



Review Article

Herbal origins provision for non-enzymatic Glycation, (NEGs) inhibition

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The aldehyde or ketone groups of reducing sugars react non-enzymatically with the free amino groups of proteins, lipids and nucleic acids leading to the formation of advanced glycation end products (AGEs). These AGEs inhibitory API (active pharmaceutical ingredients) carries a great deal of AGEs in reducing the risk to related diseases and puts the clinician in a predicament to find concise and reliable information for adequate class of drug and its anti-glycating activity. Thus far, some potentially interesting inhibitors forms herbal origins with all possible mechanisms of inhibition of AGEs. The study have focused on herbal origins inhibitors API follow which class of inhibitor. A various *in-vitro* and *in-vivo* model study the evaluation AGEs inhibitory drugs. Present discussion concluded that the investigated Armed with herbal phytochemicals specific inhibitors, glycobiologists will be able to explore the biological function of the individual phytochemicals in NEGs and AGEs.

Key words: NEGs, AGEs, hyperglycemia, glycation, Amadori products, Herbal drugs

INTRODUCTION

Diabetes mellitus (DM) is the very popular endocrine disorder that affects more than 100 million people worldwide (6% of the population). It is a systemic metabolic disease characterized by hyperglycemia, hyperlipidemia, hyperaminoacidemia, and hypoinsulinemia it leads to decrease in both insulin secretion and insulin action (Sarah *et al*, 2004). In healthy individuals, the blood glucose concentration is tightly regulated by insulin (CDC, 2011). The high blood sugar concentration that is found during diabetes is related to either insufficient insulin production (i.e., Type-1 diabetes) or resistance to insulin (i.e., Type-2 diabetes) (Araki *et al*, 1992; Horiuchi, 1996). This increased blood glucose concentration has a number of effects in the body, which include an increased risk of heart disease (Vorum *et al*, 1995), stroke (Peters, 1996), kidney disease (Iberg and Fluckiger, 1996), blindness (Stewart *et al*, 2001), and amputations (Schnolzer *et al*, 2005). Many of these complications are due to protein glycation and the formation of advanced glycation end products (Wa *et al* 2006). AGE-related complications in the body can be classified into two different areas. In one case, the

interaction of AGEs with the receptor protein for AGEs (RAGE) is responsible for a wide range of inflammatory responses which eventually lead to tissue damage (Armbuster, 1987; Abordo, *et al* 1998). The second case involves direct modification of proteins by AGEs, leading to a loss of protein function or tissue damage that results from protein cross-linking (Lapolla *et al*, 1995; Kouzuma *et al*, 2002). Different types of AGEs are known, depending on the compound they originate from. Six distinct classes of AGEs were recognized deriving from glucose (AGE-1), from other carbohydrates, such as glyceraldehydes (AGE-2), and from α -dicarbonyls, such as glycoaldehyde (AGE-3), methylglyoxal (AGE-4), glyoxal (AGE-5), 3-deoxyglucosone (AGE-6) by Takeuchi *et al*, in (2004).

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AGEs are implicated in many age related diseases such as type-II (diabetic mellitus), cardiovascular disease (the endothelial cell, collagen, fibrinogen are damaged), Alzheimer diseases (amyloid protein are side product of the reaction progressing to AGEs), Cancer (acryl-amide and other side product are related), peripheral neuropathy (the myelin is attached), and other sensory losses such as deafness (due to demyelination), and blindness (mostly due to micro-vascular damage in the retina), this range of diseases is the result of very basic level at which glycation interfere with molecular and cellular functioning throughout the body. An important part of tissue damage and of cell death associated with chronic hyperglycemia, and diabetes is mediated by free radicals. E.C.M. (Extra cellular matrix), proteins such as collagen, elastin, actin, and myosin are the backbone for architectural and functional stability of tissues cell and organs. When AGEs accumulations particularly high in E.C.M., proteins are result in intra and inter molecular cross-linking and later has been hypotized to stiffening of these proteins and believed to play an important role in etiology of various AGEs related diseases⁷. Despite the availability of the current therapies for prevention of the protein glycation and oxygen stress related diseases are still a major threat to human health. Antioxidants effectively protect against glycation derived free radicals and may have therapeutic potential for the inhibition of radical induced processes (Basta, *et al*, 2004). Moreover, plant samples with combined antioxidant, anti-glycation properties are highly desired because they can be more effective in treating various biological disorders (Cerami *et al*, 1979). For presented review given idea towards pharmaceuticals and naturaceuticals based therapeutics molecules given potential to anti-glycating effect to NEGs and AGEs formation.

