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The Effect of Herbal Interventions on Advanced Glycation End Products and Fructosamine Levels in Patients with Type 2 Diabetes

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Abstract: **Objectives:** This study examined whether short-term supplementation with dried pomegranate flowers, dried pomegranate peels, or *Peganum harmala* seeds affects advanced glycation end products (AGEs) and fructosamine in patients with type 2 diabetes mellitus (T2DM). Secondary objectives included evaluating whether diabetes duration, medication use, or biochemical parameters modify these glycation responses. **Methods:** A total of 124 adults with T2DM were randomized into four groups: Control (n = 27), Pomegranate Flower (n = 33), Pomegranate Peel (n = 33), and *P. harmala* Seed (n = 31). The control group received standard therapy alone, while intervention groups received standard therapy plus 0.896 g/day of the assigned supplement for 2 weeks. Serum AGEs and fructosamine were measured at baseline and post-intervention. Eighty-eight participants completed the trial. **Results:** Pomegranate flower and *P. harmala* were associated with increases in AGEs, suggesting potentially adverse short-term glycation effects. Fructosamine also increased with *P. harmala* and pomegranate peel, indicating no glycemic benefit during the intervention period. Higher AGEs were observed among participants using metformin or other antidiabetic medications and among those with longer diabetes duration. AGEs correlated negatively with HbA1c and positively with HDL, while fructosamine correlated positively with total cholesterol and LDL. **Conclusion:** Short-term supplementation with *P. harmala*, pomegranate flower, or pomegranate peel did not improve glycation markers and was instead linked to elevated AGEs or fructosamine. These changes appear influenced by underlying metabolic status rather than a therapeutic effect. Longer studies are needed to clarify clinical relevance and safety.
Recommendations: Future studies with larger sample sizes and longer intervention durations are needed to determine whether the observed glycation changes persist and to better evaluate long-term safety. Investigating potential synergistic effects between *P. harmala* and *Punica granatum* components may also provide further insight into their metabolic impact.

Keywords: type 2 diabetes mellitus, pomegranate, *Peganum harmala,* advanced glycation end products, fructosamine

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both [1, 2]. Prolonged elevations in blood glucose levels contribute to complications largely mediated by oxidative stress and the accumulation of advanced glycation end products (AGEs) [3, 4].

AGEs are stable molecules formed through non-enzymatic reactions between reducing sugars and free amino groups of proteins, lipids, or nucleic acids—a process known as the Maillard reaction [5]. This glycation alters the structural and functional properties of macromolecules, promoting tissue dysfunction. Under chronic hyperglycemic and oxidative conditions, AGEs accumulate in tissues, cross-link with structural proteins, and bind to receptors such as RAGE (receptor for advanced glycation end products), triggering inflammatory and oxidative pathways [6]. These molecular events contribute to the pathogenesis of diabetic complications including nephropathy, retinopathy, neuropathy, and cardiovascular disease [7].

Fructosamine, another glycation marker, reflects glycemic control over a shorter duration (2–3 weeks) and provides a sensitive indicator for short-term fluctuations in blood glucose [8, 9] . While HbA1c reflects average glucose over two to three months, fructosamine allows for earlier assessment of therapeutic effects or dietary changes. Together, AGEs and fructosamine serve as complementary markers of long- and intermediate-term glycemic and oxidative burden, and may better inform management decisions and risk stratification [5, 10, 11].

Pomegranate (*Punica granatum*) flowers and peels, along with *Peganum harmala* seeds, are promising natural sources of bioactive compounds with demonstrated antioxidant and anti-inflammatory properties that may influence protein glycation [12, 13]. These plants are rich in polyphenols—such as flavonoids, tannins, and phenolic acids—which exhibit strong free radical scavenging capacity and antioxidant activity [14, 15].

Polyphenols have been shown to suppress protein glycation and inhibit the formation of AGEs both in vitro and in vivo by neutralizing reactive carbonyl species and modulating glycation-related enzymatic pathways [10, 16]. They may also enhance broader metabolic profiles, supporting their potential role in managing diabetes-related complications [17].

Although many preclinical studies report antiglycation and antihyperglycemic effects of medicinal plants like pomegranate and *Peganum harmala*, clinical data are limited. Several

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randomized controlled trials on P. granatum seed oil or powder in patients with type 2 diabetes have shown improvements in glycemic and lipid profiles, including enhanced glucose transporter activity [18, 19]. However, these studies did not assess direct glycation markers such as AGEs or fructosamine, highlighting a gap in clinical evaluation of their antiglycation potential. *Peganum harmala* has also demonstrated antidiabetic and antioxidant effects in preclinical models, though human studies are scarce and further research is needed to assess its safety and efficacy in clinical settings [20].

