The effect of Mangosteen on Inflammation, Oxidative Status, and Hepatorenal Function in Patients with Type 2 Diabetes Mellitus

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Abstract:

Background: Oxidative stress (OS) and inflammation are significant factors in the etiology of type 2 diabetes mellitus (T2DM). Mangosteen (MG) possesses anti-inflammatory and antioxidant activities due to its high concentrations of xanthones, particularly (α-MG) and (γ-MG).

Objectives: This study aims to evaluate MG effect as an adjuvant therapy on inflammation, antioxidant activity, hepatic, and renal function among newly diagnosed T2DM patients.

Methods: This is a prospective randomized-controlled open-label study carried out over 12-week period at the National Diabetes Center for Treatment and Research. Group 1: included patients treated with sitagliptin/metformin tab. (50/1000 mg) twice daily in addition to non-pharmacological therapy (lifestyle modification), Group 2: included patients treated with sitagliptin/metformin tab. (50/1000 mg) twice daily plus MG cap. (500mg) two times daily in addition to non-pharmacological therapy (lifestyle modification). Fasting blood glucose (FBG), HbA1c, fasting serum insulin (FSI), HOMA-IR, Serum interlukin-6 (IL-6), superoxide dismutase-1 (SOD-1), liver and kidney parameters were assessed at baseline and at the end of the study.

Results: The total number of participants was 47 patients; Group 1 included 22 patients and Group 2 included 25 patients. After 12 weeks, IL-6 decreased significantly in both groups ($p<0.05$) and SOD-1 showed significant improvement in patients receiving MG ($p<0.05$). Liver and renal parameters remained within normal limits in both groups.

Conclusion: Mangosteen (MG) supplementation was safe and well tolerated and may have a potential antioxidant benefit, with no additive effect on inflammation. However, further studies are required to confirm these findings.

Keywords: Mangosteen, Type 2 diabetes mellitus, Superoxide dismutase-1, Oxidative status, Inflammation.

تأثير المانغوستين على الالتهاب، وحالة الأكسدة، ووظائف الكبد والكلى لدى مرضى السكري من النوع الثاني

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الخلاصة:

الخلفية: يُعد الإجهاد التأكسدي والالتهاب من العوامل الرئيسية المساهمة في مرض السكري من النوع الثاني. يمتلك المانغوستين خصائص مضادة للالتهابات ومضادة للأكسدة نظرًا لتركيزاته العالية من الزانثونات، وخاصة الفا-مانغوستين و كاما-مانغوستين.

الاهداف: تهدف هذه الدراسة إلى تقييم تأثير المانغوستين كعلاج مساعد على التهاب ونشاط مضادات الاكسدة ووظائف الكبد والكلى بين مرضى السكري من النوع الثاني الذين تم تشخيصهم حديثًا.

الطرق: هذه دراسة مستقبلية عشوائية مضبوطة مفتوحة التسمية، أُجريت على مدى 12 أسبوعًا في المركز الوطني لعلاج وبحوث السكري. المجموعة 1: شملت المرضى الذين عولجوا بأقراص سيتاغليبتين/ميتفورمين (50\1000ملغ) مرتين يوميًا بالإضافة إلى العلاج غير الدوائي (تعديل نمط الحياة). المجموعة 2: شملت المرضى الذين عولجوا بأقراص سيتاغليبتين/ميتفورمين (50/1000 ملغ) مرتين يوميًا بالإضافة إلى كبسولات مانغوستين (500 ملغ) مرتين يوميًا بالإضافة إلى العلاج غير الدوائي (تعديل نمط ال الحياة). تم تقييم مستوى سكر الدم الصائم، والهيموجلوبين السكري ومستوى الأنسولين في مصل الدم الصائم، ومؤشر مقاومة الأنسولين، ومستوى إنترلوكين-6 في المصل، وإنزيم سوبر أكسيد ديسميوتاز-1، ووظائف الكبد والكلى عند خط الأساس وفي نهاية الدراسة.

