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Research Article

Metabolic effects of mangosteen supplementation as an adjuvant to sitagliptin/metformin in newly diagnosed type 2 diabetes Iraqi patients

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Abstract

Type 2 diabetes mellitus often remains inadequately managed despite effective oral treatments. Mangosteen (*Garcinia mangostana*), abundant in xanthones, including α-mangostin, may have metabolic and insulin-sensitizing properties; however, clinical data are scarce. We sought to assess mangosteen (MG) as an adjunct for enhancing metabolic status in recently diagnosed Iraqi patients with type 2 diabetes. In a 90-day prospective, randomized, open-label study, patients received either sitagliptin/metformin 50/1000 mg twice daily with lifestyle modifications (n = 22) or the same regimen supplemented with MG 500 mg twice daily (n = 25). Both groups showed significant reductions in body weight, body mass index (BMI), glycated hemoglobin (HbA1c), fasting blood glucose (FBG), insulin levels, and lipid parameters ($p < 0.05$). MG supplementation resulted in greater reductions in body weight and BMI (–3.42% vs. –2.25%; $p = 0.013$) and independent improvements in total cholesterol and triglyceride levels ($p = 0.001$); however, it did not confer additional benefits for glycemic control. MG provides significant anthropometric and lipid-related benefits, potentially mediated by weight reduction and enhanced insulin sensitivity.

Keywords

Garcinia mangostana, insulin resistance, lipid profile, sitagliptin, weight loss

Introduction

Type 2 diabetes mellitus (T2DM) is a progressive illness characterized by pancreatic β-cell dysfunction and peripheral insulin resistance (IR), leading to disturbed glucose metabolism and low-grade inflammation (Zhou et al. 2022). It is a global health challenge with important social and economic costs (Dawood et al. 2024). There are many modifiable factors (obesity, sedentary behavior, physical inactivity, high-glycemic load/low-fiber diet, vitamin deficiency, smoking, and alcohol consumption (Lee et al. 2021; Bhagyamma et al. 2023; Dawood et al. 2023)) and non-modifiable factors (e.g., age, ethnicity, family history, and genetic predisposition (American Diabetes Association Professional Practice Committee 2021)) that affect the onset and progression of this chronic disease. T2DM is consistently on the increase worldwide, with rising incidence and prevalence, affecting about 10.7% of the Iraqi

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population (Jawad et al. 2024). Although many pharmacological therapies are available, many patients fail to achieve optimal glycemic and metabolic control (Bailey 2025). As diabetes is a progressive condition, management strategies evolve (Najim et al. 2024). Nevertheless, most modern drugs are associated with multiple side effects (Tran et al. 2020; Chen et al. 2021). In recent decades, there has been increasing interest in utilizing natural products as therapeutic agents, particularly for the prevention and treatment of T2DM (Dirir et al. 2022). The integration of synthetic drugs with natural compounds offers an opportunity to enhance treatment effectiveness. Furthermore, synergistic interactions between these agents may allow for dose reduction of antidiabetic medications, thereby minimizing their associated adverse effects (Blahova et al. 2021).

