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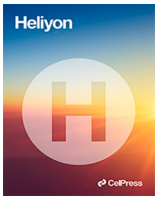

Research article

Therapeutic effect of fenugreek supplementation on type 2 diabetes mellitus: A systematic review and meta-analysis of clinical trials

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ABSTRACT

Introduction: Numerous clinical trials have investigated the effects of fenugreek, a traditional herbal medicine, on type 2 diabetes mellitus (T2DM). However, the results from these studies have been inconsistent. Therefore, we aimed to perform a meta-analysis on the effects of fenugreek supplementation on weight, body mass index (BMI), lipid profile, and glycemic indices in patients with T2DM.

Methods: We searched PubMed, Scopus, Embase, ISI Web of Science, and Cochrane Library databases to identify clinical trial studies until October 2023. The data were analyzed using a random-effects model and presented as the weighted mean difference (WMD) along with the associated 95 % confidence interval (CI).

Results: A total of 19 studies were included in the meta-analysis. The results indicated a significant impact of fenugreek supplementation on lowering fasting plasma glucose (FPG) (WMD: 20.32 mg/dl; 95 % CI: 26.65 to −13.99), hemoglobin A1C (HbA1c) (WMD: 0.54 %; 95 % CI: 0.80 to −0.28), homeostatic model assessment of insulin resistance (HOMA-IR) (WMD: 0.36; 95 % CI: 0.67 to −0.05), total cholesterol (TC) (WMD: 33.10 mg/dL; 95 % CI: 64.31 to −1.88), low-density lipoprotein cholesterol (LDL-C) (WMD: 29.14 mg/dL; 95 % CI: 55.45 to −2.83), BMI (WMD: 0.73 kg/m2; 95 % CI: 1.40 to −0.07), and increasing the high-density lipoprotein cholesterol (HDL-C) (WMD: 5.68 mg/dL; 95 % CI: 3.51 to 7.85). However, the effect on fasting insulin, triglycerides, and weight was not significant.

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Conclusions: Fenugreek supplementation has been shown to improve FPG, HbA1C, HOMA-IR, TC, LDL-C, HDL-C, and BMI in patients with T2DM. The overall results suggest that fenugreek may have protective and therapeutic effects on T2DM parameters.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic condition characterized by both high blood sugar levels (hyperglycemia) and glucose intolerance, caused by the body's impaired response to insulin, leading to increased insulin production and eventually an insulin deficiency [1]. In 2021, the prevalence of diabetes among individuals aged 20–79 was 10.5 % globally, and it is expected to increase to 12.2 % by 2045 [2]. High blood sugar, reduced insulin sensitivity, dyslipidemia, hypertension, and obesity, are common features of T2DM which often occur together rather than singly. T2DM is a complex disease that has multiple causes including environmental factors, genetic predisposition, and behavioral changes [3,4]. Therefore, it is essential to look for ways to manage these coexisting health issues at the same time [5]. Oral medications that reduce blood glucose and insulin injections, which are the conventional methods of treatment at present, have side effects and cost that make them less than ideal for some patients [6,7]. A healthy lifestyle that consists of proper nutrition, regular physical activity, and exercise can modulate the severity of T2DM [8]. Nowadays, alternative therapies that have the potential to improve metabolic parameters in T2DM have gained increasing interest [9–11]. Within this context, herbal medicine has been introduced as a supplementary method alongside drug therapy and lifestyle interventions [12,13].

Fenugreek (Trigonella foenum-graecum), an annual herb of the Leguminosae family, has medicinal properties and is often used as an anti-diabetic drug [14]. Fenugreek seeds contain a lot of carbohydrates (galactomannan and mucilaginous fiber), proteins, free amino acids (arginine, 4-hydroxyisoleucine, lysine, histidine), flavonoids, alkaloids (choline and trigonelline), saponins (similagenin, yuccagenin, diosgenin, and savsalpogenin), vitamins (A, D, B2, B12, B6), minerals, glycosides, and mucilage, all of which have curative properties in both animals and humans [15–19]. In addition, fenugreek has been shown to have various therapeutic properties, including anti-diabetic, anti-obesity, anti-inflammatory, anti-hyperlipidemic, antioxidant, anti-microbial, and anti-cancer activities [20,21]. Fenugreek's effectiveness in helping diabetics is explained by several proposed mechanisms. Trigonelline and fenugrecin are alkaloids in fenugreek that exhibit hypoglycemic activity, while insulin secretion from the pancreas is stimulated by 4-hydroxyisoleucine amino acids and soluble fibers such as glucomannan fiber which slows down the uptake of sugars from the intestine [22].