النتائج: بلغ إجمالي عدد المشاركين 47 مريضًا؛ ضمت المجموعة الأولى 22 مريضًا، والمجموعة الثانية 25 مريضًا. بعد 12 أسبوعًا، انخفض مستوى إنترلوكين-6انخفاضا ملحوضا في كلتا المجموعتين، كما أظهر مستوى إنزيم سوبرأكسيد ديسميوتاز-1تحسنا ملحوضا لدى المرضى الذين تلقوا العلاج مع المانغوستين. وظلت وظائف الكبد والكلى ضمن المعدل الطبيعي في كلتا المجموعتين. ($p<0.05$)

الاستنتاج: كان تناول مكملات المانغوستين آمناً وجيد التحمل، وقد يكون له فوائد مضادة للأكسدة، دون أي تأثير إضافي على الالتهاب. ومع ذلك، هناك حاجة إلى مزيد من الدراسات لتأكيد هذه النتائج.

الكلمات المفتاحية: مانغوستين، داء السكر النوع الثاني، سوبر اوكساید دسميوتاز-1، الحالة التاكسدية، الالتهاب.

Introduction:

Type 2 diabetes mellitus (T2DM) constitutes a significant public health issue with considerable social and economic burdens [1]. The rapid economic growth and urbanization have led to a rising incidence of diabetes in numerous regions globally [2]. The incidence and prevalence of T2DM are steadily rising, impacting around 10.7% of the Iraqi population [3]. The improvement of prevention and prognosis for T2DM has become as a critical medical concern, and recognizing the epidemiological factors related to T2DM will facilitates its mitigation [4]. Presently, most preventative strategies for T2DM focus on lifestyle modifications, including weight control, eating habits, and the management of abdominal obesity. Early screening is beneficial for those with a familial predisposition to T2DM to minimize the likelihood of developing the condition [5]. Chronic inflammation is a crucial element in the pathogenesis of T2DM and impacts insulin sensitivity [6]. Moreover, the generation of reactive oxygen species (ROS) and the consequent oxidative stress (OS) are significant factors in the development of

T2DM [7]. SOD functions as a principle antioxidant defense against ROS by catalyzing the transformation of superoxide anion into hydrogen peroxide and oxygen, which are then decomposed into water and oxygen by catalase [8]. IL-6 is a pro-inflammatory cytokine that plays a crucial role in persistent low-grade inflammation associated with T2DM [9].

While numerous conventional medications exist, the consumption of natural substances with antioxidant capabilities seems to be a beneficial treatment strategy for the prevention and control of T2DM with fewer adverse effects [10, 11]. The combination of synthetic medicines with natural substances has the potential to enhance therapeutic efficacy and may allow for a reduction in the dosage of antidiabetic agents, leading to fewer unwanted effects [12].

Among herbal remedies, Mangosteen (MG), *Garcinia mangostana Linn. (G.mangstana)*, belongs to the Clusiaceae family. This tropical tree originates from Southeast Asia. The fruit is frequently reffered to as "the queen of fruits" because of its thick sepals that collectively create a crown, in addition to its white, juicy edible pulp noted for its sweetness and pleasant aroma [13, 14]. The pericarp extract of *G. mangostana* is marked by a high concentration of bioactive molecules called xanthones, with alpha mangostin (α-MG) and gamma mangostin (γ-MG) being the predominant ingredients [15]. MG possesses anti-inflammatory and antioxidant activities attributed to the presence of these xanthones [16, 17]. The antioxidant properties of MG peel extract function via three principal mechanisms: scavenging of superoxide radical, prevention of linoleic acid peroxidation, and overall radical scavenging activity. By mitigating oxidative damage, α-MG enhances the cellular absorption of blood glucose, as found in *G. mangostana* [18]. Also, supplementation with MG extract, its isolated substances, or commercial formulations appears to have the ability to augment antioxidant enzyme activities, including SOD, catalase, and glutathione peroxidase, while concurrently diminishing oxidative stress biomarkers as malondialdehyde (MDA) and modulation of pro- and anti-inflammatory cytokines and mediators, as well as the regulation of key inflammatory signaling cascades [17, 19]. Antioxidants present in MG can neutralize hydroxyl radicals, that harm pancreatic β-cells, hence enhancing insulin production and aids in treatment of diabetes [16]. According to WHO recommendations, The intake of MG fruit by humans is deemed safe, supported by a history of traditional use for over a century without evidence of mutagenic or teratogenic effects [20]. The available studies confirmed the strong antioxidant and anti-inflammatory effects of xanthones, indicating various mechanisms through which metabolic improvements may occur [21]. Nevertheless, evidence from clinical trials remains limited, and no studies have been conducted among the diabetic Iraqi population.