Mangosteen (MG), *Garcinia mangostana* Linn. (*G. mangostana*), a species of the Clusiaceae family, is a tropical evergreen tree indigenous to Southeast Asia. Its fruit, commonly known as MG, is characterized by a reddish to dark purple exterior and is often referred to as "the queen of fruits" due to its thick sepals that collectively resemble a crown, as well as its white and juicy edible pulp noted for its sweet taste and pleasant aroma (Zonouz et al. 2023; Midin and Goh 2022; Saraswathy et al. 2022). The pericarp extract of *G. mangostana* is rich in xanthones and other polyphenolic compounds, particularly α and γ MG (Binti Zamarudin et al. 2023). The underused portion of the MG fruit possesses therapeutic potential for the prevention and treatment of metabolic diseases such as obesity, dyslipidemia, hypertension, diabetes, and its complications (Rohman et al. 2020). MG is a medicinal plant that exhibits multiple antidiabetic mechanisms of action, as demonstrated through in *vivo*, *in vitro*, and *in silico* studies. The pericarp, rind, seed, stem bark, and leaves, when extracted using ethanol, water, or vinegar, have demonstrated antidiabetic effects, including reductions in blood glucose levels and insulin resistance, enhanced plasma insulin levels, and decreased body weight and BMI (Safaei et al. 2023). Administration of α-MG, either as a supplement or as part of a diet enriched with α-MG, has been shown in various obese and diabetic rodent models, as well as *in vitro* studies and human studies, to improve diabetes markers by reducing fasting blood glucose concentration, decreasing insulinemia, improving glucose tolerance and insulin sensitivity, as assessed by HOMA-IR, and promoting glucose uptake (Yani et al. 2021; John et al. 2022). Studies have shown that MG has antihyperglycemic and antidiabetic activity. Alpha-glucosidase and alpha-amylase are enzymes that are crucial for carbohydrate digestion; therefore, its hypoglycemic properties have been hypothesized (Espirito Santo et al. 2020; Djeujo et al. 2022). MG contains antioxidants that scavenge hydroxyl radicals, which lead to the destruction of pancreatic β-cells, thereby supporting optimal insulin secretion and providing a potential remedy for diabetes (Mahmudah et al. 2021).

In addition, MG extract was able to lower cholesterol through improvement of antioxidant status, reduction of LDL oxidation, and decreased concentrations of MDA (Elmund and Hartrianti 2020). Moreover, α-mangostin has been shown to inhibit intracellular lipid accumulation and adipocyte differentiation. Given the *in vivo* distribution of α-MG among hepatic and adipose tissues, it is proposed that α-MG may serve as a potential anti-obesity agent (Arozal et al. 2020).

In a recent systematic review and network meta-analysis conducted on rodent models, MG extract produced extensive hypoglycemic and lipid-lowering effects, indicating the potential of MG extract as adjunctive therapy in diabetes (Chatatikun et al. 2024). Additional reviews have confirmed the strong antioxidant and anti-inflammatory effects of xanthones, indicating multiple mechanisms through which metabolic improvements may occur (Safaei et al. 2023). However, these promising findings are largely based on animal studies, and clinical data in humans remain limited. Moreover, no clinical trials involving diabetic Iraqi patients have examined MG supplementation.

This study aims to address this gap by assessing the metabolic impact of mangosteen capsules as an adjuvant to sitagliptin/metformin in newly diagnosed T2DM patients.

Patients and methods

Research design and participants

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

Inclusion criteria were adult patients (age > 30 years) with newly diagnosed T2DM, meeting the American Association of Clinical Endocrinologists (AACE) criteria, and having HbA1c values between 7.5% and 9%. Patients meeting the following criteria were excluded: (1) T1DM; (2) ongoing insulin or antidiabetic therapies other than the study intervention; (3) established diabetic complications, hepatic or renal conditions, or other metabolic or endocrine disorders; (4) pregnancy or lactation; and (5) receipt of drugs (steroids, contraceptives, anticoagulants, or thyroid medications) or use of other nutritional supplements or herbal remedies.

Ethical approval

All participants were asked to sign a written informed consent before the beginning of the trial. The study protocol was approved by the Scientific and Ethical Committee of the College of Pharmacy, Mustansiriyah University (Research No. 92, Approval No. 79), and approval from the National Diabetes Center for Treatment and Research, Mustansiriyah University, was obtained. **(ClinicalTrials.gov Identifier: NCT07172269).**

Outcome measure

Measurement of BMI, ICO, FBG, FSI, HbA1c, HOMA-IR, HOMA-B, TC, HDL-C, LDL-C, VLDL-C, and TG was performed in this study. All measurements were carried

out at baseline and after 90 days of treatment. To calculate BMI, body weight and height were obtained between 8:00 and 10:00 AM in fasting subjects with light clothes and without shoes. Waist circumference (WC) was assessed at the same time using a stretch-resistant tape at the midpoint between the lower edge of the last palpable rib and the superior aspect of the iliac crest.