Non-enzymatic glycation reaction

The Non-enzymatic reaction between the amino groups of amino acids, peptides and proteins and reducing sugars was first studied under defined conditions in the early by Louis Camille Maillard in 1912 (Aronson, 2003). Ever since its description in the early 1900s, the Maillard reaction has continued to be a topic of research interest. For researchers in nutrition science, harnessing the Maillard reaction has allowed for controlling food flavor, food aroma, food coloring, and food texture (Peyroux, and Sternberg, 2006). In addition to its benefits, the Maillard reaction occurring during food processing also results in

the loss of protein quality and the formation of harmful compounds with mutagenic, carcinogenic and genotoxic properties (Schmidt *et al*, 1996). During the 1970s and 1980s, researchers in clinical medicine realized that this process also occurs slowly *in-vivo*. Subsequently, Maillard reaction *In-vivo* was termed glycation, distinguished from enzymatic glycosylation. The final products of this reaction are a polymorphic group of compounds collectively referred to as Advanced Glycation End products (AGEs) (Saxena *et al*, 1996). Non-enzymatic glycation is the covalent binding of single reducing sugars (glucose, fructose, ribose, etc.) to primary amino groups in proteins, such as the ϵ -amino group of the protein lysine residue (figure 1) (Kyselova *et al*, 2004). The initial product of Maillard reaction is a labile Schiff base intermediate (Alderson *et al*, 2003). To simplify the discussions of the Maillard reactions, the adducts are frequently depicted as the more reactive open-chain forms. Formation of the Schiff base is relatively fast and highly reversible and the formation of the Amadori product from the Schiff base is slower, but much faster than the reverse reaction, so that the glycation product tends to accumulate on proteins.

The chemistry of glycation

The non-enzymatic glycation progress reaction includes three distinguishable phases: the initial stage, the intermediate stage and the late stage. In the initial phase of glycation, the carbonyl group of a reducing carbohydrate condenses with the free amino group on a protein or other amino containing molecule to form reversible glycosylamine, which is then converted to more stable Amadori products. Under appropriate condition, these Amadori products could degrade to more reactive dicarbonyls such as methylglyoxal, glyoxal and glyceraldehyde. These intermediates are responsible for most of the AGE formation due to their high reactivity. In the late stage of glycation, the Amadori product itself could with time undergo dehydration, cyclization, oxidation, and rearrangement to form AGEs. Since AGEs have been implicated in many diseases, the chemistry of how AGEs form has been extensively investigated (Metz, *et al*, 2003). This reaction involves the aldehyde group on glucose, or other reducing sugar, modifying the amino side-chain of lysine residues or the N-terminal amino groups of polypeptides. This leads to the reversible formation of a Schiff base followed by a practically irreversible rearrangement to a more stable ketoamine known as the Amadori intermediate, or fructosyl-lysine.

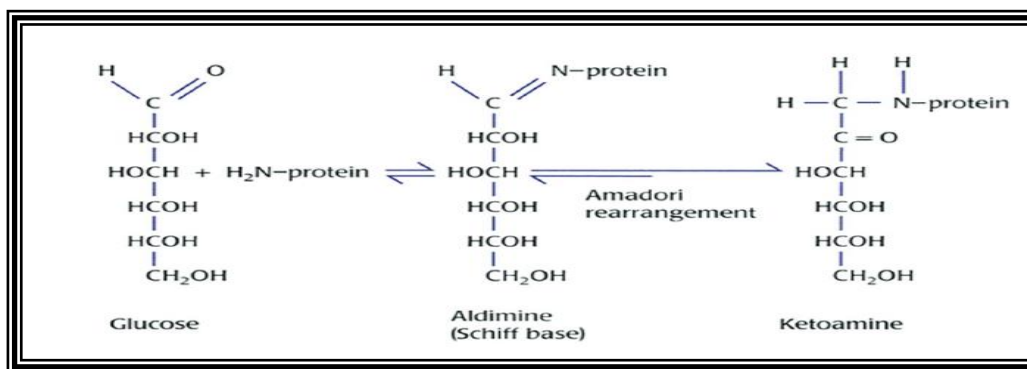


Figure 1: The initial stage of glycation resulting in the formation of a Schiff base and an Amadori product (Voziyan, and Hudson 2005).