Thus, despite promising biochemical and preclinical findings, a clear knowledge gap exists regarding the effects of these herbal extracts on glycation markers in humans. Most clinical studies to date have not examined their impact on AGEs and fructosamine—key biomarkers implicated in the long-term progression of diabetic complications.

This study aims to address that gap by investigating the short-term effects of supplementation with pomegranate flower, pomegranate peel, and *Peganum harmala* seed on serum AGEs and fructosamine levels in patients with type 2 diabetes mellitus. Specifically, the research asks: Can short-term supplementation with these herbal supplements modulate serum AGEs and fructosamine levels in type 2 diabetic patients?

The central hypothesis is that supplementation with these antioxidant-rich botanicals may reduce AGEs and fructosamine concentrations, thereby supporting their potential role as adjuvant therapies for mitigating glycation-related risks in diabetes management.

As a secondary aim, the study also explores how changes in AGEs and fructosamine relate to patient-specific variables, including diabetes duration, medication use (especially metformin and other antidiabetics), and lipid profile parameters. This may help identify clinical predictors or modifiers of glycation marker responses to herbal supplementation.

Materials and Methods

Devices and equipment

Empty capsules (500 mg) were sourced from IKO (China). The SF-400C electronic balance was manufactured by Jiangyin Suofei Electronic Technology Co., Ltd. (China). Single-use 5 mL syringes were obtained from Shree Umiya Surgical PVT. LTD. (India). Gel and clot activator tubes were acquired from Shandong Chengwu (China). The centrifugation process was performed using an NF 800R centrifuge from Nuaire Sanayi Malzemeleri Imalat Ve Ticaret A.S. (Turkey). Pipette tips and multichannel pipettes were provided by Thermo-Fischer Scientific (China). The study also employed a BioTek 800TS ELISA Microplate Reader (USA) and 11 Vortex Mixer (UK).

Herbal materials

Dried flowers of *Punica granatum* were obtained from Sulaymaniyah, Iraq, while dried peels of *P. granatum* and seeds of *Peganum harmala* were purchased from local herbal suppliers in Basrah, Iraq. The materials were commercially available for medicinal use and were procured during the autumn season (September 2024). All plant materials were visually inspected for authenticity, cleaned of extraneous matter, and stored in airtight containers at room temperature in a dry environment until use.

Kits for diagnosis

The diagnostic kits were of two main types in this study. The first one is the OxiSelect AGEs Competitive ELISA Kit, which was obtained from Cell Biolabs, Inc., San Diego, California, USA. This kit is intended to measure AGEs quantitatively in biological samples. The second diagnostic kit employed was the Glycosylated Serum Protein (GSP) Colorimetric Assay Kit, obtained from Elabscience Biotechnology Inc., Houston, Texas, USA. This kit allows a reliable determination of the glycosylation of the serum proteins in vitro by means of a colorimetric method.

Study design and participants

This single-blind, randomized controlled clinical trial was conducted at the Diabetes and Endocrinology Center, Al-Faihaa Teaching Hospital, Basra, Iraq, between October 2024 and March 2025.

A total of 125 patients with type 2 diabetes mellitus (T2DM) were screened for eligibility, of whom one was excluded for not meeting the inclusion criteria. The remaining 124 participants were randomly allocated into four groups using a computer-generated random number sequence. The randomization sequence was generated by an independent statistician, and group assignments were concealed in sealed, opaque envelopes until the point of allocation.

- Group 1 (Control, n = 27): Received standard antidiabetic therapy alone (primarily metformin 500–2000 mg/day and sulfonylureas such as glibenclamide 2.5–10 mg/day or gliclazide 30–120 mg/day).
- Group 2 (Pomegranate Flower, n = 33): Received standard therapy + 0.896 g/day of dried *Punica granatum* flowers (four capsules).
- Group 3 (Pomegranate Peel, n = 33): Received standard therapy + 0.896 g/day of dried *Punica granatum* peels (four capsules).
- Group 4 (*Peganum harmala* Seed, n = 31): Received standard therapy + 0.896 g/day of dried *Peganum harmala* seeds (four capsules).

All herbal supplements were administered for 14 days in addition to each participant's usual prescribed medication. Antidiabetic medications were continued at the doses prescribed prior to enrollment, were not standardized by the study protocol, and no planned changes in medication type or dose were made during the 14-day intervention period.

This was a single-blind study, in which the outcome assessors were blinded to group allocation, but participants and study staff were aware due to the nature of the interventions.

The control group did not receive a placebo intervention and continued standard antidiabetic therapy alone; placebo administration was not implemented due to the nature of the herbal interventions

Follow-up completion varied across groups due to participant withdrawal or loss to follow-up, resulting in 88 participants completing the study and being included in the final analysis.