$$BMI = \text{weight (kg)} / [\text{height (m)}]^2$$

$$ICO = WC\ (cm) / \text{height (cm)}$$

Study groups

Approximately 82 individuals were screened for potential enrollment; however, only 58 met the established inclusion criteria. Of those, 11 patients were excluded due to noncompliance with scheduled follow-up visits or adherence to the treatment regimen. Consequently, 47 patients completed the study. Eligible patients were randomized into two groups:

- **Group 1** included 22 patients treated with sitagliptin/metformin tablets (50/1000 mg) twice daily in addition to nonpharmacological therapy (lifestyle modification) for 90 days.
- **Group 2** included 25 patients treated with sitagliptin/metformin tablets (50/1000 mg) twice daily plus MG capsules (500 mg) twice daily in addition to nonpharmacological therapy (lifestyle modification) for 90 days.

Both groups received identical diabetes education, diet counseling, and lifestyle guidance. All patients were instructed on the proper way of medicine administration; sitagliptin/metformin tablets and MG capsules were prescribed to be taken twice daily after meals. In addition, patients' medication adherence was followed by regular phone conversations, during which patients were requested to report their daily blood glucose readings. Furthermore, patients attended monthly visits to provide medication refills, pill counting, and to report any side effects or issues related to treatment throughout the 3-month study duration.

A two-week washout period of lipid-lowering agents was implemented prior to study initiation. Patients who had been receiving such medications were instructed to discontinue them at least 14 days prior to enrollment to ensure that any metabolic changes observed were due to the study intervention rather than the effects of prior lipid-modifying therapy.

Statistical analysis

Statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). Normality was assessed using the Shapiro–Wilk test. Continuous variables were reported as mean ± standard deviation (SD) or range and were 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 or Fisher's exact test. Pearson correlation tests assessed bivariate associations, and linear regression was used to identify predictors of HbA1c change. Additionally, ANCOVA was performed to analyze differences in variables between groups after adjusting for baseline HOMA-IR. Statistical significance was defined as $p < 0.05$.

Results

Demographic characteristics

Table 1 presents the demographic data and disease characteristics of 47 patients. Comparative analysis revealed no statistically significant differences in all characteristics between the two study groups ($p \geq 0.05$).

Table 1. Demographic characteristics.

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
BMI (kg/m2)	mean ±SD	30.33 ± 3.19	28.96 ± 4.01	0.327 a
BMI groups	<24.9	2 (9.1%)	2 (8%)	0.286 c
	25–29.9	9 (40.9%)	15 (60%)	
	30–34.9	10 (45.5%)	5(20%)	
	35–40	1 (4.5%)	3 (12%)	
ICO	mean ± SD	0.55 ± 0.06	0.55 ± 0.07	0.789 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 are presented based on the normality test, either as mean ± SD or median and range; categorical data are presented as frequency and percentage. *P*-value a by independent samples *t*-test, b by Mann–Whitney test, c by chi-square test. $P \geq 0.05$ is considered nonsignificant. **Abbreviations**: BMI, body mass index; SD, standard deviation; ICO, index of central obesity; ID, Iraqi dinar; DM, diabetes mellitus.

Baseline characteristics

In Table 2, the baseline laboratory measures of both study groups revealed no statistically significant differences in all measurements between the two study groups ($p \geq 0.05$) with respect to glycemic indices and lipid profile, ensuring adequate baseline matching for subsequent analyses. In the

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
HOMA-B (%)	mean ± SD	60.86 ± 10.56	59.45 ± 15.43	0.064 a
TC (mg/dL)	mean ± SD	211.2 ± 31.2	196.3 ± 31.2	0.881 a
HDL-C (mg/dL)	mean ± SD	45.1 ± 7.6	43.3 ± 10.8	0.051 a
LDL-C (mg/dL)	mean ± SD	133.89 ± 35.69	117.68 ± 31.21	0.441 a
VLDL-C (mg/dL)	mean ± SD	32.22 ± 10.03	35.33 ± 10.28	0.589 a
TG (mg/dL)	mean ± SD	161.1 ± 50.2	176.7 ± 51.4	0.589 a

