots [174]. Recently, *Withania* and its active components were shown to scavenge free radicals and to inhibit lipid peroxydation [175]. *Withania* have been reported to suppress AGE linked fluorescence of rat's tail tendon collagen, which was explained by its antioxidant and free radical scavenging effect [176].

Melanoidins are another class of antioxidants receiving attention in recent years. These polymeric brown compounds formed in the last stage of the Maillard reaction were supposed to be involved in the color and flavor development of thermally-processed foods. They are present in food and beverages such as coffee, beer, traditional balsamic vinegar, cocoa and bread [177-179]. It seems that during coffee roasting phenolic compounds are involved in the Maillard reaction to partially form the brown, water soluble polymers known as coffee melanoidins. Physiological studies indicated that some of the coffee effects arise not from caffeine but from melanoidins [51, 180]. The high molecular weight compound (HMWC) fraction of coffee was shown to inhibit BSA glycation by acting as radical scavenger and Fe-chelator in the post-Amadori phase of the reaction and by inhibiting the production of dicarbonyl reactive compounds during glucose autoxidation [51]. Verzelloni et al. (2011) noted that this fraction is rich in melanoidins and concluded that melanoidins could be mainly responsible for the anti-glycative activity of the HMWC fraction. Also, the presence of proteins and chlorogenic acids, incorporated in the melanoidins' structure, has been reported [51].

Interestingly, the total phenolic content and honey color are predictive markers of the antioxidant activity in honey [85]. The radical-scavenging activity of honey was higher in honeys with high phenolic content and of darker color [181]. On the other hand, the color of honey may also result from non-enzymatic browning (the Maillard reaction) [182]. The brown, carbohydrates based melanoidin polymers have been shown to possess strong antioxidant activity [183]. It is thought that one of the possible mechanisms by which MRPs may act as both antioxidants and antibacterial agents, is their metal-chelating activitiy [184].

In 2010 Ye et al. uncovered the inhibitory effect of **fermentation byproducts** on AGE formation [185]. Japanese distilled spirit can be prepared from starchy substances, such as rice, barley and sweet potato. Recycled distilled residues (DRs) of rice and barley spirit as well as their vinegars inhibited the formation of N^{ε}(carboxymethyl)lysine (CML), a major

AGE in BSA model system. The high protein levels together with free lysines and arginines present in DRs of rice and barley spirits raise the possibility that these proteinaceous ingredients inhibit AGEs formation by competing with BSA for the glycation reaction. However, the low protein content in DRs of sweet potato spirit, which is accompanied by strong anti-glycation activity, argues against the above suggestion. Distilled residues and their derived vinegars are extremely complex mixtures containing caffeic acid as the dominant phenolic constituent and hence further investigations are required to elucidate the anti-glycative mechanism of DRs [185].

Vitamins and some trace elements such as zinc and selenium are also a part of the human antioxidant defence system which must be delivered by diet. For example, treatment with vitamin E prevents renal hypertrophy in streptozotocin diabetic rats [186]. Similarly, a combination of vitamins E and C administered for 12 weeks decreased lipid peroxidation and augmented the activities of antioxidant enzymes in the kidneys of stretozotocin diabetic rats. The treatment also reduced urinary albumin excretion, decreased kidney weight and reduced the thickness of the glomerular basement membrane [187]. Tocotrienol, a component of vitamin E that may accumulate more effectively in membranes than α-tocopherol [188], was shown to ameliorate experimental nephropathy in STZ-diabetic rats [189]. Pyridoxamine (PM), one of three natural forms of vitamin B_6, was also reported to inhibit the Maillard reaction and PM application in diabetic nephropathy has now progressed to a phase III clinical trials. PM inhibits post-Amadori steps of the Maillard reaction by sequestering catalytic metal ions and blocking the oxidative degradation of Amadori intermediates [190]. Besides vitamin E and PM, ***α*-lipoic acid** (ALA) also possesses a strong antioxidant properties [191]. In rat soleus muscle, inhibition of glycogen synthesis and acceleration of glucose oxidation, have been correlated with the uncoupling effect of this acid. Thus, ALA may regulate glucose metabolism in muscles in a way which does not mimic the action of insulin. It has been reported that after long-term incubation in cell culture, ALA behaves as an antioxidant, whereas after short-term incubation and quick uptake by cultured cells it may act as a pro-oxidant. By acting as an antioxidant, ALA reduces oxidative stress and the formation of AGEs and improves insulin sensitivity in skeletal muscles and liver.

Recently, the effect of citric acid on the pathogenesis of diabetic complications has been reported. Citrate, a natural, dietary chelator found in citrus fruits [192], is widely used in food products as a preservative and to enhance tartness. Oral administration of citric acid to diabetic rats delayed the development of cataracts, inhibited the accumulation of AGEs such as N^{ε}-(carboxyethyl) lysine (CEL) and CML in lens proteins. Citric acid also inhibited the development of nephropathy (albuminuria) and significantly reduced ketonemia in diabetic rats [193]. On the other hand, the administration of citric acid did not affect blood glucose or HbA_{1c} but decreased the concentration of AGEs in lens. Since citrate did not directly inhibit the formation of CEL from acetol, most probably the inhibition of CEL formation by citric acid is secondary to the inhibition of ketogenesis.

AGEs and carbonyl accumulation have been shown to decrease in Zn-co-incubated samples containing BSA and glucose [194]. Zn also inhibited glycation and β-aggregation in BSA-

containing samples. It has been suggested that during the glycation reaction, Zn prevented the β-sheet formation in albumin by promoting the native α-sheet conformation. The protection of thiol groups, which has been observed in Zn-containing samples, could be explained through one of the following three mechanisms: (1) direct binding of Zn to the thiols, (2) steric hindrance as a result of binding to other protein sites in close proximity to the thiol group or (3) a conformational change resulting from binding to another site on the protein [195].

8. Conclusion

Considering that AGEs are believed to act as major pathogenic propagators in many human diseases, and especially in diabetes and its complications, it is of great interest to identify anti-glycative substances and to examine their mode of action. The current review provides examples for the anti-glycation activity of plant-derived substances which target the essential stages of glycation through i) antiglycemic or hypoglycemic action, ii) inhibition of Amadori products formation or intervention in the post-Amadori phase of the reaction, iii) inhibition of the formation of AGEs precursors (oxidation products of sugars and early MRPs), and iv) reduction of AGEs cross-linking. This anti-glycation activity correlates with the phenolic content of the plant extracts although there is a wide range of others, nonphenolic compounds such as terpens, carotenoids, polyunsaturated fatty acids, polysaccharides, withanolides, and melanoidins which demonstrate a high potential to reduce the non-enzymatic protein glycosylation. The plant-derived anti-glycative comounds appear attractive candidates for the development of new generation therapeutics for treatment of diabetic complications and prophylaxis of aging, and point to the importance of an antioxidant-rich diet, as part of the overall diabetes management strategy.

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