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Advanced Glycation End Products in Type 2 Diabetes Mellitus: Pathophysiological Insights and the Potential Role of Punica granatum and Peganum harmala as Natural Antiglycation Agents

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Abstract: *Advanced Glycation End Products (AGEs) are a diverse collection of harmful compounds that originate from the non-enzymatic reaction of reducing sugars with proteins, lipids or nucleic acids. Their formation is accelerated in the presence of chronic hyperglycemia, which results as a major contributor for the initiation and progression of T2DM associated complications. The accumulation of AGEs and their ligand-receptor RAGE cause oxidative stress, inflammation, endothelial dysfunction and tissue damage that aggravate the morbidity from diabetes. Traditional antidiabetic treatments mainly focus on hypoglycemic effects and are less effective in directly inhibiting the formation of AGEs or attenuating AGE-induced cellular injury. Therefore, there is a growing interest toward the natural agents possessing antioxidant and antiglycation activities. Of these, Punica granatum (pomegranate) and Peganum harmala (Syrian rue) have attracted considerable attention owing to their high level of polyphenols, flavonoids, and alkaloids with proven antiglycation, anti-inflammatory and insulin-sensitizing effects. The knowledge of the promise of these natural agents may help to formulate new strategies aiming at supplement or adjuvant treatments for decreasing problems related to AGE in diabetes.*

Keywords—Advanced glycation end products; Type 2 diabetes mellitus; *Punica granatum*; *Peganum harmala*; Antiglycation

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterized by long-term hyperglycemia as a consequence of insulin resistance, deficient insulin secretion or both (1). Besides dysregulation of glucose metabolism, T2DM is also characterized by chronic microvascular and macrovascular complications such as nephropathy, neuropathy, retinopathy, and cardiovascular diseases (2). These complications continue to be a major source of morbidity and mortality in diabetes, focusing the attention on molecular mechanisms that are not solely gravid by control of the glucose. (3)

A core biochemistry-based mechanism leading to the progression of diabetic complications is formation and accumulation of AGEs. AGEs are produced by a non-enzymatic glycation where reducing sugars react with amino groups of proteins, lipids or nucleic acids. This is greatly enhanced under hyperglycemic and oxidative stress, which are highly prevalent in T2DM. AGEs accumulate in tissues and circulation over time, and induce deleterious changes in the structure of biomolecules and their function (4).

Traditional antidiabetic agents are effective in reducing blood glucose levels, but have a limited effect on AGE formation and AGE-induced tissue damage. This constraint has stimulated increasing interest in alternative and complementary approaches that intervene directly with oxidative stress- and glycation-targeted actions. In this scenario, medicinal plants with abundant bioactive constituents have attracted much attention because of their pleiotropic biological effects and favorable toxicity profile (5).

Punica granatum (pomegranate) and *Peganum harmala* (Syrian rue) are medicinal plants. pomegranate and *Peganum harmala*, respectively, both of which have been used in traditional Middle Eastern and Asian remedies for the control of metabolic/ inflammatory diseases. A vast number of polyphenols, flavonoids and tannins is contained in pomegranate blossoms and peels with potent antioxidant and antiglycation activities (6). Also, seeds from *Peganum harmala* have β-carboline alkaloids like harmine and harmaline that have antioxidant, anti-inflammatory as well as insulin-sensitizing effects (7). Hence, it may be that these plants have the potential to attenuate AGEs formation and subsequently reduce AGE-mediated oxidative and inflammatory injury; this was also shown in some emerging experimental studies. (8,9)

This review is organized to highlight the relationship between AGEs and T2DM, with a point of focus on possible role of *Punica granatum* and *Peganum harmala* as natural antiglycation agents. Here we summarize mechanistic and preclinical evidence to guide the conduct of future studies examining the clinical relevance of these botanicals in the management of AGE-related diabetic complications.

2. Pathophysiology of T2DM

The main pathophysiological mechanisms involved in T2DM can be outlined as follows: (As shown in Figure 1).

- The Insulin Resistance and β-cell Dysfunction (10,11). (As shown in Figure 1).

- Inflammation and Adipose Tissue Dysfunction (12,13).
- Hepatic Glucose Dysregulation (14,15).
- Mitochondrial Dysfunction and Oxidative Stress: (16,17).
- Gut Microbiota Alterations and Incretin Dysregulation (18,19).