Continuous data are presented based on the normality test, either as mean ± SD or median and range. *P*-value a by independent samples *t*-test, b by Mann–Whitney test. $P \geq 0.05$ is considered nonsignificant. **Abbreviations:** FBG, fasting blood glucose; FSI, fasting serum insulin; HbA1c, glycosylated hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-B, homeostasis model assessment of beta-cell function; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; VLDL, very low-density lipoprotein cholesterol; TG, triglyceride. **Reference range:** FBG (74–109 mg/dL); FSI (2.6–24.9 µU/mL); HbA1c (4.0–6.0%); HOMA-IR (< 2.5); HOMA-B (70–120%); TC (< 200 mg/dL); HDL-C (> 40 mg/dL); LDL-C (< 130 mg/dL); VLDL-C (< 30 mg/dL); TG (< 150 mg/dL).

intervention Group 2 T2DM patients, the median range of FBG and HbA1c was 171.8–290 mg/dL and 7.5%–8.4%, respectively. In addition, the lipid profile showed slight elevations in LDL-C and TG (117.68 ± 31.21 mg/dL) and (176.7 ± 51.4 mg/dL), respectively.

The effect of mangosteen supplements on anthropometric measurements

As Table 3 shows, the mean weight reduction over 3 months was 1.79 kg in Group 1 and significantly greater in intervention Group 2 patients, reaching 2.64 kg ($p = 0.013$). Both groups exhibited significant decreases in BMI and ICO; however, the reduction was more pronounced in Group 2. Specifically, the mean BMI reduction rate in Group 2 was −3.42%, which was significantly higher than the −2.25% observed in Group 1 ($p = 0.013$). The reduction rate in Group 2 was also higher in terms of ICO (−3.33% vs. −1.64%); however, it was insignificant ($p = 0.758$).

Table 3. Change of baseline anthropometric measurements post-treatment in study groups.

Variables		G1		G2		*P*-value a
		mean	±SD	mean	±SD	
Weight Kg	Baseline	84.95	9.72	84.77	13.92	0.224
	After 3 months	83.16	10.05	82.13	13.75	0.213
	P-value b	<0.001		<0.001		
	Δ	−1.79	1.51	−2.64	3.17	0.013
	Δ %	−2.25	1.87	−3.42	4.15	0.013
BMI Kg/m2	Baseline	30.34	3.2	28.96	4.01	0.33
	After 3 months	29.68	3.24	28.04	3.95	0.335
	P-value b	<0.001		<0.001		
	Δ	-0.65	0.55	−0.92	1.09	0.018
	Δ %	−2.25	1.87	−3.42	4.15	0.013
ICO	Baseline	0.545	0.06	0.552	0.07	754
	After 3 months	0.536	0.06	0.535	0.07	0.695
	P-value b	0.02		<0.001		
	Δ	−0.01	0.02	−0.02	0.01	0.753
	Δ I%	−1.64	3.29	−3.33	2.27	0.758

P-value a by independent samples *t*-test is used 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 the same group. $P < 0.05$ is considered significant.

The effect of mangosteen supplements on glycemic control measures

Short-term (FBG) and long-term (HbA1c) glycemic control indicators showed significant reductions in both study groups after 3 months. Although the median reduction in FBG was greater in Group 1 compared to Group 2 (−82.3% vs. −77.8%), the difference was not statistically significant ($p = 0.258$). HbA1c percentage changes were comparable between groups (−29% vs. −28.8%, $p = 0.773$). Similarly, fasting insulin levels declined significantly in both groups after 3 months ($p < 0.001$), with a greater, yet statistically insignificant, mean change in Group 1 compared to Group 2 (−58.5% vs. −54.5%, $p = 0.563$). Insulin resistance markers, including HOMA-IR and HOMA-B, also showed significant improvements post-intervention ($p < 0.001$); percentage changes were comparable between groups as well ($p = 0.291$), as detailed in Table 4.

Table 4. Changes of baseline glycemic control factors post-treatment in study groups.

