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## Review article

## Anti-glycative potential of triterpenes: A mini-review

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## ARTICLE INFO

## Article history:

Received 1 September 2011

Received in revised form

31 October 2011

Accepted 1 November 2011

Available online 2 February 2012

## Keywords:

advanced glycation end-products

chronic diseases

glycation

triterpenes

## ABSTRACT

Triterpene compounds occur naturally in many herbs and plant foods. Triterpenes such as ursolic, oleanolic, and betulinic acid definitely possess antioxidative and anti-inflammatory activities as well as an inhibitory effect on advanced glycation end-product (AGE) formation. Furthermore, the effects of triterpenes upon the activity and expression of aldose reductase, sorbitol dehydrogenase, and glyoxalase I, enzymes involved in the polyol pathway, have been examined, with positive results reported. These studies indicate triterpenes as potent antiglycative agents, suggesting that they can benefit the prevention of and/or therapy for glycation-related diseases such as diabetes mellitus and Alzheimer's disease. Further studies should examine their impact on receptors of AGE (RAGEs) and AGE–RAGE interaction in order to bolster the antiglycative application of these natural compounds.

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## 1. Introduction

Glycative stress from excessive production of advanced glycation end-products (AGEs) is an important contributor for the pathogenesis of several diseases such as diabetes. Several enzymes are involved in the process of AGEs formation. Thus, any agent(s) with the ability to inhibit AGE generation, and decline the activity of responsible enzyme(s) may potentially prevent or attenuate glycation stress and retard the development of associated diseases.

## 2. Triterpenes

Triterpenes are originally synthesized by plants as metabolites, and are abundant in the plant kingdom in the form of free acids or aglycones [1,2]. So far, both the structure and the

chemical characteristics of at least 80 distinct types have been identified, many triterpenes having been long used as flavors, pigments, polymers, fibers, glues, and waxes. In many Asian countries, some serve formal medical purposes (including folk medicine) to prevent or treat a variety of diseases [3,4]. Recent decades have seen more attention paid to the bioactivities of triterpenoids, earning them consideration as important sources of medications and/or complementary medicines.

According to their structural traits, triterpenes are grouped into euphanes, taraxanes, oleananes, lupaneps, ursanes and baccharanes, with ursanes and oleananes as the major triterpene skeletons in higher plants, including many herbs or plant foods we regularly consume [5,6]. In plant foods, common ursane- and oleanane-type triterpenoids are pentacyclic triterpenes: oleanolic acid, ursolic acid, maslinic acid, uvaol, and erythrodiol. Other groups of triterpenes occur widely in edible or inedible plants.

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Although the content of these pentacyclic triterpenes in edible plants depends on the species, season, and conditions of cultivation, these triterpenes has been reported to be present in herbs such ground ivy (*Glechoma hederacea*), plantain (*Plantago major* L.), thyme (*Thymus vulgaris*), glossy privet (*Ligustrum lucidum* Fructus), and hawthorn fruit (*Crataegi Pinnatifidae* Fructus); fresh fruits such as apple (*Malus domestica* Borkh), blueberry (*Vaccinium dunalianum*), guava (*Psidium guajava*), persimmon (*Diospyros kaki* L.), and loquat (*Eriobotrya japonica*); and vegetables such as olive (*Olea europaea* L.), daylily (*Hemerocallis fulva* L.), spinach (*Spinacia oleracea* L.), and leaf mustard (*Brassica juncea*) [7–9].

Since the consumption of vegetables and fruit is always encouraged in order to improve their health, ever more interest has been raised in understanding the contribution of these special plant food component(s) to health. Therefore, exploring and elucidating the bioactivity and mode of action of triterpenes merits our attention.

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### 3. Bioactivities of triterpenes

Some studies report such compounds as possessing *in vitro* and/or *in vivo* vasodilatory effects [10,11] and anti-inflammatory, antioxidative, and anticancer activities, suggesting that they are potent agents for preventing and/or attenuating disease.

#### 3.1. Anti-oxidative effects

The overproduction of reactive oxygen species (ROSs) and reactive nitrogen species such as the superoxide anion ( $O_2^{\cdot-}$ ), hydrogen peroxide, the hydroxyl radical, or nitric oxide has been considered to be a crucial contributor to the development and progression of chronic diseases associated with oxidative stress, e.g., aging, diabetes mellitus, cancer, atherosclerosis, infection, cirrhosis, and Parkinsonism [12–14].