The overall enrollment, randomization, allocation, and analysis process is illustrated in Figure 1 (CONSORT 2010 flow diagram).

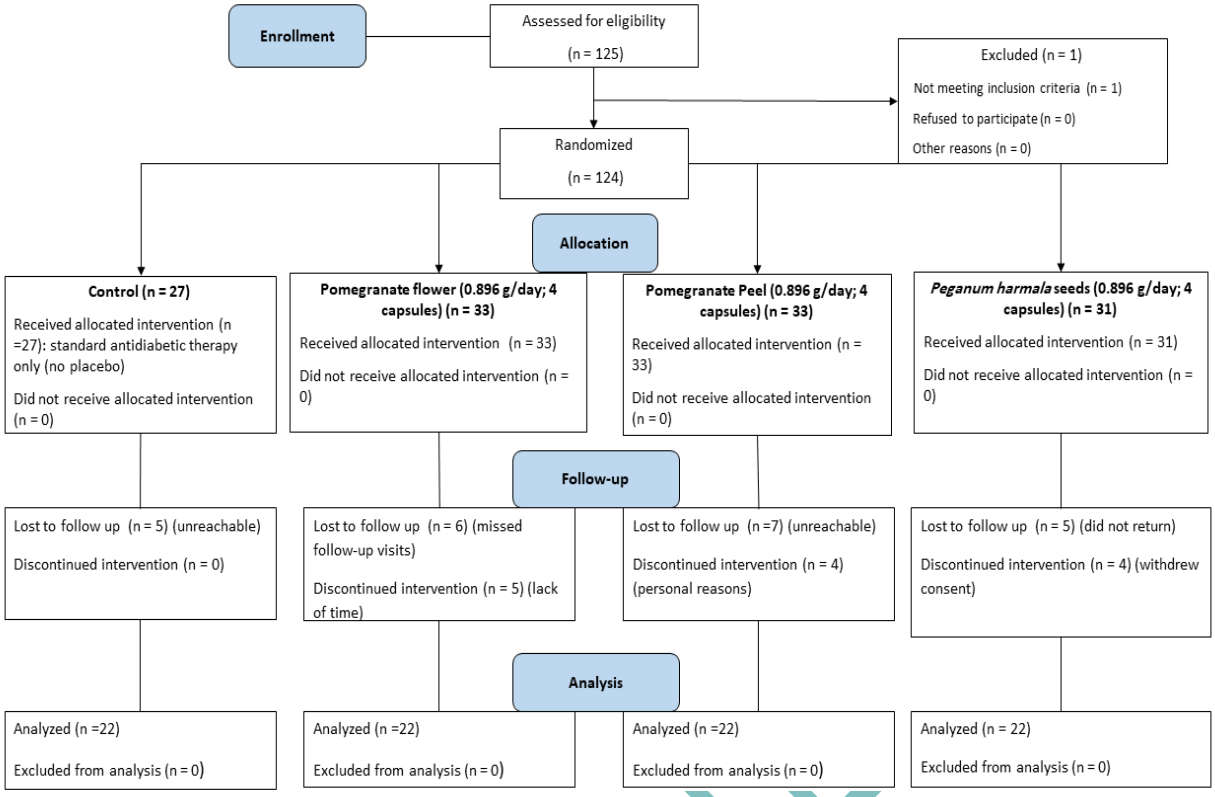

Figure (1): CONSORT 2010 flow diagram illustrating participant enrollment, randomization, allocation, follow-up, and analysis across the four study groups: Control (standard antidiabetic therapy only; no placebo administered), *Punica granatum* flower (0.896 g/day), *Punica granatum* peel (0.896 g/day), and *Peganum harmala* seed (0.896 g/day)

Sample size estimation

The required sample size was estimated a priori using G*Power (version 3.1.9.7) for a one-way ANOVA comparing four independent groups. Parameters were set as: effect size (f) = 0.40 (large), α = 0.05, and statistical power (1 − β) = 0.80. The analysis indicated that a minimum of 76 participants (≈ 19 per group) was required. To ensure sufficient power and account for expected attrition, 124 participants were initially enrolled. After screening and follow-up losses, 88 participants completed the study and were included in the final analysis [21].

Dietary and Lifestyle Monitoring

Participants were instructed to maintain their usual diet and physical activity during the 14-day intervention period. They were not asked to avoid or consume dietary AGE-rich foods, and the use of additional supplements or herbal products was prohibited. While detailed dietary intake was not recorded, participants were advised to keep their habits consistent. Adherence to medications and study supplements was supervised by the attending physicians.

Inclusion criteria

Inclusion criteria required participants to be adults aged 30–60 years with a confirmed diagnosis of type 2 diabetes.