Variables		G1		G2		*P*-value a
		mean	±SD	mean	±SD	
FBG mg/dL*	Baseline	196.8	177.3–293.4	201.4	171.8–290	0.22*
	After 3 months	103.5	88.6–146.6	115.2	87.5–198.3	0.047*
	P-value b	**<0.001**		**<0.001**		
	Δ	−91.1	−168.8– −57	−88.1	−187.7– −42.4	0.536
	Δ %	−82.3	135.5– −38.9	−77.8	−183.5– −24.7	0.258
HbA1C %*	Baseline	8.3	7.4–9	8.4	7.5–9.1	0.765*
	After 3 months	6.3	4.8–7.2	6.3	5.4–7.9	0.806*
	P-value b	**<0.001***		**<0.001***		
	Δ	−1.9	−3.1– −1.2	−1.8	−2.9– −0.9	0.781
	Δ %	−29	−46.6– −15.7	−28.8	−47.5– −13.2	0.773
FSI µU/mL	Baseline	22.9	4	23.3	4.2	0.749
	After 3 months	14.9	3.8	15.7	4.6	0.39
	P-value b	**<0.001**		**<0.001**		
	Δ	−8	2.9	−7.6	2.9	0.791
	Δ %	−58.5	29.2	−54.5	25.6	0.563
HOMA-IR	Baseline	11.4	2.8	12.0	2.6	0.434
	After 3 months	4.0	1.1	4.6	1.7	0.145
	P-value b	**<0.001**		**<0.001**		
	Δ	−7.5	2.3	−7.4	2.2	0.73
	Δ %	−198.4	74.8	−182.7	85.2	0.392
HOMA-B %	Baseline	60.9	10.6	59.5	15.4	0.064
	After 3 months	129.7	44.2	115.7	57.1	0.527
	P-value b	**<0.001**		**<0.001**		
	Δ	68.9	39.1	56.3	50.6	0.456
	Δ %	48.1	20.2	40.9	22.5	0.291

* Data are presented as median and range. *P*-value a is by Independent Sample T test to compare between the two groups for normally distributed data and by Independent Sample Mann–Whitney U test for non-normally distributed data (*); *P*-value b by Related Samples T test is statistically used to compare between pre- and post-treatment results in the same group for normally distributed data and by Related Samples Wilcoxon signed-rank test for non-normally distributed data (*). *P*-value < 0.05 is considered significant.

The effect of mangosteen supplements on lipid profile

As shown in Table 5, a significant reduction in TC and LDL-C levels was observed in both groups after 3 months of treatment compared to baseline. A greater reduction in VLDL-C and triglycerides was observed following 3 months of supplement administration ($p < 0.001$); however, the reduction rate was not significantly different from that in Group 1. HDL levels remained stable in both groups throughout the study period.

Table 5. Change of baseline lipid profile post-treatment in study groups.

Variables		Treatment only		Treatment with added supplement		*P*-Value a
		Mean	±SD	mean	±SD	
TC mg/dL	Baseline	211.17	31.21	196.29	31.21	0.881
	After 3 months	193.35	23.71	172.34	28.18	0.142
	P-value b	**0.003**		**0.001**		
	Δ	−17.82	24.52	−23.96	30.12	0.425
	Δ %	−9.55	12.21	−15.70	20.0	0.095
HDL-C mg/dL	Baseline	45.06	7.60	43.28	10.81	0.51
	After 3 months	46.62	8.18	44.24	10.16	242
	P-value b	0.147		0.327		
	Δ	1.56	4.86	0.96	4.80	0.904
	Δ %	2.50	11.4	1.94	11.50	0.842
LDL-C mg/dL	Baseline	133.89	35.69	117.68	31.21	0.441
	After 3 months	117.73	24.14	101.48	26.63	0.799
	P-value b	**0.009**		**0.009**		
	Δ	−16.16	26.37	−16.20	28.66	0.914
	Δ %	−14.43	23.91	−21.37	38.43	0.254
VLDL-C mg/dL	Baseline	32.22	10.03	35.30	10.28	0.589
	After 3 months	29.00	12.71	26.62	7.46	0.402
	P-value b	0.095		**<0.001**		
	Δ	−3.22	8.64	−8.72	7.23	0.68
	Δ %	−16.57	30.14	−34.76	29.27	0.671
TG mg/dL	Baseline	161.09	50.16	176.67	51.42	0.589
	After 3 months	145.00	63.56	133.09	37.29	0.402
	P-value b	0.095		**<0.001**		
	Δ	−16.10	43.19	−43.58	36.16	0.68
	Δ %	−16.60	30.10	−34.80	29.30	0.672

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 the same group. *P*-value < 0.05 is considered significant.