Inhibitors against AGE formation

Perhaps the most promising approach to AGE inhibition is the prevention of AGE formation. Not only the end-products but also, highly reactive intermediates responsible in their formation, that are toxic to the cells such as glyoxal (GO), methylglyoxal (MGO), glycolaldehyde (GLA), and CML, N-carboxyethyllysine have to be targeted in designing inhibitors that specially react with each committed step and intermediates products of important pathways (Baynes, 1991). Another factor to be considered in the search and development of AGE inhibitors is the fact that glycoxidised proteins generate ROS (reactive oxygen species), and induce oxidative stress through the reaction with RAGE. Also, ROS is generated by other reactions cascade of AGE formation such as MG, and Schiff base pathways leading to lipo-oxidation and oxidative damage (McPherson *et al*, 1998). Thus antioxidants also may be considered to have a role in the inhibition of non-enzymatic glycation.

Non-enzymatic glycation Inhibitors and their classification

An efficient inhibitor of non-enzymatic glycation should inhibit glucose-derived AGE generation and cross-link formation (Saxena, *et al*, 1996). A large number and ever increasing number of synthetic and natural "AGE Inhibitors" have been reported in past. because the mechanisms of non-enzymatic glycation or AGEs formation and cross-linking involve complex sequential and parallel reactions that are poorly understood (Zhang, C., A. Sun, 2010) had proposed a simple scheme that identifies common targets for AGEs inhibition, a guide and basis for rational design of new AGE inhibitors, a classification of existing AGE inhibitors. AGE inhibitors can be classified in six categories or types (Ahmed, 2005)

1. **Type-A** : sugar competitors are compounds that react with free amino groups of protein to modify them in order to prevent sugar attachment to protein, (amino group capping agents)
2. **Type-B**: This class of inhibitors reacts with aldose and ketose sugars, inactivating them before they react with

amino groups of proteins. These compounds act on more than one step of glycation cascade (Hipkiss. and Bronson, 2011).

3. **Type-C**: Antioxidants and metal chelators. This class of AGE inhibitors is likely to interfere with other types of reaction *in-vivo*. The C-1 type would be chelators such as DETAPAC, phytate, desferoxamine and penicillamine, and the type-C-2 inhibitors would be antioxidants, such as vitamin-C or E.
4. **Type-D**: inhibitors such as AG and L-arginine (Satyavati, 1987), trap reactive dicarbonyl intermediates (GO, MGO, glycolaldehyde and glucosones) to form substituted triazines. Some reactive dicarbonyls may be elevated in diabetic through metabolic imbalance distinct from non-enzymatic glycation
5. **Type-E**: Amadori adducts inhibitors, it includes AG (TypeE1), and also compounds that have potential for enzymatic de-glycation at the Amadori level (Gupta, *et al*, 2005).
6. **Type-F**: Inhibitors cross-link breakers. This group reduces AGE toxicity by breaking protein-AGE cross-linking.

There are also numbers of novel AGE inhibitors such as zinc and nano-particles, whose inhibition mechanisms are still under investigation.

AGEs inhibition of herbal origin

Plants have been used from ancient times to attempt cures for diseases and to relieve physical suffering. Ancient peoples all had acquired some knowledge of medicinal plants (Shankar, *et al* 1980). Medicinal plants Phytochemicals have the advantage of having little or no side effects. With the increasing popularity of herbal medicine, physician required at least some basic knowledge about traditional medicine. Furthermore, some of the traditional plant based remedies or at least components derived from medicinal plants or herbs, may one day become part of mainstream treatment (Sajithlal *et al*, 1998).