Patients were diagnosed by a specialized endocrinologist at the Faiha Specialized Diabetes, Endocrine, and Metabolism Center (Basrah, Iraq), according to the diagnostic criteria of the American Diabetes Association (ADA, 2024) [22].

Exclusion criteria

Exclusion criteria encompassed patients with type 1 diabetes, those on insulin therapy, pregnant or breastfeeding women, individuals with malignancies, or those undergoing chemotherapy.

Preparation of herbal supplements

A simple technique was used involving grinding dried *Punica granatum* flowers, *P. granatum* peels, and *Peganum harmala* seeds into fine powders using a grinder. The powders were then manually filled into empty gelatin capsules (capacity: 500 mg) for oral administration. The weight variation test was performed in accordance with USP <905> to ensure uniformity among capsules.

Daily Dose Calculation

Each patient received four capsules daily. The total daily intake of the herbal powder was calculated by multiplying the average fill weight by the number of capsules taken per day:

Daily Dose (g) = Number of capsules × Average fill weight Daily Dose = 4 × 0.224 = 0.896 g of fine powder per day.

This dose is consistent with previous human studies that used between 750 mg and 1000 mg/day of *Punica granatum* preparations (Hosseini et al., 2016; Farahat et al., 2025) and lies within the ethnopharmacologically accepted range for *Peganum harmala [20, 23, 24]*. Due to capsule-filling capacity limitations, the nearest achievable equivalent to 1 g/day was 0.896 g, which can therefore be considered approximately 900 mg/day.

Blood collection and laboratory analysis

Venous blood samples (5 mL) were drawn by a qualified nurse before and after the 2-week intervention period. Whole blood was collected in a clot activator tube. Serum was separated and analyzed for AGEs and fructosamine. The two-week duration was selected to correspond to the lifespan of

fructosamine (≈2–3 weeks), allowing early detection of short-term glycation changes.

Statistical analysis

All analyses were performed using SPSS version 26 and MedCalc version 12. Data normality was assessed using the Kolmogorov–Smirnov test. For normally distributed variables, within-group differences were evaluated using paired t-tests and between-group comparisons using one-way ANOVA with Tukey's post hoc test; Cohen's *f* was reported as the effect size for ANOVA models. For non-normally distributed variables, within-group changes were analyzed using the Wilcoxon signed-rank test, and between-group differences using the Kruskal–Wallis test followed by Dunn's test with Bonferroni correction for multiple comparisons. Cohen's *d* was used to quantify within-group effect sizes.

Subgroup analyses and correlation tests were preplanned and conducted using Mann–Whitney U, Kruskal–Wallis, or Spearman's correlation, as appropriate. Statistical significance was defined as $p < 0.05$.

Results

Advanced Glycation End Products and Fructosamine (Primary Outcomes)

Statistically significant post-intervention increases in AGEs were observed in the Pomegranate Flower (median change +39.3%) and *Peganum harmala* (+27.2%) groups ($p < 0.05$), both showing meaningful within-group change, supported by their overall large between-group effect size (Cohen's $f = 0.51$). Non-significant changes in the Peel and Control groups were not associated with notable effect magnitudes. Between-group comparisons were significant ($p = 0.001$), and post hoc testing showed that the Flower group differed from the Control group; Peel group differed from the Flower group, while the Harmala group differed from both Peel and Control. Although the direction of changes was consistent, the clinical relevance of these short-term increases remains uncertain.

Fructosamine increased significantly in the Harmala (+20.2%) and Peel (+17.1%) groups ($p < 0.05$), with a moderate overall between-group effect (Cohen's $f = 0.37$). Changes in the Flower and Control groups were non-significant and therefore not associated with meaningful effect sizes. Post hoc comparisons indicated that the Flower group differed from Control; Peel differed from Control and Flower; and Harmala differed from Flower, Peel, and Control. Despite statistical significance in several comparisons, considerable variability and overlapping ranges support cautious interpretation. Full data are presented in Table 1.

Overall, while multiple comparisons reached statistical significance, the magnitude and consistency of biochemical changes varied across groups, and the short intervention duration limits conclusions regarding longer-term effects on glycation pathways.

Table (1): Comparison of serum AGEs and fructosamine levels before and after 2-week intervention among study groups of patients with type 2 diabetes mellitus (n = 88).

