Advances in Biochemistry & Applications in Medicine

Chapter 10 ISBN: 978-81-935757-1-0

Anti-advanced glycation end product therapies in diabetic vascular complications

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Abstract

Advanced glycation end products (AGEs) are formed by non-enzymatic reaction between reducing sugars and proteins, lipids or nucleic acids. Interaction of AGE with its receptor; receptor for advanced glycation end product (RAGE) elicit various signal transduction pathway leading to vascular complications in diabetes mellitus (DM). Therefore, inhibition of AGE may be a useful strategy to ameliorate pathogenesis of several diseases including diabetic vascular complications. Several AGE inhibitors have been identified till date, which differ from each other in their mechanisms of action, although all have the same outcome, and lead to reduction in AGE formation or accumulation. Therefore, anti-AGEs drugs are also being intensively studied in the recent time. Therapies that target multiple pathways may indeed be more successful than those that target one pathway alone. It remains to be determined whether a combination of hemodynamic and metabolic pathways is more effective than any individual therapy in preventing diabetes-associated injury. Therapies against the AGE-mediated effect can act through diverse pathways, like inhibiting the production of Amadori products, decreasing AGE-RAGE interaction, detoxifying dicarbonyl intermediates and interrupting biochemical pathways that impact on AGE levels. However, food and drug administration does not approve any agents for AGE modification to date, though some such medications are in clinical and preclinical testing.

In this chapter, various agents which are known as inhibitors of formation of AGE and AGE breakers reported till date are being discussed. Also, exploring the existing drugs in AGE inhibition, which are developed for other therapeutic interventions have been demonstrated to be potent inhibitors of glycation and AGE formation.

Keywords: advanced glycation end product; diabetes mellitus; receptor for advanced glycation end product; anti-AGE therapy

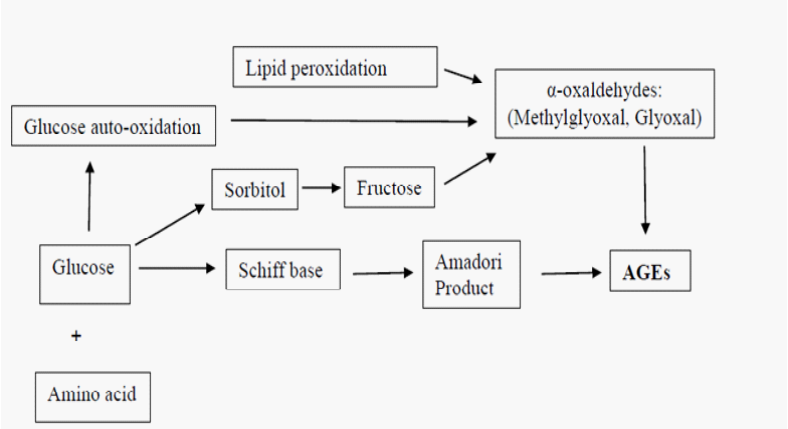
1. Advanced Glycation End Product (AGE)

Hyperglycemia facilitates formation of advanced glycation end product (AGE). AGEs are heterogeneous compounds that are formed mainly via the Maillard reaction. The formation of AGE has been first identified in 1992 by Maillard and is known as the Maillard or "Browning" reaction. The Maillard reaction occurs when reducing sugar reacts in a non-enzymatic way with amino group of proteins, lipids or DNA [1]. The Maillard reaction has been considered for years in the food industry because its products add a desirable colour and taste to foods. Association of AGE with certain pathological conditions such as diabetes mellitus(DM), cardiovascular disease, Alzheimer's disease and also aging process has drawn increasing attention towards the role of AGEs in these diseases [2, 3].

1.1. Formation of advanced glycation end product (AGE)

The formation of AGE through the Maillard reaction occurs in three phases as shown in **Figure 1**. First, glucose attached to a free amino acid (mainly lysine and arginine) of a protein, in a non-enzymatic way to form a Schiff base which has a carbon to nitrogen double bond where the nitrogen is not attached to hydrogen. The initiation of this step depends on glucose concentration and takes place within hours. If concentration of glucose decreases, this reaction is reversible. During the second phase, the Schiff base undergoes chemical rearrangement over a period of days and form Amadori products. The Amadori products are more stable compound but the reaction is still reversible. They, undergo complicated chemical rearrangement (oxidations, reductions, and hydrations) and form cross-linked proteins. This process takes place in weeks or months. These are very stable and accumulate in the cells and interfere with protein function [4].