This study aims to evaluate MG effect as an adjuvant therapy on inflammation, antioxidant activity, hepatic, and renal function among newly diagnosed T2DM patients.

Patients and Method

This is a prospective randomized-controlled open-label study performed from September 2024 to May 2025 at the National Diabetes Center for Treatment and Research/ Mustansiriyah University/ Baghdad/ Iraq.

Participants meet the following Inclusion criteria:

- Diagnosed with T2DM according to American Association of Clinical Endocrinologists (AACE)
- Newly diagnosed T2DM patients (within 0-7 months of diagnosis) who had not received prior anti-diabetic therapy.

- Adult T2DM patients more than 30 years old.
- T2DM patients HbA1c between 7.5%-9%.

Various exclusion criteria were established for avoiding interaction with the study design, which include:

- T2DM patients receiving any anti-diabetic treatment other than the study intervention or T2DM patients receiving insulin therapy.
- Patients with T2DM complications, having liver disease, kidney disease, having other metabolic or endocrine disorders.
- Patients receiving drugs (steroids, contraceptives, anticoagulants and thyroid medications) or using other nutritional supplements or herbal remedies that may interfere with lab results.

All patients provided written consent after being fully briefed about the protocol before beginning the study. The proposal was reviewed and approved by the Scientific and Ethical Committee of the College of Pharmacy/ Mustansiriyah University (Research No. 92, Approval No. 79), and the National Diabetes Center for Treatment and Research/ Mustansiriyah University agreement was obtained. (ClinicalTrials.gov Identifier: NCT07172269).

Measurement of FBG, HbA1c, FSI, HOMA-IR, IL-6, SOD-1, AST, ALT, ALP, urea, creatinine, and albumin to creatinine ratio (ACR) was performed in this study. All measurements were conducted at baseline and after 12 weeks of treatment.

The study groups were allocated according to the following flow chart as in Figure (1):