Parameters	Control N=22	Flowers N=22	Peels N=22	Harmel seeds N=22	Cohen's *f*	P-value
AGEs (ug/dl)						
Before	18 (12.7 - 31.4)	14.2 (11.3 - 19.5)a	20 (8.2 - 39.1)b	13.6 (11.6 - 21.6)ac	**0.65**	**<0.00001**
After	19.7 (14.5 - 32.5)	20.1 (11.1 - 26.8)	18.2 (9.2 - 24.8)	18.6 (12.9 - 29.1)	**0.26**	**0.1737**
P-Value	**0.0853**	**0.0001**	**0.9224**	**0.0004**		
Median Change	8.3 (-41.7 - 125.7)	39.3 (-24 - 129.1)a	5.3(-73.9 - 178.7)b	27.2(-15.1-142.5) ac	**0.51**	**0.00123**
% PT with Declining	6 (27.3%)	3 (13.6%)	10 (45.5%) b	4 (18.2%)		**0.0796**
% PT with NON	16 (72.7%)	19 (86.4%)	12 (54.5%)	18 (81.8%)		
Cohen's *d*	0.04	0.16	0.02	0.12		
Fructose amine (g/dl)						
Before	3.2 (2.4 - 8.4)	2.3 (1.1 - 3.9) a	2.1 (1.3 - 3.3) ab	3.1 (2.3 - 6.3) bc	**0.285**	**<0.00001**
After	3.1 (2.1 - 6)	2.1 (1 - 4.2) a	2.5 (1.6 - 4.9) ab	3.7 (2.3 - 7.8) ab	**0.9**	**<0.00001**
P-Value	**0.3219**	**0.0537**	**0.0143**	**0.0340**		
Median Change	-4 (-55.2 - 74)	-8.3 (-47.1 - 35.5)	17.1 (-34 - 111.3) ab	20.2(-53.4 -139.3)ab	**0.37**	**0.00041**
% PT with Declining	13 (59.1%)	16 (72.7%)	6 (27.3%)	7 (31.8%)		**0.0057**
% PT with NON	9 (40.9%)	6 (27.3%)	16 (72.7%)	15 (68.2%)		
Cohen's d	0.01	0.01	0.01	0.02		

Normal distribution tested by Kolmogorov-Smirnov Normal Test
Values are presented as *median (range)* due to non-normal distribution (Kolmogorov–Smirnov test). Between-group comparisons were performed using the Kruskal–Wallis test, followed by Dunn's test with Bonferroni correction for multiple pairwise comparisons. Within-group (pre- vs post-intervention) comparisons were analyzed using the Wilcoxon signed-rank test.
[a] significantly different from control value
[b] significantly different from flowers value
[c] significantly different from Peels value
P value <0.05 considered significant
d=0.2 small,0.5 medium,0.8 large effect of sample size
f = 0.1 small, 0.25 medium, =0.4 large effect

Subgroup and Correlation Analyses

Among metformin users, AGEs increased significantly ($p = 0.0002$); a similar pattern was seen in non-users ($p = 0.0403$). Fructosamine changes were not significant in either group. Baseline fructosamine was significantly higher in metformin users than in non-users ($p = 0.028$), but this difference diminished post-intervention. These findings highlight metabolic variability based on background therapy, though causality cannot be inferred. Results are summarized in Table 2.

Table (2): Comparison of serum AGEs and fructosamine levels before and after 2-week intervention among metformin users and non-users with type 2 diabetes mellitus (n = 88).

Parameters	Patient without Metformin N=21	Patient with Metformin N=67	P-value
AGES (ug/dl)			
Before	16.4 (9.5 - 23.6)	14.7 (8.2 - 39.1)	0.2993
After	19.6 (13.1 - 24.2)	19 (9.2 - 32.5)	0.6990
P-Value	**0.0403**	**0.0002**	
% Change	25.5 (-24.7 - 101.1)	20.6 (-73.9 - 178.7)	0.8717
% PT with Declining	8 (38.1%)	15 (22.4%)	0.1656
% PT with NON	13 (61.9%)	52 (77.6%)	
Fructoseamine (g/dl)			
Before	2.4 (1.3 - 3.7)	2.9 (1.07 - 8.4)	0.028
After	2.3 (1.6 - 5.4)	2.67 (0.98 - 7.8)	0.077
P-Value	**0.4813**	**0.3677**	
% Change	9.5 (-17.4 - 82)	1.9 (-55.2 - 139.3)	0.872
% PT with Declining	9 (42.9%)	33 (49.3%)	0.628
% PT with NON	12 (57.1%)	34 (50.7%)	

Values are presented as *median (range)* due to non-normal distribution (Kolmogorov–Smirnov test). Between-group comparisons were analyzed by the independent-samples Mann–Whitney U test, and within-group (pre- vs post-intervention) comparisons by the Wilcoxon signed-rank test.
A $p < 0.05$ was considered statistically significant.

AGEs increased significantly only in patients with diabetes duration >5 years (p = 0.0001), while the increase among those with ≤5 years did not reach statistical significance (p = 0.0560). Fructosamine levels did not change significantly in either subgroup. This pattern may reflect cumulative metabolic stress or differing oxidative environments in long-standing diabetes.

Comparative data are shown in Table 3.