Other pathways can also form AGE alongwith the Maillard reaction. For instance, the autoxidation of glucose and the peroxidation of lipids into dicarbonyl derivatives such as α-oxaldehydes (glyoxal, methylglyoxal) and 3-deoxyglucosone by an increase in oxidative stress can lead to formation of AGE [5]. Another pathway for the formation of AGE is through polyol pathway, where glucose is converted to sorbitol by the enzyme aldose reductase and then to fructose by action of sorbitol dehydrogenase. Fructose metabolites such as fructose 3-phosphate converted into α-oxaldehydes to form AGE [6,7].



(Adapted from: Ojigbo., 2014 [8])
Figure 1: Formation of AGE

1.2. AGE-mediated pathogenesis

Advanced glycation end product (AGE) and its interaction with RAGE mediated-intracellular consequences has been reported in several diseases including diabetic vascular complications. High levels of blood AGE and enhanced expression of RAGE is associated with activation of various downstream signaling cascades such as activation of MAP kinases and JAK/STAT pathway. These pathways lead to the activation of nuclear factor-kappa B (NF-κB) which induces various target genes such as pro-inflammatory genes, cytokines (e.g.TGF-β1, CTGF) and other adhesion molecules (e.g. VCAM-1). In addition, AGE-RAGE interaction also enhanced production of reactive oxygen species (ROS) via activation of nicotinamide adenine dihydrogen phosphate (NADPH) oxidase.This enhanced oxidative stress and inflammation implicated in the development and induction of vascular complications in diabetes mellitus (DM) [9,10]. Besides a receptor-mediated action, AGEs are also responsible for alteration in protein function and theirstructure which lead to impaired cell function [11].

2. Inhibitor of Formation of AGE and AGE-Cleaving Agents

Various agents as inhibitor of formation of AGE or AGE breaker have been reported in several studies [12,13]. The following are the agents which known for their anti-AGE properties.

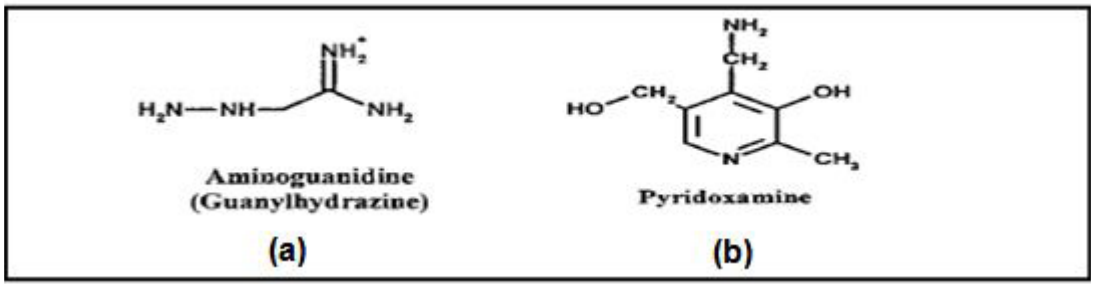
2.1. Aminoguanidine

Aminoguanidine (AG) [**Figure 2 (a)**], nucleophilic hydrazine compound, is known as pharmacological inhibitor of AGE [14]. It was the first drug designed to inhibit the glycation process by inhibiting the conversion of early stage products into AGE. It prevents the formation of advanced glycation end product by reacting with Amadori-derived fragmentation products such as 3-deoxyglucosone, methylglyoxal, and glyoxal and also by trapping of reactive carbonyl intermediates in the Maillard reaction [15]. Inhibitory effect of AG for vascular complications has been observed in experimental DM and has beneficial for diabetes related

vascular complications [16].

2.2. Pyridoxamine

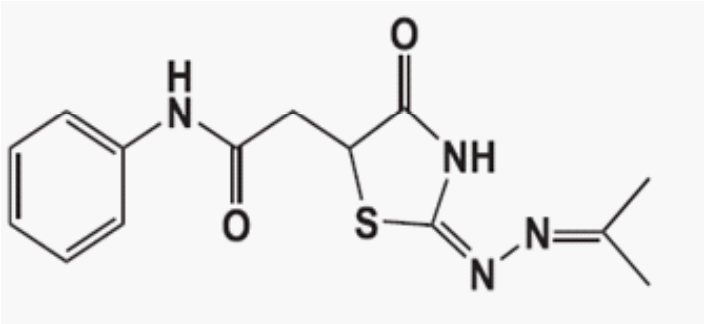
Pyridoxamine [**Figure 2 (b)**], is natural form of vitamin B_6. It also inhibits the formation of AGE. Pyridoxamine has multiple mechanisms of action such as blocking of oxidation of the Amadori intermediate, trapping of reactive carbonyl and dicarbonyl compounds derived from the Amadori compound, chelation of metal ion catalysts of oxidation and scavenging of reactive oxygen species (ROS) [17, 18]. It delays the development of diabetic nephropathy in animal models of both Type 1 and Type 2 diabetic nephropathy [19, 20].