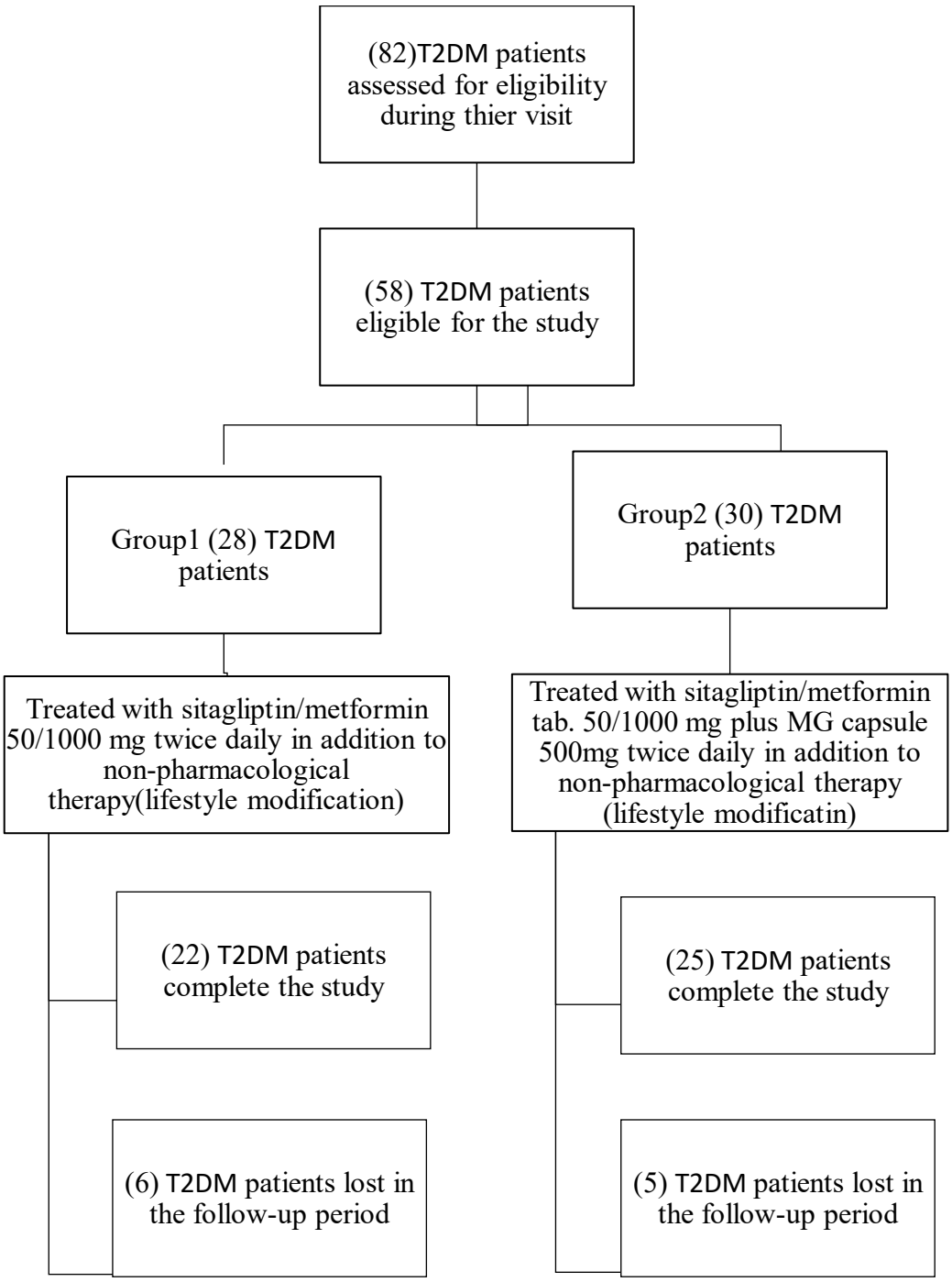

Figure (1): Study group flow chart

Both groups were provided with the same diabetes information, dietary counseling, and lifestyle guidance. All patients were advised on the correct method of medication administration, which included sitagliptin and metformin tablets, as well as MG capsules, prescribed to be taken twice daily after meals. Furthermore, patients' adherence to treatment was monitored through regular phone calls, during which they were asked to report their daily blood glucose levels. Additionally, subjects attended monthly

checkups to get medicine refills, count their pills, and report any side effects or treatment-related concerns during the 12 weeks study period.

Statistical analyses were conducted utilizing SPSS version 25 (IBM Corp., Armonk, NY, USA). Normality was assessed with the Shapiro–Wilk test. Continuous variables were reported as mean ± standard deviation (SD) or range, and compared using the Independent Samples T-test or Mann-Whitney U test, as appropriate. The Paired Samples T-test or Wilcoxon signed-rank test was applied for within-group comparisons. Group comparisons for categorical data were performed using the Chi-square test, with Fisher's exact test. Additionally, ANCOVA was performed to analyze differences in variables between the two groups after adjusting for baseline HOMA-IR. Statistical significance was defined as $p < 0.05$.

Results

Patients Demographics and Disease Characteristics

The study enrolled 47 T2DM patients, comprising 22 patients as controls receiving standard treatment (Group 1) and 25 patients receiving the supplement in addition to their standard treatment (Group 2). Patients in the intervention Group 2 had a mean age of 44.8 ± 8.53 years and were predominantly male patients (56%). Their college education level of patients (44%) mostly resides in urban areas. The majority of patients (80%) had no other comorbidity. A family history of T2DM was present in most patients (76% in G2, 63.6% in G1). The median duration of T2DM was 1.5-2 months. Comparative analysis revealed no statistically significant differences in all characteristics between the two study groups ($p \geq 0.05$), as presented in Table (1).

Table (1) Patients demographics and disease characteristics of study groups.