Table (3): Comparison of serum AGEs and fructosamine levels before and after 2-week intervention according to diabetes duration in patients with type 2 diabetes mellitus (n = 88).

Parameters	≤5 years N=41	>5 years N=47	P-value
AGES (ug/dl)			
Before	15.2 (8.2 - 39.1)	15.9 (8.9 - 29)	0.6544
After	19 (10.2 - 26.8)	19.8 (9.2 - 32.5)	0.2316
P-Value	**0.0560**	**0.0001**	
% Change	12.4 (-73.9 - 129.1)	23.2 (-68.3 - 178.7)	0.2938
% PT with Declining	13 (31.7%)	10 (21.3%)	0.2693
% PT with NON	28 (68.3%)	37 (78.7%)	
Fructose amine (g/dl)			
Before	2.8 (1.45 - 8.43)	2.67 (1.07 - 7.43)	0.9633
After	2.6 (1.55 distribution- 6.03)	2.6 (0.98 - 7.8)	0.7285
P-Value	**0.2679**	**0.7222**	
% Change	3.8 (-53.4 - 82.7)	0 (-55.2 - 139.3)	0.5141
% PT with Declining	19 (46.3%)	23 (48.9%)	0.8090
% PT with NON	22 (53.7%)	24 (51.1%)	

Values are presented as *median (range)* due to non-normal distribution (Kolmogorov–Smirnov test). Between-group comparisons were assessed using the independent-samples Mann–Whitney U test, and within-group (pre- vs post-intervention) differences by the Wilcoxon signed-rank test.
A $p < 0.05$ was considered statistically significant.

Among patients receiving antidiabetic medications, AGEs increased significantly (p = 0.0001), while non-medicated patients showed a non-significant trend (p = 0.0649). Fructosamine remained statistically unchanged in both groups. Although statistically significant, the observed differences were modest, and confounding effects from medication regimens cannot be excluded. Findings are presented in Table 4.

Table (4): Comparison of serum AGEs and fructosamine levels before and after 2-week intervention in patients with and without antidiabetic medications

Parameters	Patient without Antidiabetics medications N=17	Patient with Antidiabetics medications N=71	P-value
AGES (ug/dl)			
Before	16.6 (9.5 - 23.6)	14.7 (8.2 - 39.1)	0.3522
After	19.1 (13.1 - 24.2)	19.4 (9.2 - 32.5)	0.8907
P-Value	**0.0649**	**0.0001**	
% Change	21.1 (-24.7 - 101.1)	20.6 (-73.9 - 178.7)	0.5260
% PT with Declining	8 (47.1%)	17 (23.9%)	0.0591
% PT with NON	9 (52.9%)	54 (76.1%)	
Fructoseamine (g/dl)			
Before	2.4 (1.3 - 3.7)	2.9 (1.07 - 8.4)	0.0227
After	2.17 (1.6 - 5.4)	2.67 (0.98 - 7.8)	0.0667
P-Value	**0.2553**	**0.4843**	
% Change	21.1 (-24.7 – 101.1)	20.6 (-73.9 – 178.7)	0.5260
% PT with Declining	7 (41.2%)	35 (49.3%)	0.5494
% PT with NON	10 (58.8%)	36 (50.7%)	

Values are presented as *median (range)* due to non-normal distribution (Kolmogorov–Smirnov test).
Between-group comparisons were performed using the independent-samples Mann–Whitney U test, and within-group comparisons by the Wilcoxon signed-rank test.
A $p < 0.05$ was considered statistically significant.

AGEs changes were negatively correlated with HbA1c (r = –0.263, p = 0.012), suggesting that individuals with high HbA1c may experience less AGE accumulation. A positive correlation was found between AGEs and HDL (r = 0.219, p = 0.039), though the physiological significance remains unclear. Fructosamine changes correlated positively with total cholesterol (r = 0.238, p = 0.024) and LDL (r = 0.257, p = 0.015). These relationships highlight possible links between lipid status and glycation dynamics. No other correlations were statistically significant. These results are shown in Table 5.

Table (5): Correlation between clinical and biochemical parameters and percentage changes in serum AGEs and fructosamine levels.