It is widely known that these ROSs and reactive nitrogen species can, via their free radical property, directly attach to the cell apparatus, or can, by acting as signal transduction mediators, regulate the expression of genes involved in cell differentiation and/or apoptosis. This, in turn, evokes oxidative injury, impairs the antioxidative defense system, and causes organ malfunction [15–17]. These free radicals can mediate the gene expression associated with the local or systemic immune system, which subsequently promotes inflammatory reactions and causes inflammatory damage [18,19]. Many *in vitro* and *in vivo* studies highlight the fact that triterpenes possess antioxidative activity via scavenging free radicals, enhancing the activities of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione S-transferase, while sparing nonenzymatic antioxidants such as reduced glutathione, ascorbic acid, and alpha-tocopherol [20–22].

Taken together, the above pieces of evidence supports the fact that triterpenes, through attenuating oxidative stress, retard the development and/or delay the progression of chronic diseases. However, human and even clinical studies are required to further confirm the antioxidative protection bestowed by these triterpenes.

#### 3.2. Anti-inflammatory effect

Inflammation is a normal process whereby the body wards off invaders and repairs tissue damage. Many T-helper cell type 1 and 2 cytokines and chemokines such as interleukin 1-beta (IL-1 $\beta$ ), IL-6, IL-10, tumor necrosis factor alpha (TNF- $\alpha$ ), monocyte chemoattractant protein 1 (MCP-1), and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), are essential for the host immune/defense system to protect against stimuli such as pathogens and chemical agents [23–25].

However, as seen in pathological situations such as diabetes mellitus, cancer, and cardiovascular disease, the overproduction of certain inflammatory molecules leads to cytokine imbalance, evokes inflammatory injury, or even causes tissue destruction. In addition, these cytokines and chemokines can activate macrophages and/or mediate factors involved in pathological processes, which in turn favors the development of acute and chronic disease. For example, IL-8 promotes angiogenesis and transforming growth factor beta-1 (TGF- $\beta$ 1) and enhances fibrosis in cancer [26,27]. The use of appropriate agent(s) with an anti-inflammatory effect could the diminish overproduction of inflammatory stimuli, thus delaying disease progression.

The anti-inflammatory effects and possible modes of action of triterpenes in cell lines, animals, and even humans have been reported [28–30]. These studies indicate that triterpenes regulate both upstream and downstream inflammatory factors, and inhibit the expression, activity, and production of cytokines and/or chemokines, which may consequently alleviate inflammatory stress and mitigate the progression of chronic disease.

#### 3.3. Other bioactivities

**Antitumor.** Betulinic acid directly triggers mitochondrial membrane permeabilization and causes apoptosis in cancer cells [31]. Ursolic and oleanolic acid cause apoptosis in hepatoma cells, reducing mitochondrial membrane potential and Na<sup>+</sup>-K<sup>+</sup>-ATPase activity [32].

**Antiviral.** Glycyrrhizin and its derivatives may protect liver cells against damage induced by chronic hepatitis B or C [33].

**Antiobesity.** Ursolic acid may stimulate lipolysis by translocating hormone-sensitive lipase and decreasing perilipin A expression, as well as upregulating adipose triglyceride lipase in primary culture adipocytes [34].

Based on the above *in vitro* and *in vivo* protective effects and actions, these triterpenes are considered to be potent medicinal compounds, even candidates for new drug development. Information is also available regarding their effect against glycation, another important pathological process involved in many chronic diseases.

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### 4. Glycation and chronic diseases

Non-enzymatic glycation with the formation of Maillard reaction products, also known as advanced glycation end-products (AGEs), is implicated in the pathogenesis of many chronic diseases, e.g., diabetes mellitus, Alzheimer's disease, atherosclerosis, osteoarthritis, inflammatory arthritis, and

cataracts [35–37]. Any agent capable of inhibiting the formation of AGEs may potentially decrease glycative stress and prevent or delay the progression of glycation-related disease.

It is well known that hyperglycemia (as in diabetes) enhances glucose metabolism through the polyol pathway [38]. Aldose reductase, the first and rate-limiting enzyme in this polyol pathway, reduces glucose to sorbitol, which is further metabolized to fructose by sorbitol dehydrogenase (SDH), the second enzyme in this pathway [39,40]. This flux through SDH and elevated fructose level promotes AGE formation and contributes to microvascular abnormalities [41,42]. On the other hand, glyoxalase I (GLI), part of the glyoxalase system present in the cytosol of cells, metabolizes physiologically reactive alpha-carbonyl compounds such as glyoxal and methylglyoxal, and consequently decreases the available precursors for AGEs formation [43].