Variable		G1	G2	P value
Age (years)	mean ±SD	45.41 ±7.54	44.8±8.53	0.551 [a]
Sex	Female	11 (50%)	11 (44%)	0.681
	Male	11 (50%)	14 (56%)	
Weight (kg)	mean ±SD	86.2±11.3	86± 13.6	0.735 [a]
Education Level	Primary	6 (27.3%)	6 (24%)	0.463 [c]
	Secondary	4 (18.2%)	1 (4%)	
	High school	5 (22.7%)	7 (28%)	
	College	7 (31.8%)	11 (44%)	
Monthly Income (ID)	<50K ID	10 (45.5%)	9 (36%)	0.51 [c]
	>50K ID	12 (54.5%)	16 (64%)	
Residency	Urban	12 (54.5%)	18 (72%)	0.214 [c]
	Rural	10 (45.5%)	7 (28)	
Alcohol Use	No	22 (100)	24 (96%)	0.532 [c]
	Yes	0	1 (4%)	
Smoking History	No	17 (77.3%)	19 (76%)	0.918 [c]
	Yes	5 (22.7%)	6 (24%)	
Other Chronic Diseases	No	13 (59.1%)	20 (80%)	0.118 [c]
	Hypertension	9 (40.9%)	5 (20%)	
Family History of T2DM	No	8 (36.4%)	6 (24%)	0.355 [c]
	Yes	14(63.6%)	19 (76%)	
Duration of T2DM (months)	Median (range)	1.5 (0-7)	2 (0-6)	0.728 [b]

Continuous data presented based on normality test either as mean±SD or *median and range; categoric data presented as frequency and percentage. P- value [a] by independent sample T test, [b] by Mann Whitney Test, [c] by Chi Square test. P value ≥ 0.05 is considered nonsignificant.*
Abbreviations: SD, standard deviation; ID, Iraqi dinar; T2DM, Type 2 Diabetes Milletus.

Baseline Laboratory Measurements of Study Groups

The baseline lab measures of both study groups 1 and 2 demonstrated no statistically significant differences across most baseline parameters between the two study groups (p ≥ 0.05) except for urea, which showed a statistically significant difference between groups. Liver and renal function parameters were within the normal range, Table (2).

Table (2): Baseline measurement of study groups.

Baseline measurements		G1	G2	P value
FBG (mg/dL)	median (range)	196.8 (177.3-293.4)	201.4 (171.8-290)	0.22 [b]
FSI (µIU/mL)	mean ±SD	22.9±4	23.3±4.2	0.749 [a]
HbA1c (%)	median (range)	8.3 (7.4-9)	8.4 (7.5-8.4)	0.765 [b]
HOMA-IR	mean ±SD	11.41±2.83	11.99±2.64	0.434 [a]
ALT (U/L)	mean ±SD	22.7±4.7	25.3±5.6	0.489 a
AST (U/L)	Median (range)	27.2 (16.3-31.6)	24.6 (15.3-36.8)	0.509 [a]
ALP (U/L)	mean ±SD	79.4± 9.1	80±9.1	0.809 [a]
Urea (mg/dL)	mean ±SD	29.99±3.1	30.3±1.6	**0.008 [a]**
Creatinine (mg/dL)	mean ±SD	0.97±0.12	0.92±0.09	0.323 [a]
ACR (mg/mmol)	median (range)	2.18±0.55	2.28±0.59	0.376 [b]

Continuous data presented based on normality test either as mean±SD or median and range. P- value [a] by independent sample T test, [b] by Mann Whitney Test. P value ≥ 0.05 is considered nonsignificant
Abbreviations: SOD-1, super oxide dismutase-1; IL-6 interleukin-6; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase, ALP, Alkaline Phosphatase; ACR, Albumin-to-Creatinine Ratio.

Reference range: FBG (74-109mg/dL); FSI (2.6-24.9µU/Ml); HbA1c (4.0-6.0%); HOMA-IR (< 2.5); ALT (Males: up to 41 U/L, Females: up to 33 U/L); AST (Males: up to 40 U/L, Females: up to 32 U/L); ALP (Males 40-129 U/L, Females 35-104 U/L); Urea (16.6-48.5 mg/dL); Creatinine (Females (0.50-0.90 mg/dL), Males (0.70-1.20 mg/dL); ACR (< 3.4 mg/mmol).