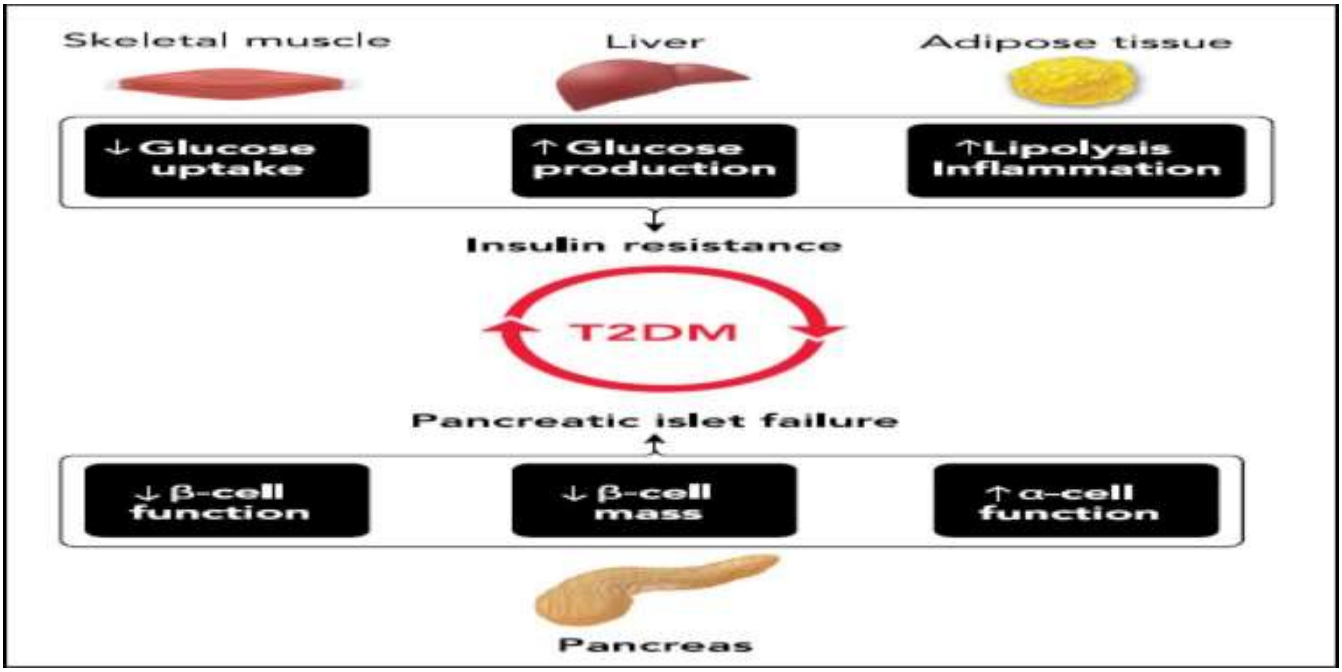

Fig. 1. *Pathophysiology of T2DM (20).*

3. **Diagnosis and Monitoring of T2DM**

Typical symptoms include polyuria, polydipsia, weight loss, and blurred vision. Prolonged hyperglycemia leads to retinopathy, nephropathy, neuropathy, and higher cardiovascular risk (1).

American Diabetes Association (ADA) recommends pre-meal glucose 80–130 mg/dL and post-meal <180 mg/dL (1).

Diagnosis is based on ADA guidelines (1). As shown in Table 1.

Table 1: Diagnostic Criteria of DM.

No.	Diagnostic Test	Criteria
1	Fasting Blood Glucose (FBG)	≥126 mg/dL after 8-hour fasting.
2	Oral Glucose Tolerance Test (OGTT)	≥200 mg/dL after 2 hours of 75 g glucose.
3	Glycated Hemoglobin (HbA1C) Test	≥6.5%.
4	Random Blood Glucose (RBG)	≥200 mg/dL with symptoms.

Monitoring guides treatment decisions and prevents complications. As shown in Table 2.

Table 2: Glucose Monitoring Biomarkers.

No.	Test	Description
1	Self-Monitoring of Blood Glucose (SMBG)	Daily finger-prick tests track glucose, though invasive; sensor-based patches offer alternatives (21).
2	HbA1C Test	Reflects 2–3 months glucose average; target <7% to reduce long-term risks (1).
3	Urine Microalbumin Test	Detects early kidney damage in diabetes (22).