Because aldose reductase, SDH, and GLI are key factors involved in endogenous glycation reactions, and responsible for the formation and degradation of AGEs, the development of new drugs to mediate this pathway and lower glycative stress should pay more attention to these enzymes. That is, any agent with the ability to suppress the activity and/or expression of aldose reductase and SDH, as well as enhance GLI activity and expression, may curb these glycation reactions and AGE production.

## 5. AGEs and receptors for AGEs

AGEs are a complex product mixture, formed mainly by reactions between reducing sugars such as glucose, ribose and ascorbate, and the amino groups of lysine or arginine residues from proteins or other moieties (lipids or nucleic acids), followed by Amadori rearrangement.

Next to glucose, reactive dicarbonyl compounds such as methylglyoxal are also precursors for the formation of (extra) cellular AGEs [44]. Methylglyoxal can react with arginine and lysine residues to form imidazolone adducts and N<sup>ε</sup>-(carboxyethyl)lysine (CEL), respectively [45]. That is, AGEs are mixtures of protein-bound nitrogen- and oxygen-containing heterocyclic compounds, formed via a complex cascade of dehydration, condensation, fragmentation, oxidation, and cyclization reactions. Except for pentosidine and N<sup>ε</sup>-(carboxymethyl)lysine (CML), the structures of many AGEs have not yet been characterized. Although reducing AGEs present in circulation and/or in tissues improve the attenuation of glycative stress, both decreasing AGE formation and increasing AGE degradation and excretion pose a big challenge when developing an anti-AGE drug based on the properties of irreversibly cross-linked, heterogeneous, insoluble protein aggregates.

Glycated hemoglobin, CML, glycated albumin, and pentosidine are common AGEs present in the circulation of patients with diabetes mellitus or Alzheimer's disease, where they may serve as markers of disease progression [46,47]. Circulating AGEs could be from two sources: exogenous and endogenous. The former is from the diet (food); the latter are synthesized in the tissues under normal and pathological conditions. The intake of food rich in glycative products contributes to enriching the circulating AGE pool and elevates

glycative stress [48]. Individuals with glycation-related diseases should thus limit their dietary intake of AGE-containing foods.

Endogenous AGEs may be formed during natural aging, while the progression of diabetes, renal failure, and/or neurodegenerative disease raises endogenous AGE production. The tissue content of AGEs depends on the rates and levels of AGE formation and degradation. Accumulation of AGEs during natural aging is ascribed to the time-dependent nature of advanced glycation coupled with greater oxidative stress, in addition to the progressive reduction in the capacity to neutralize oxidative stress [49]. It is well known that hyperglycemia and oxidative stress accelerate the accumulation of AGEs especially; oxidative stress boosts AGE production via glycooxidation and lipid peroxidation [50,51]. On the other hand, AGE degradation is determined by ligation to macrophage scavenger receptors, protein turnover rate, and renal capability for clearance [52].

### 5.1. AGEs in diabetes mellitus

AGEs play an important role in the pathogenesis of diabetes-related macro- and microvascular complications: the circulating level of AGEs indicates the clinical stage of patients with diabetic complications such as nephropathy [53,54].

Renal tubular and interstitial cells are direct targets for increased glycative damage. An elevated glucose level stimulates the tubular cells to secrete vasoactive hormones such as angiotensin II, TGF- $\beta$ , and matrix proteins [55]. These not only lead to AGE formation in the target cells, but also activate intracellular signal transduction systems, generate free oxygen radicals such ROS, and induce redox-sensitive transcription factor and nuclear factor kappa B (NF- $\kappa$ B), while promoting the expression of genes associated with NF- $\kappa$ B-mediated inflammation, such as IL-6 [56,57]. On the other hand, circulating AGEs are reabsorbed and metabolized by the proximal tubular epithelial cells.

Massive AGEs, as seen in diabetic nephropathy, spawn renal cellular hypertrophy via decreased protein breakdown [58]. The kidneys are thus vulnerable to AGEs, which can activate various intracellular second messengers such as mitogen-activated protein kinase and nitric oxide synthase, subsequently inducing the expression of adhesion molecules and the production of inflammatory cytokines, as seen in diabetic cardiomyopathy and retinopathy [59,60]. These studies link AGEs to oxidative and inflammatory injury in diabetes. Lowering the level of AGEs in the circulation and the organs is necessary in order to alleviate or delay these complications.

### 5.2. AGEs in Alzheimer's disease

Two major neuropathological hallmarks are present in the brains of patients with Alzheimer's disease: extracellular senile plaques and intracellular neurofibrillary tangles. Senile plaques contain a core of  $\beta$ -amyloid ( $A\beta$ ) peptide, and neurofibrillary tangles contain hyperphosphorylated microtubule-associated protein tau [61]. AGEs can be detected in both neurofibrillary tangles and senile plaques, in which CML has been found to be localized in the cytoplasm of neurons,

astrocytes, and microglia in both aged brains and the brains of those with Alzheimer's disease [62,63].