(Adapted from: Booth et al., 1997 [21])
Figure 2: Chemical structure of (a) Aminoguanidine and (b) Pyridoxamine

2.3. OPB-9195

OPB 9195 [(±)-2-isopropylidenhydrazono-4-oxo-thiazolidin-5-ylacetalinide][**Figure 3**], is a synthetic thiazolidine derivative. It decreases AGE production as cross-link breaker and inhibits cross-linking of AGE [22, 23]. It has shown inhibitory actions on glycoxidation and lipoxidation reactions and decrease the formation of AGE and dicarbonyl intermediates [24].

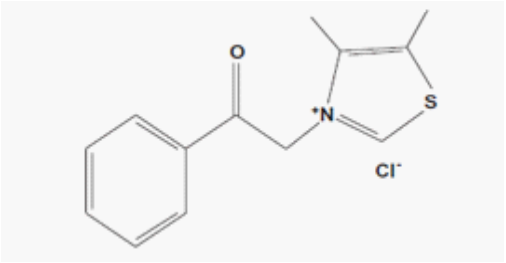


(Adapted from: Nagai et al., 2012 [25])
Figure 3. Chemical structure of OPB-9195

2.4. Alagebrium (ALT-711)

Alagebrium (ALT-711) [**Figure 4**], is another potential cross-link breaker. ALT-711, a small easily synthesized compound (3-phenacyl- 4, 5-dimethylthiazolium chloride) was developed for heart failure and systolic hypertension [26]. Its treatment has been found to significantly decrease plaque area or complexity within the thoracic and abdominal aortas and inhibited the accumulation of AGE-modified collagens in the aortas in animal model [27]. It

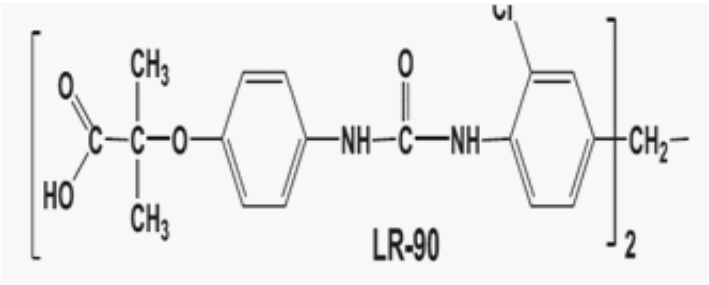
also decreased AGEs and collagen accumulation in the diabetic kidneys, inhibited glomerulosclerosis and tubulointerstitial injury in streptozotocin-induced diabetic rats [28].



(Adapted from: Dhar et al., 2012 [29])
Figure 4: Chemical structure of Alagebrium

2.5. LR-90

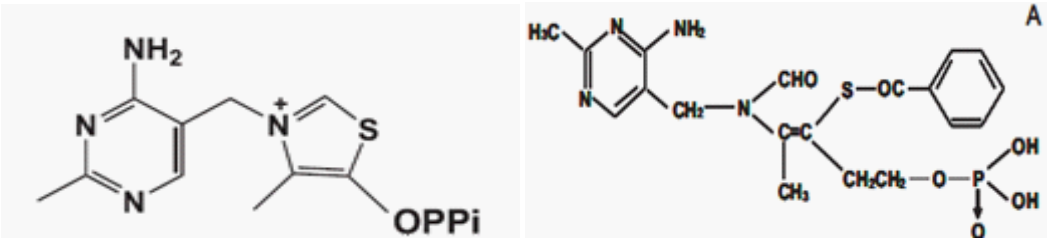
LR-90; 4-4'-(2 chlorophenylureido phenoxyisobutyric acid) [**Figure 5**], is an aromatic compound. LRs were named after their developers as Lalezari-Rahbar (LR) compounds [30]. It inhibits AGE production by chelating transition metals that catalyze the production of AGE. In experimental diabetic models, it has been shown to reduce the formation of AGE, oxidative stress and prevent the progression of nephropathy [31].