Parameters	AGEs conc Changed		Fructosamine conc. Changes	
	R value	P-value	R value	P-value
Age	-0.130	0.327	0.088	0.561
Height	0.061	0.575	0.157	0.142
Weight	-0.116	0.282	-0.060	0.581
BMI	-0.180	0.092	-0.168	0.115
Time since DX	-0.167	0.118	0.028	0.794
W/H ratio	0.081	0.450	0.165	0.141
Hb	-0.116	0.978	-0.087	0.420
HbA1C (%)	-0.263	0.012	0.087	0.421
RBS	-0.102	0.345	0.186	0.082
FBS	-0.133	0.216	0.158	0.140
TC	-0.021	0.845	0.238	0.024
TG	-0.117	0.276	0.101	0.346
LDL	0.076	0.481	0.257	0.015
HDL	0.219	0.039	-0.024	0.822
VLDL	-0.084	0.438	0.058	0.591

Correlation coefficients (R values) were calculated using Spearman's rank correlation test.
R value interpretation:
• 0.00–0.10: very weak or no correlation
• 0.10–0.30: weak correlation
• 0.30–0.50: moderate correlation
• 0.50–0.70: strong correlation
• >0.70: very strong correlation
Positive R values indicate direct correlations, while negative values indicate inverse relationships.
A $p < 0.05$ was considered statistically significant.

Discussion

This study examined the effects of pomegranate flower, pomegranate peel, and *Peganum harmala* seed supplementation on advanced glycation end products (AGEs) and fructosamine in patients with type 2 diabetes mellitus (T2DM). The findings provide insights into early glycation dynamics and the metabolic interactions between glycemic status, lipid profiles, and phytochemicals.

Regarding AGEs, significant increases were observed in the Pomegranate Flower and Harmal groups. These results contradict earlier in vitro findings by Amri et al. (2022), who reported potent anti-glycation effects of pomegranate flower extract [12]. However, Goh and Cooper (2008) noted that oxidative stress can independently enhance AGE formation regardless of glucose levels [25]. This suggests that oxidative stress, inflammation, or dietary AGE intake may have overridden the extracts' antioxidant effects. The rise in AGEs in the Harmal group may be attributed to the pro-oxidant properties of β-carboline alkaloids. Harmine, a principal compound in *Peganum harmala*, has been shown to induce oxidative stress and mitochondrial dysfunction at high concentrations [26], and β-carbolines promote ROS formation in vitro [27]. Although Moloudizargari et al. (2013) described antioxidant effects of *P. harmala* at therapeutic doses, they also noted a context-dependent shift toward pro-oxidant activity [20], suggesting a dose-dependent alteration in pharmacological action that may explain the observed increase in AGEs.

Given this pharmacodynamic profile, it is important to note that *P. harmala*'s β-carboline alkaloids possess MAO-inhibitory and neuroactive properties that can produce dose-related adverse effects, including neurotoxicity or hepatotoxicity. While no adverse events were observed in this short study, the potential for toxicity at higher or prolonged exposure warrants caution [28–30].

Similarly, pomegranate flower polyphenols may exhibit dual redox activity; ellagitannins and flavonoids can undergo auto-oxidation under oxidative conditions, generating ROS and facilitating AGE formation [31]. This redox-dependent effect may have contributed to the observed increase in AGEs. Marked baseline differences in AGEs among groups suggest variability influenced by external factors. Dietary AGEs from high-temperature cooking can raise circulating AGEs [32], and oxidative stress and inflammation from dietary or metabolic sources may also promote AGE accumulation [33, 34]. These variables likely explain the baseline heterogeneity.

Fructosamine levels significantly increased in the Peel and Harmal groups, while non-significant decreases were seen in the Flower and Control groups. P. harmala has been linked to glucose dysregulation in animal models [35], whereas pomegranate seed oil has shown glycemic stabilization [36]. These discrepancies suggest differential effects of various pomegranate components on glycemic control. The transient increase in fructosamine may reflect short-term glycemic variability rather than chronic hyperglycemia. Harmaline, a β-carboline alkaloid, may elevate norepinephrine via monoamine oxidase inhibition, increasing hepatic glucose output [37]. High polyphenol levels in pomegranate peel may also induce temporary metabolic shifts [31]. Given fructosamine's short half-life (2–3 weeks)[11], these changes likely reflect acute effects. Baseline variability in fructosamine may stem from differences in oxidative stress, inflammation, protein metabolism, or renal function [9, 32]. These factors, unaccounted for in the intervention, could have influenced initial measurements.

A significant post-intervention increase in AGEs was observed in both metformin users and non-users. While metformin has antioxidant properties, its effects may be diminished in advanced disease or under sustained oxidative stress [38, 39]. This may explain the lack of protective effect. In contrast, Tanaka et al. (1999) observed reduced AGEs with metformin in diabetic rats [40], suggesting context-specific effects. AGEs also increased among non-metformin users, possibly due to limited glycemic control and the inability of dietary or supplemental interventions alone to reduce AGE levels [41]. Pharmacologic interventions in early-stage diabetes may yield better outcomes, as reported by Monnier et al. (2005) [42]. The elevation in AGEs among non-users may reflect the cumulative burden of unmitigated hyperglycemia [43]. Fructosamine levels did not differ significantly between metformin users and non-users, consistent with findings by John et al. (2023) [44]. This may reflect the stability of fructosamine as a short-term glycemic index and its limited sensitivity to oxidative shifts [45]. While baseline fructosamine was higher in metformin users, this difference resolved post-intervention. This may reflect improved glycemic control in a group with initially worse

metabolic status, as metformin is often prescribed in more advanced cases [46, 47].