Although it remains unclear whether the AGEs present in brain tissue are endogenously synthesized and/or derived from an exogenous dietary intake, several studies have illustrated the accumulation of CML and pentosidine, two major AGE molecules, as being highly associated with the progression of Alzheimer's disease [64,65]; this strongly suggests a crucial role for AGEs in the pathogenesis of this condition. AGEs could directly cause neuronal cell apoptosis by acting as neurotoxins or promoting inflammatory injury and/or as proinflammatory molecule stimulators [66,67]. Deposition of AGEs on the neurovascular wall not only impairs brain function, but also expedites the deterioration of dementia.

CML, along with its glycation-specific precursor hexitol-lysine, is markedly increased in neurons from patients with Alzheimer's disease, especially those with intracellular neurofibrillary pathology [68]. Oxidative stress affects all classes of macromolecule (sugar, lipids, proteins, and DNA), and contributes to an early response in many chronic neurodegenerative diseases, including the normal aging process and Alzheimer's disease. The reported increase of hexitol-lysine or CML is partially due to lipid peroxidation [69], inevitably producing neuronal dysfunction. The oxidative stress hypothesis of Alzheimer's disease suggests that the generation of AGEs in brain tissue is accelerated by an overproduction of oxygen-derived free radicals in cerebrovascular disorders [70].

### 5.3. AGEs in cancer

The impact of AGEs on the development and progression of cancer has recently attracted more attention. Hypoxia, a microenvironment for tumor cell adaptation, also favors the generation of AGEs by way of oxidative stress and/or damage to cell membranes [71]. AGEs diminish the vascular barrier function and enhance the expression of vascular endothelial growth factor and vascular cell adhesion molecule 1, as well as disturbing the balance of cellular coagulant–anticoagulant properties, thus promoting angiogenesis and tumor growth [72,73]. Methylglyoxal derived from polyol pathways forms adducts with DNA nucleic acid bases and results in the production of the AGE molecule N2-(1-carboxyethyl)-2'-deoxyguanosine, an indicator of DNA damage or mutation [74]. These findings indicate that elevated AGEs level in the circulation could facilitate the growth of an already established malignant tumor.

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## 6. Receptors for AGEs

The receptor for AGE, also called as RAGE, is expressed by a variety of cells, including endothelial and tubular epithelial cells. RAGEs can engage diverse ligands associated with distinct pathological processes. One class of RAGE ligands reacting with AGEs occurs in diabetes, renal failure, or amyloidoses, and is responsible for deterioration in diabetes mellitus and Alzheimer's disease. Elevated RAGE expression has been noted in various cells under diabetic conditions [75], since hyperglycemia is a major stimulator of the production of

RAGE ligands with a capacity to interact with AGEs in the circulation and tissues. AGEs derived from the diet or endogenous sources also enhance RAGE expression [76].

In the development of Alzheimer's disease, RAGE acts as a signal transduction receptor for A $\beta$  peptide that has accumulated in the affected brain parenchyma and cerebral vasculature. This aggravates neuronal stress and neuroinflammation, and finally impairs memory and learning [77]. RAGE also acts as ligand for S100/calgranulins, high-mobility group box 1 and beta-sheet fibrils, which generates proinflammatory and prothrombotic molecules and ROSs; this eventually leads to augmented damage in the target tissues, such as atherosclerotic plaques and cardiac infarction [78,79]. The targets of RAGE ligands include tumor cells, neurons, endothelial cells, Caco-2 epithelial cells, podocytes, smooth muscle cells, and microglial cells, and RAGE ligands may trigger diverse signaling cascades (MAPKs, p21ras, ERK1/2, p38, JNK, and Jak/STAT) in these targets [80,81].

These RAGEs and ligands play independent roles in the pathology of several diseases, but the AGE–RAGE interaction merits attention as it directly activates many crucial signaling mechanisms. It has been indicated that AGE–RAGE interaction stimulates O $_2^{\cdot -}$  production, raises oxidative stress [82], evokes vascular inflammation and thrombosis via activating NF- $\kappa$ B [83,84], and enhances the expression of adhesion molecules, chemokines, proinflammatory cytokines, matrix metalloproteinases and the upregulation of RAGE itself [85,86]. Consequently, NF- $\kappa$ B induces the expression of downstream genes encoding TNF- $\alpha$ , IL-6, and MCP-1, which in turn promote inflammatory reactions and cause impairment in the target tissues [87,88].