Correlation analysis between metabolic parameters

A strong positive correlation was observed between ΔFBG and ΔHOMA-IR in Group 1 (r = 0.644, $p = 0.001$) and was even more pronounced in Group 2 (r = 0.830, $p < 0.001$). Conversely, ΔFBG demonstrated a strong negative correlation with ΔHOMA-B in both groups, Group 1 (r = −0.747, $p < 0.001$) and Group 2 (r = −0.813, $p < 0.001$). These findings suggest that improved glycemic control is associated with enhanced insulin sensitivity and β-cell function, particularly in Group 2 (Table 6). The reduction in ΔHbA1c demonstrated a significant, strong association with decreased BMI (r = 0.643, $p = 0.001$) and a moderate correlation with improved ICO (r = 0.555, $p = 0.004$) in Group 2 patients only. These findings suggest that weight loss in Group 2 patients contributed to enhanced long-term glycemic control.

Table 6. The correlation of post-treatment fasting glucose and HbA1c levels with other parameters.

Measurement after 3 months	G1				G2			
	ΔFBG		ΔHbA1c		ΔFBG		ΔHbA1c	
	R	*P*-value	r	*P*-value	r	*P*-value	r	*P*-value
ΔHOMA-IR	0.644	**0.001**	-0.075	0.736	0.830	**<0.001**	0.155	0.458
ΔHOMA-B	-0.747	**<0.001**	0.233	0.296	-0.813	**<0.001**	−0.389	0.054
ΔFSI	0.081	0.122	0.808	<0.001	0.221	0.287	−0.085	0.687
Δ BMI	-0.326	0.140	0.415	0.055	0.082	0.697	0.643	**0.001**
Δ ICO	-0.033	0.885	0.14	0.535	0.074	0.725	0.555	**0.004**
ΔTC	-0.340	0.121	0.063	0.775	-0.003	0.988	−0.042	0.841
ΔHDL-C	0.111	0.623	0.175	0.437	0.384	0.058	0.161	0.441
Δ LDL-C	-0.234	0.294	-0.105	0.642	-0.127	0.545	−0.124	0.556
ΔVLDL-C	-0.195	0.385	0.459	0.032	0.173	0.408	0.273	0.187
ΔTG	-0.195	0.385	0.459	0.032	0.173	0.408	0.273	0.187

Pearson correlation.

Regression analysis for intervention study group (G2)

Estimates of HbA1c were determined for the regression coefficients in Group 2 to find significant predictors. The regression model is well predictive, as it explains 57.6% of the variability in the outcome HbA1c levels ($R^2 = 0.576$), and the model is overall statistically valid based on $p = 0.021$ (Table 7). Out of all the variables studied, only the rate of BMI change proved to be an independent predictor (Fig. 1). More specifically, the analysis shows that every 1% lower BMI is associated with a significant 1.45% lower HbA1c (95% CI: 0.577–2.3, $p = 0.003$), which indicates that weight loss is the most dominant modifiable determinant of improved long-term glycemic control in this population.

Table 7. Estimated regression coefficients for HbA1c percent change for Group 2 patients.

		Δ HB A1c %	
Δ BMI %	1.45	0.577–2.3	**0.003**
Δ HOMA-IR%	0.015	−0.026–2.3	0.456
Δ TG %	−0.076	−0.254–0.6	0.384
Δ TC %	−0.089	−0.414–0.10	0.571
Δ HDL-C%	0.092	−0.025–0.24	0.115
R2		0.576	
Adjusted R2		0.401	
P-value		**0.021**	

Linear regression.