4	Continuous Glucose Monitoring (CGM)	Provides real-time glucose trends, improving control and treatment adjustment (23).
5	Lipid Profile	Detects diabetic dyslipidemia, important for cardiovascular risk management (24).
6	Glycosylated Serum Protein (GSP)	Fructosamine or GSP reflects 2–4 weeks glycemic control; useful for short-term monitoring and detecting fluctuations not captured by HbA1C (25).
7	Advanced Glycation End Products (AGEs)	Reliable index of long-term glycemic control, reflecting years of hyperglycemia. Can be measured non-invasively (e.g., skin autofluorescence) (26-28).

4. Advanced Glycation End Products and It's Formation Process in the Human Body

AGEs are heterogenous compounds and comprise a wide range of biomolecules that is produced via the non-enzymatic reaction between proteins, lipids or nucleic acids by the reducing sugars. This reaction (Maillard process) is endogenous but prominently accelerated through hyperglycemia, oxidative stress and chronic inflammation. AGEs are important in both physiological aging and the pathogenesis of many diseases such as diabetes mellitus, cardiovascular disorders, and neurodegenerative processes (29).

The generation of AGEs involves a non-enzymatic interaction between reducing sugars and biomolecules, which can be considered in several steps. In an initial stage, Schiff Base Formation takes place in a fast and reversible kinetics between reducing sugars (glucose, fructose) and freeamino groups of proteins, lipids or nucleic acids to give rise to labile Schiff bases (30). Then, in the intermediate stage, Schiff bases are rearranged to more stable products (still reversible) of Amadori (31). In the reactive stage, Amadori products break down into highly reactive intermediates such as methylglyoxal and glyoxal, which accelerate oxidative stress and protein modification (32). The late stage involves irreversible AGE formation, where through oxidation and polymerization, reactive intermediates are converted into stable AGEs such as carboxymethyl-lysine (CML) and pentosidine, which accumulate in tissues (32). Finally, AGEs interact with their receptor (RAGE activation), triggering oxidative stress, inflammation, and cellular dysfunction, which play key roles in diabetes complications (33). As shown in Figure 2.

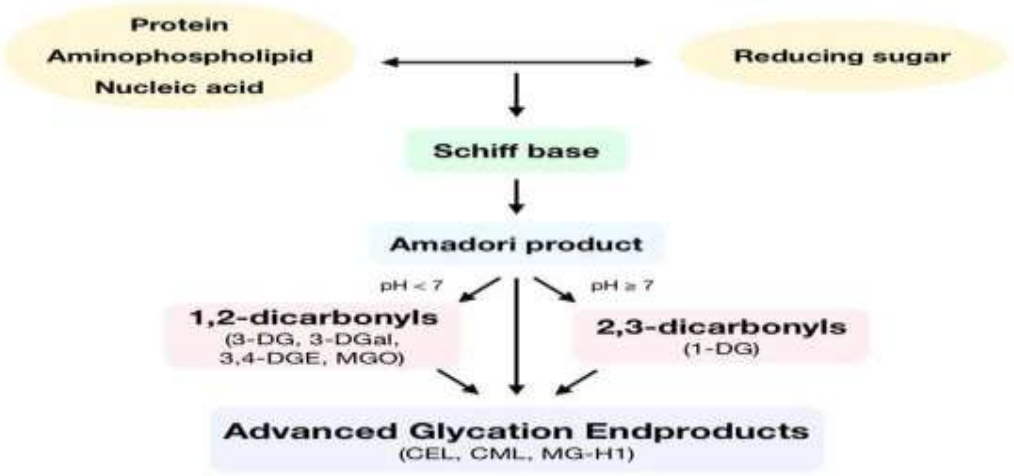

Fig. 2. *Formation Process of AGEs in the Human Body (34).*

5. Central Role of Advanced Glycation End Products (AGEs) in the Pathogenesis of Type 2 Diabetes Mellitus

AGEs have major contribution to the development of insulin resistance through influencing insulin receptor signal transduction and β-cell function. They also interact with RAGE, causing inflammation pathways, activating the over-expression of pro-inflammatory cytokines (TNF-α, IL-6) and ROS. These molecular changes lead to decreased glucose uptake in peripheral tissues and impaired insulin action, which aggravates the progression of diabetes (35).