The Effect of Mangosteen Supplements on Inflammatory and antioxidant Markers

A modest increase in SOD-1 levels was observed in both groups, reaching statistical significance only in Group 2. However, the rate of change did not differ significantly between the groups (Table 3).

In contrast, IL-6 levels demonstrated a modest yet significant reduction in both cohorts. The mean reduction in Group1 was comparable to that in Group 2 (−5% vs. −6.3%; p = 0.293).

Table (3): Change of baseline inflammatory markers post treatment in study groups.

Variables		G1 (mean±SD)	G2 (mean±SD)	P-value [a]
SOD-1 Pg/mL	Baseline	3324.5 ± 472.8	2868.3 ± 411.9	0.328
	After 3 months	3377.2 ± 447	2920.6 ± 428.7	0.858
	P-value [b]	0.138	**0.041**	
	Δ	52.8 ±160.4	52.2 ± 120.9	0.156
	Δ %	1.6 ± 4.8	1.7 ± 4.3	0.461
IL-6 Pg/mL	Baseline	5.4 ± 1.5	4.8 ± 1.2	0.422
	After 3 months	5.1 ± 1.4	4.5 ± 1.2	0.796
	P-value [b]	**0.001**	**0.003**	
	Δ	-0.267 ± 0.32	-0.268 ± 0.41	0.937
	Δ %	-5 ± 5.3	-6.3 ± 10.1	0.293

P-value [a]by Independent Sample T test to compare between the two groups;
P-value [b]by Related Samples T test is statistically used to compare between pre-and post-treatment results in same group. P value < 0.05is considered significant.

The Effect of Mangosteen Supplements on Liver Enzymes

As Table (4) presents, data indicate that neither the treatment alone nor the treatment with supplemented induced changes of liver enzymes after three months. While slightly higher reduction rates of ALT, AST, and ALP were observed in Group2 compared to Group1 patients, these changes did not reach statistical significance, with p-values of 0.156, 0.966, and 0.056, respectively.

Table (4): Change of baseline Liver enzymes post treatment in study groups

Variables		G1 (mean±SD)	G2 (mean±SD)	P-value [a]
ALT U/L	Baseline	22.7 ± 4.7	25.3 ± 5.6	0.489
	After 3 months	22.8 ± 4.8	25.3 ± 5.8	0.199
	P-value [b]	0.951	0.944	
	Δ	0.04 ± 2.7	0.06 ± 4	**0.032**
	Δ %	-0.9 ± 12.7	-1.5 ± 16.7	0.156
AST* U/L	Baseline	27.2 (16.3-31.6)	26.2 (7.6-32.7)	0.509*
	After 3 months	24.6 (16.5-30.5)	23.2 (13.4-36.8)	0.957*
	P-value [b]	0.284*	0.757*	
	Δ	-1.05 (-7.8-3.7)	-1.2 (-5.8-6.4)	0.966*
	Δ %	-3.7 (-36.1-16.5)	-4.5 (-41.7-43.3)	0.966*
ALP U/L	Baseline	79.4 ± 9.1	80 ± 9.1	0.809
	After 3 months	79.5 ± 9.1	80.6 ± 11	0.433
	P-value [b]	0.846	0.606	
	Δ	0.15 ± 3.5	0.6 ± 5.7	**0.035**
	Δ %	0.1 ± 4.6	0.3 ± 7.2	0.056

*** Data presented as median and range. Parametric data were analyzed using the independent samples t-test for between-group comparisons [a] and the paired t-test for within-group comparisons [b].Non-parametric data were analyzed using the Mann–Whitney U test for between-group comparisons and the Wilcoxon signed-rank test for within-group comparisons*.P value < 0.05 is considered significant.**

The Effect of Mangosteen Supplements on Renal Function

Results in Table (5) and revealed minimal increase in blood urea was observed in Group1 after 3 months of treatment (29.99 vs 31.08 mg/dL, p=0.236), although levels remained within the normal range. In contrast, Group 2 exhibited a slight but statistically significant reduction of urea levels (30.25 vs 28.22 mg/dL, p= 0.003). However, the difference in urea reduction rate between the two groups was insignificant (p=0.196).