(Adapted from: Nagai et al., 2012 [25])
Figure 5: Chemical structure of LR-90

2.6. Thiamine and Benfotiamine

Thiamine [**Figure 6 (a)**] is vitamin B_1 and benfotiamine [**Figure 6 (b)**] which is derivative of vitamin B_1 show AGE-lowering properties. These are also known to decrease the formation of reducing sugars and intermediates from the polyol pathway [32]. Both thiamine and benfotiamine have beneficial role in experimental models of diabetic nephropathy [33]. Furthermore, administration of benfotiamine to type 2 diabetes mellitus (T2DM) patients, who consumed a high AGE content diet, reduced the circulating AGE levels [34].

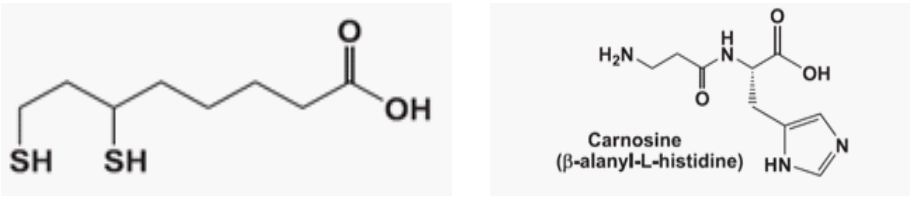


(a) **(b)**

(Adapted from: Nagai et al., 2012 [25]) (Adapted from: Yadav et al., 2009 [35])
Figure 6: Chemical structure of (a) Thiamine pyrophosphate and (b) Benfotiamine

2.7. Lipoic acid and carnosine

Lipoic acid [**Figure 7 (a)**] and carnosine [**Figure 7 (b)**] act as an antiglycating agent and reduce the rate of formation of AGEs. These compounds have shown their anti-AGE role through carbonyl-trapping activity as well as potent chelating activity [36].

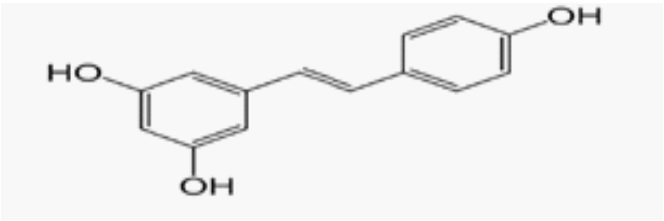


(a) **(b)**

Adapted from Nagai et al; 2012 [25]
Figure 7: Chemical structure of (a) Lipoic acid and (b) Carnosine

3. Resveratrol

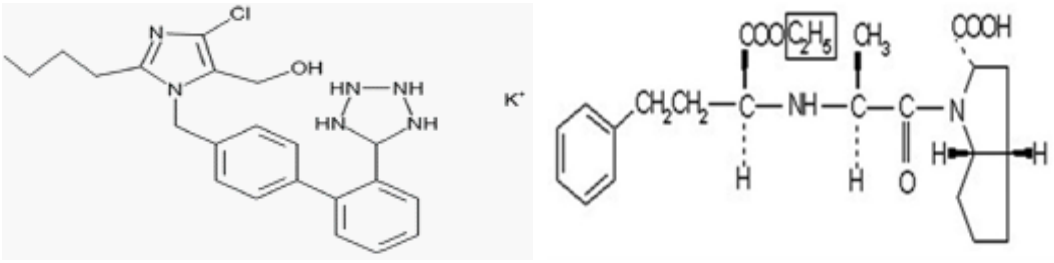
Resveratrol (RSV; 3, 4, 5-trihydroxy-trans-stilbene) [**Figure 8**], is a stilbenoid, a type of natural phenol, found in plants and red wines. It is a member of a group of plant compound called polyphenols [37]. RSV has gained considerable attention because of its beneficial effects as anti-oxidant, anti-inflammatory, anti-atherosclerotic, and anti-cancer properties [38, 39]. However, RSV have also ability to inhibit the formation of AGE and several studies have shown its anti-AGE role in pathogenesis of diseases [26, 40, 41].