Over-accumulation of AGEs in diabetes is a central factor that promotes the development of insulin resistance, chronic

inflammation and vascular disorder, which drive microvascular and macrovascular complications (36).

AGEs deposition is found to be closely associated with diabetes mediated-microvascular complications, that includes: Diabetic nephropathy (AGEs implement renal fibrosis and glomerular damage, leads to proteinuria, and ultimate kidney damage), Diabetic retinopathy (AGE-induced vascular endothelial damage enhances retinal neo-vascularization that increase the risk of vision loss), and Diabetic neuropathy (AGEs are responsible for oxidative stress and neuroinflammation, resulting in neurodegeneration affecting both sensory and motor nerve functions) (36).

AGEs generation also has an important impact on macrovascular complications including atherosclerosis and cardiovascular diseases via: induction of LDL oxidation resulting in plaque formation and arterial stiffness that upregulate vascular stiffness and endothelial dysfunction which ultimately contribute to hypertension and reduced blood flow. Also, enhancing inflammatory responses, which heighten the risk of myocardial infarction and stroke (37). As shown in Figure 3.

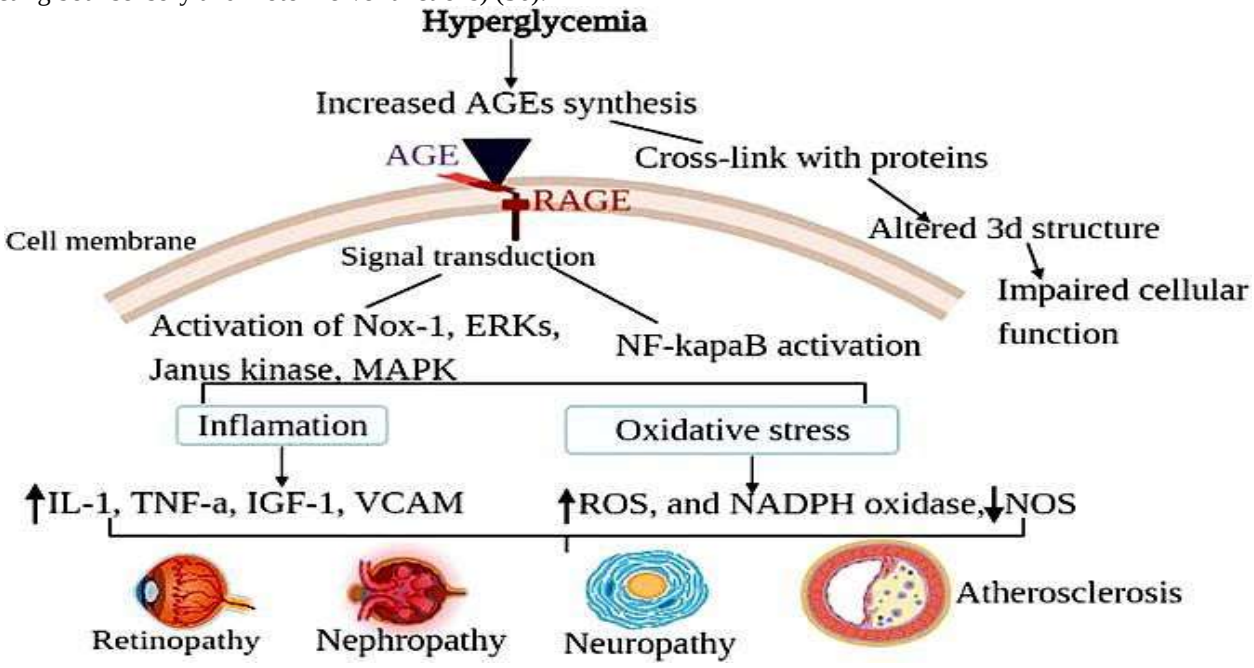

Fig. 3. *AGEs and complications of T2DM (38).*

6. Molecular Mechanisms Linking AGEs to Diabetic Complications

AGEs mediate diabetic disease in two main ways. The first process is: Structural Modification of Biomolecules; where the AGEs cause irreversible cross-linking, with long-lived proteins (collagen, elastin and albumin), hence, effects the functioning of these molecules. This alteration leads also to vascular and tissue stiffness, that promotes endothelial dysfunction, alternate connective tissue distensibility, leading to an increase in ageing of vasculature change enzymatic activity, interfering with normal metabolism (39).