Regarding creatinine, a significant lower level was noted in Group1 following treatment (0.97 vs 0.88 mg/dL p=0.005), although the reduction rate was not significantly different from that of Group 2 (-10.56 vs -5.2 mg/dL p=0.650). The changes in creatinine and ACR were minimal and did not reach statistical significance between groups.

Table (5): Change of baseline renal function parameters post treatment in study groups.

Variables		G1 (mean ± SD)	G2 (mean ± SD)	P-value [a]
Urea mg/Dl	Baseline	29.99 ± 3.07	30.25 ± 1.62	**0.008**
	After 3 months	31.08 ± 5.29	28.22 ± 3.2	**0.011**
	P-value [b]	0.236	**0.003**	
	Δ	1.09 ± 4.2	-2.04 ± 3.06	0.059
	Δ %	1.44 ± 15.68	-8.38 ± 12.13	0.196
Creatinine mg/dL	Baseline	0.97 ± 0.12	0.92 ± 0.09	0.323
	After 3 months	0.88 ± 0.12	0.88 ± 0.1	0.598
	P-value [b]	**0.005**	0.115	
	Δ	-0.08 ± 0.12	-0.04 ± 0.12	0.770
	Δ %	-10.56 ± 15.16	-5.2 ± 13.37	0.650
ACR* mg/mmol	Baseline	2.09 (1.3-3.3)	2.3 (1.1-3.3)	0.376*
	After 3 months	2.4 (1.2-3.4)	2.2 (1.1-3.31)	0.974*
	P-value [b]	0.485*	0.904 *	
	Δ	0.03 (-1.02-1.3)	-0.08 (-1.2-1.5)	0.725*
	Δ %	1.1 (-52.6-44.8)	-3.8 (-62.7-57.1)	0.551*

*** Data presented as median and range. Parametric data were analyzed using the independent samples t-test for between-group comparisons [a] and the paired t-test for within-group comparisons [b].**

Non-parametric data were analyzed using the Mann–Whitney U test for between-group comparisons and the Wilcoxon signed-rank test for within-group comparisons*.

P value < 0.05 is considered significant.

Corrected ANCOVA Model

The ANCOVA analysis (Table 6), controlling for baseline (HOMA-IR), revealed significant group differences in oxidative stress markers after three months of treatment. Most notably, SOD-1 showed highly significant variation (F=6.263, p=0.004). While inflammatory marker IL-6 differences showed a trend but did not reach significance. The highly significant result for HOMA-IR itself (F=12.293, p<0.001) confirms its strong influence as a covariate in the model.

Table (6): Groups variation after adjusting to baseline HOMA-IR.

Variable	F-value	p-value
HOMA-IR	12.293	**<0.001**
SOD-1	6.263	**0.004**
IL-6	2.864	0.068

Discussion

Previous reports stated a notable correlation exists among hyperglycemia, OS generated by hyperglycemia, inflammation, and the onset and development of T2DM [22]. A reduction in SOD enzymes could exacerbate the sensitivity to OS in individuals with T2DM [23]. The increased circulating level of IL-6 independently predicts T2DM and is implicated in the progression of inflammation, insulin resistance (IR), and β-cell dysfunction [24].

The results of the current study reported further improvement in SOD-1 level in both groups, with a statistically significant improvement mainly within patients receiving MG group after 3 months of treatment. Nevertheless, there are no marked changes between groups. On the other hand, IL-6 levels decreased significantly with comparable reductions in both groups over the study period. This suggests that the known anti-inflammatory and antioxidant effects of sitagliptin and metformin, as explored by several studies, could mask or reduce any further benefits offered by MG [25, 26].