Although it is well known that glycative stress from AGEs, RAGEs, and their interaction play a key role in the progression of diabetes mellitus and Alzheimer's disease, the influence of the AGE–RAGE axis on cancer pathology cannot be ignored, since ROSs and cytokines generated from this axis contribute to oxidative and inflammatory DNA damage and initialize carcinogenesis. Besides AGEs and A $\beta$ , RAGE can bind to other ligands, such as low-density lipoprotein and calgranulins.

The impact of AGEs, RAGEs, RAGE ligands, and their interaction on human health is not limited to glycative stress. Thus, any strategy against glycation-associated chronic diseases must consider: (1) reducing the level of AGEs in the circulation; (2) lowering the level of other RAGE ligands in the circulation; and (3) impeding the interaction of RAGE and its ligands. Any inhibitor(s) blocking AGE formation, suppressing RAGE expression, or interrupting the AGE–RAGE interaction could be a potential candidate for treating diabetes mellitus, Alzheimer's disease, and other glycation-related diseases.

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## 7. Antiglycative potential of triterpenes

Circulating AGEs could be derived from the diet or from endogenous generation. Pentosidine and furosine can be detected in many foods [89,90]. Foods cooked by baking or deep frying also contain high amounts of AGEs [90,91]. In order to reduce circulating levels of AGEs from exogenous sources, the consumption of such foods rich in glycative products should be avoided.

Endogenous AGEs could be formed between reducing the sugars and amino acids present in the blood and/or tissues. Unfortunately, there is a large pool of reducing sugars and amino acids in the human body, and decreasing the intake of reducing sugars and amino acids may not be a good idea because the limitation might impair nutritional status. The alternative is to ingest other natural compound(s) with anti-glycative activities to interfere with AGE formation and/or mediate AGE metabolism.

An *in vitro* inhibitory effect of triterpenes such as astragalosides upon the formation of AGEs such as CML has been reported [92–94]. The results of these studies suggest that triterpenes can halt the interactions between reducing sugars and amino acids, reducing AGE formation and alleviating glycativ stress via a nonenzymatic action. Both oxidative and inflammatory stress favor the glycation process; the anti-oxidative and anti-inflammatory effects of several triterpenes, such as ursolic acid and erythrodiol, have already been demonstrated [95–97]. It is quite possible that these triterpenes indirectly attenuate glycation via mitigating oxidative and inflammatory stress.

On the other hand, it is reported that oleanolic and ursolic acid can mediate the activity and/or expression of aldose reductase, SDH, and GLI [98,99]. These authors have indicated that suppression caused by aldose reductase and SDH decreases endogenous AGE generation as well as glycativ stress. By upregulating GLI, the metabolism of AGEs is facilitated, and the accumulation of AGEs in the circulation and tissues diminished.

Obviously, the clinical application of any agent with an ability to mediate the enzymes involved in the polyol pathway will be highly beneficial, making it worthwhile to investigate the effect of other triterpenes on the activity and expression of these enzymes. So far, less information is available regarding the impact of triterpenes on RAGE expression and AGE–RAGE interaction. It is clear that suppressing RAGE or interrupting the AGE–RAGE interaction can more effectively mitigate glycativ damage and/or retard pathological progression. The exploration of new natural agents and their modes of action is warranted in order to fight glycation-associated disease.

### 7.1. Blood–brain barrier

One challenge of research focused on triterpenes is their bioavailability. The development of any pharmacological substance acting against Alzheimer's disease has to consider whether this agent can pass through the blood–brain barrier, a tightly packed layer of endothelial cells that surrounds the brain to block high-molecular weight molecules from entering it. The blood–brain barrier not only impedes the influx of intravascular substances from the blood to the brain, but also regulates the transport of substances from blood to brain or from brain to blood via several transport systems such as carrier-mediated transport, active efflux transport, and receptor-mediated transport [100,101]. The blood–brain barrier is vital to brain A $\beta$  homeostasis and regulates A $\beta$  transport [102]. Triterpenes with an ability to pass through the blood–brain barrier can provide greater anti-glycativ potential in the prevention and/or therapy of Alzheimer's disease.

## 8. Conclusion

Triterpenes are compounds that are naturally present in many plant foods. Based on their marked action against AGE formation, their antioxidative and anti-inflammatory activities, and their regulatory effects on aldose reductase and GLI, these agents may be of benefit in the prevention of and therapy for glycation-associated diseases such as diabetes mellitus and Alzheimer's disease. Future study must probe the effects of triterpenes upon RAGEs, AGE–RAGE interaction, and penetration of the blood–brain barrier.

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