The second pathway is: Activation of RAGE and Cellular Dysfunction, in which the binding of AGEs to their principal receptor, RAGE (Receptor for Advanced Glycation End Products), initiates inflammatory and oxidative stress reactions. This activation results in chronic inflammation through the nuclear factor-kappa B (NF-kB) stimulation, Endothelial dysfunction with consequent atherosclerosis and hypertension, Excess of oxidative stress contributing to diabetes complications, neurodegeneration and renal failure (40).

7. Limitations of Conventional Therapies in Targeting AGE-Related Damage

Growing interest has been focusing on herbal medicine as a process of developing the therapeutic potential of herbs on diabetes and its complications.

Traditional therapy for type 2 diabetes mellitus is mainly to control glucose; however, little is known about the role of oxidative stress and the formation of AGEs. Consequently, there is active investigation of natural agents that help providing additional protective effects against diabetic complications (41).

Medicinal plants contain numerous bioactive compounds, including polyphenols, flavonoids, and alkaloids, which possess strong antioxidant and anti-inflammatory effects. These natural substances help alleviate oxidative stress and reduce AGEs formation, a key contributor to diabetic complications. It has been reported that antioxidants from plants can inhibit non-enzymatic glycation reactions affecting

the generation of AGEs and production of potential damage (42).

8. *Punica granatum* as a Natural Modulator of AGE Formation and Activity

The commonly known fruit-bearing shrub or small tree, *Punica granatum* (Pomegranate) from the Lythraceae family. it is widely grown in Mediterranean countries and some areas of Asia. t is also a well-known edible and medicinal plant, containing many nutrients with high health benefits and have higher biological activities in the flower and peel (43). As shown in Figure 4.

Both pomegranate flowers and peels are rich in bioactive compounds including polyphenols, flavonoids, tannins, anthocyanins, organic acid that may provide antioxidant, anti-inflammatory and anti-glycation effect to lower the formation of AGEs (44).

Pomegranate is well known for several thousands of years in traditional medicine like Persian, Unani and Ayurvedic system of medicine. And the different parts, especially the flowers and peels, have traditionally been used to regulate symptoms similar to diabetes such as thirst and frequent urination. These were the early application from the ancient medical texts in Middle East and South Asia (45).

In recent years, pomegranate has received scientific attention for it's potential to reduction of AGEs. Its effects may contribute to prevent AGEs formation and metabolic health in T2DM patients (46).

In a diabetic mice model (type 2 diabetic mice), researchers found that the pomegranate peel extract lowered AGEs in the blood drastically. This decline in AGEs levels closely corresponded to declines seen in several markers of diabetes, including blood sugar. Furthermore, its role as an antioxidant implies that pomegranate might also reduce oxidative stress, a major trigger in the formation of AGEs (47).

Another report shows that pomegranate flavanoids may be used as a therapeutic treatment against streptozotocin-induced diabetic nephropathy in rats. In addition, the accumulation of AGEs in tissues, mainly in the kidney, were significantly reduced and this resulted in better renal function. The results reveal that pomegranate extracts might be a promising adjuvant for the inhibition of diabetic nephropathy through convenient reduction in AGEs accumulation (48).

These animal studies suggest that pomegranate extracts, particularly from the peel and flowers, could reduce AGEs formation and associated oxidative stress in diabetes. But further human studies are needed to validate these findings.

Fig. 4. *Punica granatum Plant (49).*

9. *Peganum harmala* and Its Antiglycation Potential in Type 2 Diabetes Mellitus

Peganum harmala, commonly known as (Syrian rue) or (Harmal), is a perennial herbaceous plant from the (Zygophyllaceae) family. The plant has been traditionally utilized in herbal medicine due to its antioxidant, antimicrobial, and antidiabetic effects (50). As shown in Figure 5.

Peganum harmala seeds contain diverse bioactive compounds, including alkaloids (harmine, harmaline, harman, harmalol), polyphenols, flavonoids, tannins, and saponins, which collectively exert antioxidant, anti-inflammatory, and antiglycation effects important for reducing AGEs formation (51).

Peganum harmala, is a plant that has been used for centuries in traditional medicine in various parts of the world, such as Middle East and Asia. It is medicinally important and known worldwide as therapeutic plant, especially in diabetes. Seeds of *Peganum harmala* have been prescribed as a folk medicine for the regulation of blood glucose and the treatment of diabetic complications. This use of the plant has an old history and in traditional Persian and Arabic systems of medicine it is well-known as a plant capable of controlling hyperglycemia and based on this inducing health in diabetic patients (52).