Additionally, adjusting the baseline for IR of both revealed significant difference after 3 months toward the increase in SOD-1 levels in the intervention group receiving MG adjuvant, meanwhile, IL-6 levels did not reach statistical significance differences between both groups. These findings may suggest a potential antioxidant activity of MG by enhancing the activity of SOD-1, which could contribute to long-term protection against oxidative damage in type 2 diabetes. However, this observation should be interpreted cautiously, as it was evident only after statistical adjustment and not in the primary analysis; therefore, further studies are needed to confirm this finding.

In line with the current findings, *Munandar et al.* in 2021 reported a substantial rise in SOD levels and a decrease in MDA concentration after 90 days of *Garcinia mangostana* pericarp extract administration in patients with a high Framingham risk score [27]. Consistent findings were observed in a recent randomized study enrolling T2DM patients, where MG supplementation for 3 months led to a significant increase in SOD and decreases in IL-6, TNF-α, IL-1, hs-CRP, and MDA levels compared to placebo [28]. In a similar study, giving obese adults a maximum of 18 ounces of MG juice blend per day for 8 weeks significantly lowered their CRP levels. There were no significant changes in other inflammatory cytokines or lipid peroxidation parameters [29]. In addition, mechanistic evidence from in vitro study showed that MG peel extract and its xanthones compounds significantly inhibited IL-6, IL-1, COX-2, and NO in LPS-induced RAW264.7 Cells [30]. Collectively, these findings confirm the antioxidant and anti-inflammatory ability of MG in a variety of clinical and experimental models.

A variety of preclinical and clinical research have assessed the safety profile of MG demonstrating its hepatoprotective and renoprotective features, which suggest a significant metabolic safety margin and systemic antioxidant advantages. A recent investigation on rats exhibiting insulin

resistance, shown that α-MG supplementation ameliorated liver damage induced by a high-fat, high-glucose diet, and low-dose streptozotocin. Adninistration of α-MG led to a substantial reduction in ALT and AST levels. Subsequent histological examination revealed a diminished quantity of fat in the liver and decreased inflammation, suggesting that α-MG may act as a therapeutic agent for liver problems linked to IR and could serve as an alternative to metformin [31]. A study revealed that the incorporation of MG vinegar rind to streptozotocin-induced diabetic mice fed a high-fat diet markedly diminished ALT and AST levels, while elevating bilirubin levels and hepatic antioxidant enzyme activity, suggesting reduced liver damage and improved antioxidant defense mechanisms [32]. Moreover, a randomized, double blind, placebo-controlled clinical research examined the effects of daily intake of MG based beverage over 30 days in healthy persons. The results indicated that liver function enzymes (ALT and AST) and the renal function marker (creatinine) showed no changes following the intervention [33]. A further trial verified that there were no notable alterations in liver enzymes or renal indicators after 16 weeks of Meratrim administration in overweight subjects [34].

In agreement, serum levels of ALT, AST, and ALP remained within normal ranges after 12 weeks of treatment in the present study, with no significant changes observed between groups. An assessment of renal function indicators (urea, creatinine, and ACR) also revealed no adverse changes following MG use. Urea levels exhibited a slight, although substantial decrease in the patients receiving MG ($p < 0.05$), whereas serum creatinine and ACR levels remained stable ($p > 0.05$), such findings was not of important concern. Although a statistically significant difference in baseline urea was observed, all values were within the normal range, suggesting limited clinical relevance. However, this baseline imbalance represents a limitation and should be considered when interpreting the renal outcomes.

Despite these findings, certain limitations should be considered. The inclusion of newly diagnosed patients (within 0–7 months) may represent a limitation, as early initiation of pharmacotherapy and lifestyle modification can lead to substantial improvements in metabolic parameters. This may reduce the ability to detect the additional effect of MG supplementation. Also, the relatively small sample size and single-center design may limit the statistical power and generalizability of the findings to a wider population of patients with type 2 diabetes mellitus. Furthermore, the open-label design of the study may introduce bias related to patient awareness and behavioral changes, and the absence of a placebo control limits the ability to attribute the observed effects solely to MG supplementation.

Conclusion

Mangosteen (MG) supplementation was safe and well tolerated and may have potential antioxidant benefits, with no additive effect on inflammation. However, further studies are required to confirm these findings.

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