Corrected ANCOVA model

The ANCOVA analysis (Table 8), controlling for baseline HOMA-IR, revealed significant group differences in several metabolic markers after 3 months of treatment. Most notably, triglycerides showed highly significant variation (F = 8.508, $p = 0.001$), and TC (F = 7.732, $p = 0.001$). While HDL did not reach significance. Interestingly, after

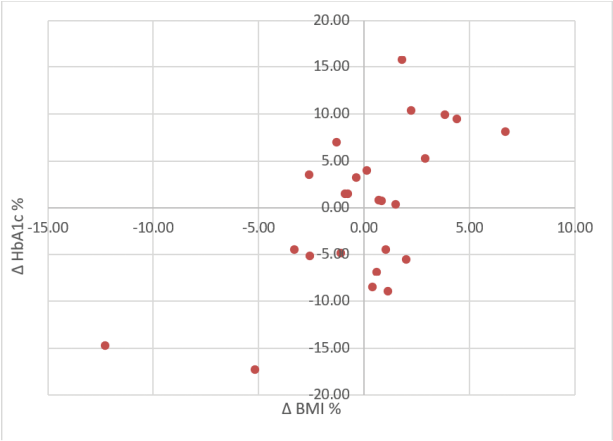


Figure 1. Partial regression plots showing the correlation of ΔHbA1c % and ΔBMI %.

Table 8. Group variation after adjusting for baseline HOMA-IR.

Variable	F-value	*P*-value
BMI	1.598	0.214
HOMA-IR	12.293	<0.001
TC	7.732	0.001
HDL-C	2.212	0.122
TG	8.508	0.001

accounting for baseline insulin resistance, BMI no longer showed significant between-group differences (F = 1.598, $p = 0.214$). The highly significant result for HOMA-IR itself (F = 12.293, $p < 0.001$) confirms its strong influence as a covariate in the model.

Discussion

The effect of mangosteen supplementation on anthropometric measurements in T2DM patients

The present study demonstrated significant reductions in body weight and BMI among patients in both groups after 3 months, with a notable reduction among those receiving MG as an adjuvant alongside standard therapy (−3.42% vs. −2.25%, respectively). This benefit was observed in the context of similar baseline characteristics and standard care, suggesting a clinically relevant additive effect of MG supplementation. These findings are consistent with earlier preclinical and clinical studies supporting the anti-obesity potential of MG and its primary bioactive constituents. For example, Labban et al. in 2021 reported that MG extract, alone or in combination with curcumin, reduced body weight and BMI in obese rats fed a high-fat diet, suggesting a synergistic effect on adiposity regulation (Labban et al. 2021). Furthermore, MG extract activated AMPK and SIRT1 signaling pathways, contributing to suppression of adipogenesis and promotion of lipid catabolism in high-fat-fed mice (Chae et al. 2016). Animal studies provide even clearer evidence, attributing robust decreases in total and visceral fat to mangosteen's xanthones and anthocyanins via mechanisms involving activation of AMPK, reduction of PPARγ expression, and enhanced fat oxidation.

The effect of mangosteen supplementation on metabolic measures

The mechanism underlying the control of plasma glucose levels and HbA1c in T2DM patients involves several potential pathways. Enhanced insulin sensitivity improves insulin signaling pathways, facilitating glucose uptake into cells and reducing IR (Demir et al. 2021). The elevation in FSI levels and IR are major metabolic consequences of hyperglycemia in T2DM patients (Cefalu et al. 2011). In early T2DM, the elevation in plasma levels of insulin (hyperinsulinemia) develops because cells fail to take in glucose due to an abnormal response to insulin, causing the pancreas to release additional insulin to sustain normal blood sugar levels; consequently, hyperinsulinemia is a persistent and essential characteristic of IR (Fazio et al. 2024). Evidence suggests that MG may improve glycemic status by influencing glucose metabolism and insulin sensitivity. Additionally, xanthone compounds extracted from MG pericarps can reduce postprandial blood glucose levels following food intake by inhibiting the activity of amylase and α-glucosidase enzymes (Chen et al. 2021).