Their reports of some natural substances or Phytochemicals is isolated from plants with non-enzymatic

glycation or AGEs inhibitory effects. The *Curcuma longa* rhizomes have been reported to possess anti-diabetic properties as its alcoholic extracts possess active constituents showing blood glucose lowering activity in alloxan induced diabetic rats. The purified curcumin was more effective than turmeric (Yamaguchi *et al*, 2000) [41], and it has antioxidant and anti-inflammatory properties (Kim and Kim (2003)). The screening plant extracts anti-oxidative property, such as, curcumin, rutin, garcinol and flavonoid-rich extracts, have been shown to prevent AGEs formation *In-vitro* and *In-vivo*. Arbutin (hydroquinone- β -D-glucopyranoside) is a naturally occurring compound found in various plant

species of diverse family such as Ericaceae (*Arctostaphylos* spp.), Betulaceae (*Betula alba*) and Rosaceae (*Pyrus communis* L.) (Petkou *et al*, 2002). Arbutin, possessed an *in vitro* antiglycation activity (Arom 2005). Extracts of 24 herbs and spices were tested for the ability to inhibit glycation of albumin. The most potent inhibitors included extracts of cloves, ground Jamaican allspice, and cinnamon, sage, marjoram, tarragon, and rosemary. The concentration of phenolics that inhibited glycation by 50% was typically 4–12 $\mu\text{g}\cdot\text{ml}^{-1}$. Relative to total phenolic concentration extracts of powdered ginger and bay leaves were less effective than expected, and black pepper was more effective (Rebecca *et al*. 2008).

Table2: Medicinal plants used in non-enzymatic glycation inhibition activity

Medicinal plants	Mode of action for AGEs inhibition	References
<i>Withania somnifera</i>	scavenge free radicals and inhibit lipid peroxidation	(Babu, <i>et al</i> , 1998, Khan and gothalwal, 2015)
<i>Allium sativum</i> ,	Antioxidant activity	(Sheikh, <i>et al</i> , 2006)
<i>Plantago asiatica</i>	antioxidant activity	Choi, <i>et al</i> , 2004
<i>Pueraria lobata</i>	-----	(Jang <i>et al</i> , 2006)
<i>Phyllanthus emblica</i>	Antioxidant activity	(Chaiyasut, and Chansakaow, 2007)
<i>Kaempferia parviflora</i>	Antioxidant /metal chelators	(Jame, <i>et al</i> , 2011)
<i>Globba wintii</i>	Antioxidant /metal chelators	(Jame, <i>et al</i> , 2011)
<i>Hibiscus cannabinus</i>	Antioxidant activity	(Jame, <i>et al</i> , 2011)
<i>Eulophia nuda</i>	inhibit Maillard products	(Yadav <i>et al</i> , 2012)
<i>Calendula officinalis</i>	inhibited aldose reductase	(Younus and Anwar, 2016)
<i>Empetrum nigrum L</i>	Antioxidant activity	(Younus and Anwar, 2016)
<i>Chrysanthemum species</i>	free radical and metal scavengers	(Younus and Anwar, 2016)
<i>Nigella sativa</i>	inhibit Maillard products	(Younus and Anwar, 2016)
<i>Juglans regia</i>	Antioxidant activity	(Younus and Anwar, 2016)

CONCLUSION

Hyperglycemic complications provide an alternative to herbal drugs with comparable results in various *in-vitro* and *in-vivo* models. Synthetic drug treatment due to unwanted side effects the efficacies of these compounds are debatable and there is a demand for new compounds for the treatment of diabetes. Furthermore, naturally occurring phytochemicals with anti-diabetic and antiglycating activities are relatively nontoxic, inexpensive and available in an ingestible form. Hence, plants have been suggested as a rich, as yet unexplored source of potentially useful anti-glycating drugs. However, only a few have been subjected to detailed scientific investigation due to a lack of mechanism-based *in vitro* assays. Naturaceuticals has been shown to improve outcome in hyperglycemia complication with NEGs and AGEs formation. There is growing evidence to support and improvement in NEGs and AGEs related complications. In the future, targeting the phytochemicals which responsible for antiglycating activity and molecular staging with NEGs and AGEs in applying QASAR, Molecular docking and other bioinformatics tools for Pharmacological evaluation. The Natural phyto-pharmaceutics may play major role to resolve these conditions in near future.

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