Adapted from: Kim et al., 2014 [42]
Figure 8: Chemical structure of Resveratrol

4. Antihypertensive Drugs

Recently, it has been shown that antihypertensive drugs such as losartan, olmesartan, and hydralazine, seem to inhibit formation of AGE [43-45]. Ramipril [**Figure 9 (a)**] and losartan [**Figure 9 (b)**] are widely used anti-hypertensive drugs in the treatment of diabetic nephropathy [46, 47]. These drugs have shown that in addition to their hemodynamic role, they have added additional benefit of reducing AGE formation and accumulation [48, 49]. The mechanisms of action of these drugs with regard to decrease AGE by trapping reactive carbonyls, hydroxyl and also via chelation of metal ions have been reported [44]. Ramipril and valsartan have reduced AGE accumulation in kidneys of STZ-induced diabetic rats [48, 50]. The AGE inhibiting property of ARB and ACEI has opened more possibilities for newer therapeutic interventions.



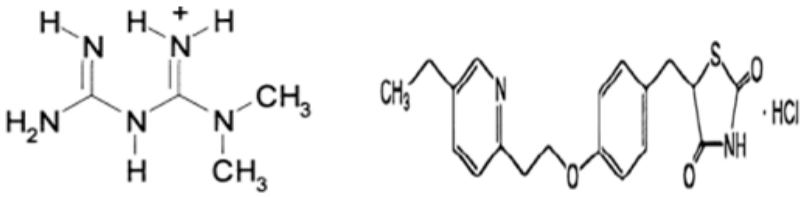
(a) **(b)**

(Adapted from: Diego et al., 2010 [51]) (Adapted from: Das et al., 2015 [52])
Figure 9: Chemical structure of (a) Ramipril and (b) Losartan

5. Hypoglycemic Drugs

By minimizing hyperglycemia, oral hypoglycemic agents can decrease the formation of AGE, but some have other AGE preventive mechanisms as well. Metformin and pioglitazone are anti-hypoglycemic drugs used routinely in the treatment of diabetes.

Metformin (1, 1-dimethylbiguanide)[**Figure 10 (a)**], is an orally effective synthetic anti-hyperglycemic drug, is structurally similar to aminoguinidine [53]. The mechanism of action of metformin with regard to inhibition of AGE formation is trapping of reactive carbonyl molecules through presence of its guanidine moiety [54]. It inhibits glycation at multiple steps with maximum effect observed in post Amadori stages [55].



(a) **(b)**

(Adapted from: Khouri et al., 2004 [56]) (Adapted from: Prakash et al., 2013 [57])
Figure 10: Chemical structure of (a) Metformin and (b) Pioglitazone

Pioglitazone (5-(4-(2-5 Ethylpyridin-2-yl) ethoxy) benzyl) thiazolidine-2, 4-dione hydrochloride)[**Figure 10 (b)**], is an oral anti-diabetic drug used in the treatment of type 2 diabetes mellitus (T2DM) or adult onset diabetes. It is known as oral and well-tolerated drug for diabetes, proved to have a role in anti-AGE treatment because of their peroxisome proliferator-activated receptor (PPAR) γ-agonist activity, which determine an increase in soluble RAGE (sRAGE) expression, which is inversely associated with atherosclerosis. The reduction of endothelial RAGE expression by Thiazolidinediones (TZD) such as rosiglitazone and pioglitazone have been reported by Marx et al. (2004) [58]. It anti-AGE action is similar to metformin in trapping dicarbonyl compounds. It also has metal-chelation property [55].

6. Soluble AGE-Binding Peptides

Soluble RAGE, which is isoform of full length RAGE bind to RAGE ligand such as

AGE, thus preventing RAGE activation and prevent cellular dysfunction [59].

7. Anti-RAGE agents

Recently, several molecules such as low-molecular weight heparin and neutralizing anti-RAGE antibodies which inhibit RAGE, which is receptor for AGE, have been identified-beneficial towards the inhibition of AGE-mediated consequences. They block the RAGE and inhibit the AGE-RAGE interaction [60-62].

8. Glycemic Control

Hyperglycemic environment has been associated with enhanced formation of AGE, making obvious that the good glycemic control can reduce the total body AGE pool. Decrease in AGE levels improved the glycemic control in diabetic rats has been reported by Odetti et al. 1996 [63].