In the current study, there was a significant improvement in the metabolic status of both study groups after 3 months of treatment by decreasing the levels of FBG, HbA1c, FSI, and HOMA-IR, respectively, alongside an increase in HOMA-B. This suggests an attenuation of compensatory hyperinsulinemia rather than deterioration of β-cell function, in parallel with improvements in glycemic control and HOMA-IR. A previous prospective cohort study by Handayani et al. (2020) demonstrated that supplementary MG extract (2520 mg/day for 90 days) significantly lowered HbA1c levels compared to placebo in T2DM patients with elevated cardiovascular risk, with no significant difference in FBG. Another quasi-experimental study conducted by Anam et al. (2017), enrolling T2DM patients, found that daily consumption of MG rind decoction for one week led to a significant reduction in FBG compared to control.

Experimentally, there are contradictory findings regarding MG direct glycemic effects, which revealed that both the ethanolic extract of mangosteen rind (EEMR) and pure α-MG markedly elevated serum insulin and reduced blood glucose levels in hyperglycemic rats, having effects close to those of glibenclamide (Prayitno et al. 2021). In addition, long-term α-MG supplementation (200 mg/kg/day) has anti-hyperglycemic and anti-hyperlipidemic properties while enhancing insulin sensitivity through improvement of β-cell functionality in type 2 diabetic rats over both 8 and 40 weeks (Mekseepralard et al. 2015). In the same context, a study found that α-MG enhances insulin secretion and protects pancreatic β-cells from oxidative damage *in vitro* (Lee et al. 2018). Moreover, ethanolic extract of MG pericarp significantly lowered blood glucose levels in normoglycemic and streptozoto-

cin-induced diabetic rats, improved lipid profile, and increased pancreatic β-cell mass, supporting the traditional use of MG in glycemic control (Taher et al. 2016).

Patients receiving MG in the current study demonstrated a stronger positive correlation between FBG change and HOMA-IR and a negative correlation with HOMA-B compared to patients on standard therapy. Furthermore, significant correlations were observed in those on MG adjuvant regarding changes in HbA1c and reductions in BMI and ICO. Regression analysis further identified BMI changes as the strongest independent predictor of HbA1c improvement in the MG group (each 1% reduction in BMI corresponds to a 1.45% decrease in HbA1c). These results confirm the significant interrelation between weight and glycemic control with MG supplementation given as an add-on to conventional therapy, and the present work indicates that weight loss is the best modifiable determinant of long-term glycemic control in this study.

Limitations

This study is not without its limitations, which warrant mention. The first point is that the sample size is relatively small (n = 47), and the study itself is designed at a single center, which may limit the generalizability of the findings to the global population (diabetes population). Second, although the intervention lasted 90 days, the long-term safety and prolonged metabolic efficacy of mangosteen supplementation have not been established. Lastly, the open-label nature of the study rather than double-blinding could also lead to potential performance and ascertainment biases. These preliminary observations justify confirmation in larger studies in the form of future rigorous, multicenter, double-blind randomized controlled trials, which are therefore recommended.

Conclusion

Compared to standard treatment alone, *Garcinia mangostana* showed beneficial metabolic effects on body weight and lipid metabolism. Nevertheless, the effect on glycemia seems to remain modest in the context of effective dual therapy. In conclusion, this study has found *Garcinia mangostana* to be a potentially beneficial adjuvant therapy for the metabolic status of patients with early T2DM.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

Clinical trials: ClinicalTrials.gov Identifier: NCT07172269.

The authors declared that no experiments on humans or human tissues were performed for the present study.

Informed consent from the humans, donors or donors' representatives: the Scientific and Ethical Committee of the College of Pharmacy/ Mustansiriyah University (Research No. 92, Approval No. 79).

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Use of AI

AI was used for language proofreading.

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Author contributions

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Data availability

Underlying data. Zenodo: Demographic details and clinical data. https://doi.org/10.5281/zenodo.17979254. This project contains the following underlying data:

Research data.xlsx (demographic details and clinical data).

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

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