When diabetic rats were treated with *Peganum harmala* seed extract, the results showed extract had some beneficial effects on not only reduction in oxidative stress but also improvement of some biochemical markers that could imply decrease in AGEs accumulation. Although they did not measure the actual AGEs, the study demonstrated the extract's efficacy in oxidative stress and blood sugar (53). This animal study suggests that *Peganum harmala* seed can reduce AGEs levels.

Fig. 5. *Peganum harmala Plant (54).*

10. Comparative Mechanisms of *Punica granatum* and *Peganum harmala* in AGE Modulation

Although *Punica granatum* and *Peganum harmala* differ in their phytochemical composition, both plants share several overlapping mechanisms that contribute to their antiglycation effects. The most common mechanism that they share is their great antioxidant activity, which decrease oxidative stress and block glycoxidation reactions for AGEs formation. They are also scavengers for free radicals and could prevent oxidative damage of biomolecules in the body (55,56).

Another prevalent pathway is the blockade of reactive carbonyl species, which are vital intermediary stages from early glycated products to AGEs. Through damping down the most reactive compounds, each plant retards buildup of these irreversible AGEs (57,58).

Nevertheless, every plant has features that favour it in particular. *Punica granatum* is noted to be especially effective in the maintenance of endothelial function and vascular health, mainly by increasing nitric oxide availability (59). Additionally, AGE–RAGE signaling inhibition seems to be a common pathway since active compounds from pomegranate have been reported to decrease the level of RAGE expression and subsequently inflammatory responses as well (60). By contrast, effects of *Peganum harmala* on insulin sensitivity and inflammation are more prominent (61). These addtives characteristics argue in favour of combined or complementary use of these botanicals for the broader protection against AGEs against diabetes-associated complications.

11. Clinical Relevance of AGEs as Biomarkers and Therapeutic Targets

Advanced Glycation End Products (AGEs) have emerged as clinically useful biomarkers of cumulative metabolic stress in diabetes. Unlike brief summary measures of glycemia, AGEs are long-term indexes reflecting chronic glycemic and oxidative stress both being so important in indicating diabetes evolution/consequences. Determination of circulating AGEs and other related markers, such as fructosamine, reflects both short- and intermediate-term glycemic control and glycation load (62,63).

AGEs are an attractive therapeutic target because medicine target processes that continue unabated despite only modest improvements in hyperglycemia. Inhibition of AGEs accumulation might be the possible strategy to retard micro- and macrovascular complications, ameliorate tissue function and improve metabolic control in T2DM. Thus, natural antiglycation agents may serve as an important supplement to traditional antidiabetic drugs (64).

12. Research Gaps and Future Perspectives

Although there is strong experimental evidence of the antiglycation potential of *Punica granatum* and *Peganum harmala*, many research gaps still exist. The majority of this information is from in vitro and animal models, as there are relatively few well-designed clinical trials implemented where AGEs was the main outcome measured in human populations. Moreover, the preferable dose regimens, long-term safety and possible interactions with classical antidiabetic drugs still merit attention.

The future studies should prioritize randomized controlled trials on the effects of these botanicals on circulating AGEs, fructosamine, and oxidative stress markers in T2DM patients. Clarifying their organ-specific molecular targets in human tissues will provide a more comprehensive understanding of their therapeutic implications, and subsequent data can favor evidence-based inclusion of these derivatives into the management toolbox for diabetes.

13. Conclusion

Advanced glycation end products are involving in the pathophysiology of type 2 diabetes mellitus and related complications by meditating oxidative stress, vascular inflammation, endothelial disfunction and insulin resistance. The degree of AGE-induced damage cannot always be resolved by conventional therapeutic strategies alone. An increasing body of evidence indicates that *Punica granatum and Peganum harmala* have notable antiglycation, antioxidant, anti-inflammatory activities that could be beneficial as additional therapeutic modalities.

Through simultaneously acting against a variety of pathogenic pathways, these medicinal plants provide a potential natural approach for the suppression of AGEs accumulation and intervention in diabetic complications. More clinical studies are needed before these results can be translated for use as potential additional therapies of T2DM in the clinic.

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