9. Dietary AGEs Restriction

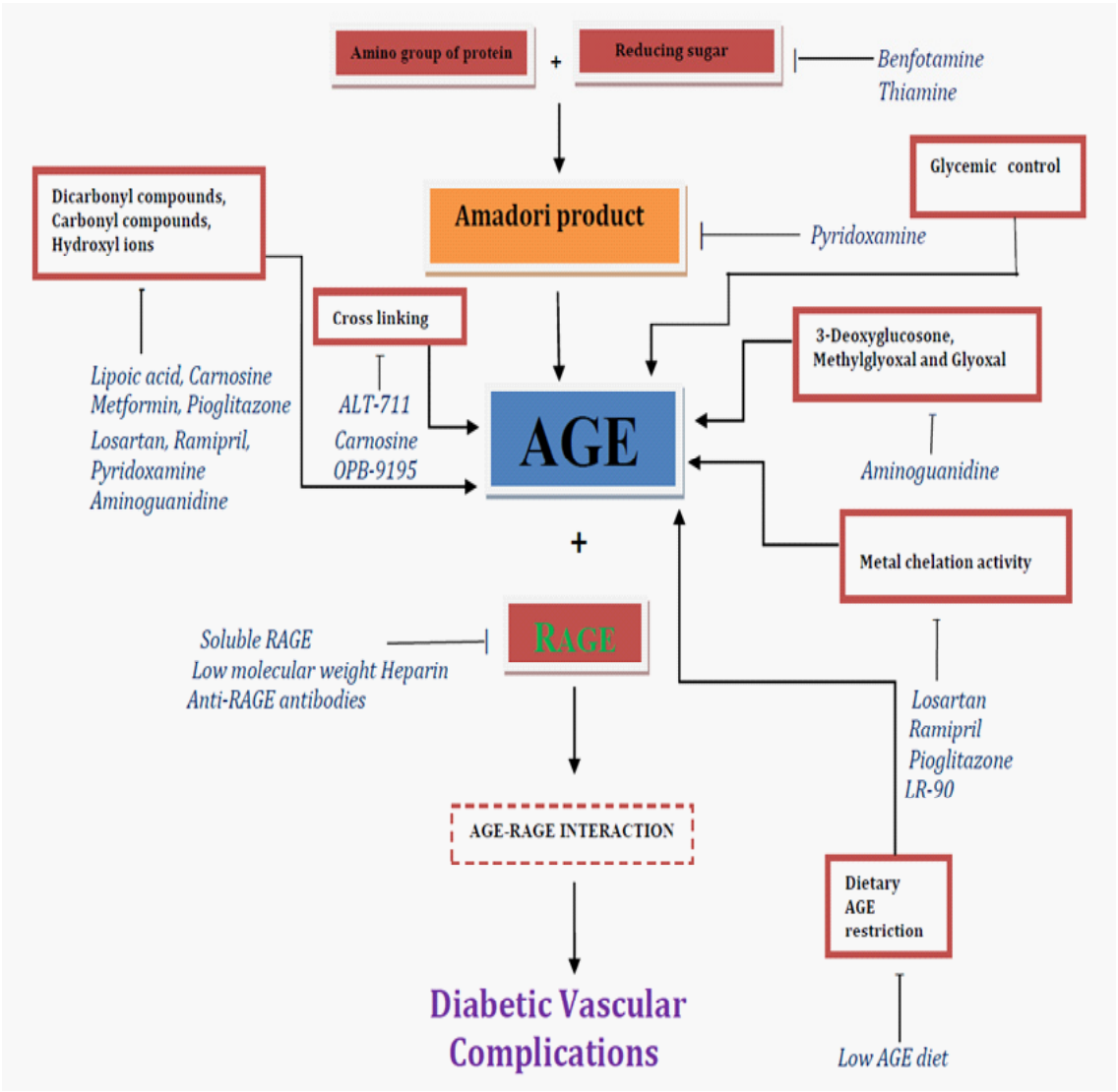
Dietary AGE intake is a significant determinant of circulating and tissue AGE levels [64, 65]. Studies have shown that a low-AGE diet results in decreased serum AGE levels, inflammatory markers levels such as C-reactive protein, total body AGE pool and AGE- related pathology [66-68].

10. Antioxidants

In several studies although antioxidants have been proposed as anti-AGE agents however, further studies are needed with the purpose of establish the effectiveness of antioxidant treatment in reduction of AGE levels [69-73].

11. Conclusion

It is well established that AGEs are involved in the pathogenesis of various diseases, however, the mechanism involved is yet to be fully elucidated. Several efforts have been made in the past decade towards development of drugs, which can inhibit AGEs formation and accumulation without any significant breakthrough. Anti-AGE strategies acting synergistically with conventional approaches may be an important therapeutic option for amelioration of AGE-mediated consequences. Finding newer anti-AGE therapeutics with lesser toxicity level is extremely essential for arresting vascular complications in T2DM.



Inhibitory action of compounds (|—)

Figure 11. Inhibitory action of anti-AGE compounds

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