Longer diabetes duration (>5 years) was associated with a significant increase in AGEs, supporting the link between chronic hyperglycemia, oxidative stress, and AGE accumulation [25]. In contrast, those with ≤5 years' duration showed only a borderline rise. Genuth et al. (2005) noted that individual variability in oxidative status and renal clearance also influences AGE levels [48]. Fructosamine levels, however, were not significantly associated with diabetes duration, as their short-term sensitivity limits correlation with chronic disease markers [49].

AGEs rose significantly in medicated patients, while changes in non-medicated individuals were non-significant. Sulfonylureas may promote AGE formation under oxidative conditions [50], and cumulative glycemic exposure may explain greater AGE increases in medicated individuals [51]. Non-medicated participants may have had milder disease and lower glycation risk. Baseline fructosamine was significantly higher in medicated patients, likely reflecting longer disease duration or insulin resistance [52]. However, post-intervention changes were non-significant, possibly due to short study duration, adherence variability, and lifestyle factors [53].

Most correlations between glycation markers and clinical parameters were non-significant. However, AGEs showed a negative correlation with HbA1c, likely due to differences in marker kinetics: HbA1c reflects short-term glycemia, while AGEs reflect chronic exposure and oxidative burden [54, 55]. A positive correlation between AGEs and HDL may indicate the presence of glycated or dysfunctional HDL, common in diabetes [56, 57]. Fructosamine positively correlated with total cholesterol and LDL, supporting the link between dyslipidemia and early protein glycation [58, 59].

Overall, although some supplements appeared to elevate AGEs or fructosamine levels, these results should be interpreted with caution. The observed increases likely reflect complex metabolic interactions, including baseline oxidative stress, disease chronicity, and differences in phytochemical concentrations, rather than a direct pro-glycation effect of the extracts themselves. Further dose-response and long-term studies are warranted before definitive conclusions can be drawn regarding the safety or efficacy of these herbal preparations in glycemic management.

Conclusion

This study showed that short-term supplementation with pomegranate flower, pomegranate peel, and *Peganum harmala seeds* influenced glycation markers in patients with type 2 diabetes. Pomegranate flower and harmala were associated with increased AGEs, while harmala and peel raised fructosamine levels. These effects varied across treatment groups and appeared to be influenced by diabetes duration, medication use, and baseline metabolic status. The observed correlations between glycation markers and lipid parameters suggest a potential interplay between dyslipidemia and protein glycation. Overall, the findings reflect complex metabolic interactions rather than consistent antiglycation effects, highlighting the need for cautious interpretation and further long-term, dose-controlled studies.

Recommendations

1. Conduct longer-duration intervention studies to determine whether the observed glycation changes persist and to evaluate long-term safety.
2. Include larger sample sizes in future trials to improve statistical power and generalizability.
3. Explore potential synergistic effects of combining *P. harmala* and *P. granatum* components within the same treatment protocol.

Limitations

1. The study duration was short (2 weeks); although sufficient for detecting early biochemical changes, longer follow-up is needed to determine persistence and safety.
2. The modest sample size (n = 88) may limit generalizability; however, it remains appropriate for an exploratory design and comparable to similar short-term herbal trials.
3. Dietary intake and lifestyle factors were not controlled, which may have influenced glycation and lipid markers.
4. The absence of placebo capsules in the control group may introduce minor behavioral bias, though the use of objective biochemical outcomes and blinded assessments likely minimized this.
5. Variations in medication use, oxidative status, and baseline metabolic conditions may have contributed to the observed increases in AGEs and fructosamine.

Disclosure Statements

- **Ethics approval:** All procedures involving human participants in this investigation were carried out in line with the ethical standards outlined in the Declaration of Helsinki. The study protocol received formal approval from the Ethics Committee at the College of Pharmacy, University of Basrah (Approval Code: EC66), dated November 12, 2024.
- **Consent for publication:** Not applicable
- **Availability of data and materials:** Raw data will be available when requested by the corresponding author.
- **Author's contribution:** Eman Falih Al-Yasiri (Experiment; Data Collection; Patient Follow up; Writing; Revision and Editing; Final Approval), Jubran K. Hassan (Concept and Design; Supervision; Statistical Analysis; Revision and Editing; Final Approval), Ammar M.S. Almomin (Clinical Assessment; Patient Management; Treatment Prescription; Referral for Laboratory Analysis; Supervision; Revision and Editing; Final Approval).
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