Previous studies on the effects of fenugreek supplementation in patients with T2DM have yielded inconsistent results. Some randomized controlled trials (RCTs) have shown beneficial effects of fenugreek, while others have found no significant impact on T2DM outcomes [13,23–26]. Though fenugreek is proposed to improve T2DM through various mechanisms, the research so far has not clearly elucidated its precise effects or causative pathways. Consequently, the overall impact of fenugreek supplementation on key T2DM indicators like glycemic control, lipid profile, and obesity measures remains uncertain. Given the mixed evidence, further investigation through systematic review and meta-analysis is warranted to synthesize the current literature on fenugreek's efficacy in T2DM.

It should be noted that some recent systematic reviews and meta-analyses also have examined the effects of fenugreek supplementation in patients with diabetes, prediabetes, and dyslipidemia [27–30]. Furthermore, earlier reviews [5,29] overlooked numerous studies, and more research has been conducted and published on the influence of fenugreek on T2DM since then. However, this study will provide a quantitative synthesis and critical analysis of up-to-date evidence regarding fenugreek's therapeutic potential in T2DM. By shedding light on the effectiveness of fenugreek supplementation, the results of our study will contribute to understanding its place in the evidence-based treatment of T2DM. Additionally, we will conduct comprehensive subgroup and sensitivity analyses to uncover the reasons for variations across different trials. Previous research has indicated that fenugreek supplementation may have a beneficial effect on T2DM biomarkers [27–30]. However, a comprehensive systematic review and meta-analysis evaluating the strength of the supporting data for this effect has not been conducted yet. Therefore, this comprehensive systematic review and meta-analysis aims to evaluate the effects of fenugreek supplementation on obesity indices (body weight (BW), and body mass index (BMI)), glycemic factors (fasting plasma glucose (FPG), fasting insulin, hemoglobin A1C (HbA1c), homeostatic model assessment of insulin resistance (HOMA-IR)), and lipid profile (total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)) in T2DM patients.

1.1. Methods

This study was performed in accordance with the PRISMA guidelines [31] (Supplementary Table 1). It has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the code CRD42023467126. The ethics committee of Tabriz University of Medical Sciences approved the study protocol (IR.TBZMED.VCR.REC.1402.319).

1.2. Search strategy

The present systematic review and meta-analysis of clinical trials used the PICO model, which consisted of the population (adult participants with T2DM), intervention (consumption of fenugreek), comparison (placebo/control group), and outcomes (FPG, HbA1c, insulin, HOMA-IR, TG, TC, LDL-C, HDL-C, BW, and BMI). We conducted a systematic search of electronic databases, including PubMed, Scopus, Embase, ISI Web of Science, and Cochrane Library, to identify clinical trials assessing the effects of fenugreek supplements on

patients with T2DM from the study inception until October 2023. No restriction was applied for publication year or language. We applied the following keywords in our search strategy: (Trigonella OR Fenugreek OR Fenugreeks OR Foenumgraecum OR foenum OR graecum) AND (intervention OR Intervention Study OR Intervention Studies OR intervention* OR controlled trial OR random OR randomly OR placebo OR clinical trial OR trial OR randomized controlled trial OR randomized clinical trial OR RCT OR blinded OR double-blinded OR clinical trials OR trials) AND (Type 2 Diabetes Mellitus OR Type 2 Diabetes OR T2DM OR Diabetes Mellitus, Type II). Moreover, a manual search of reference lists of related studies was performed to prevent the omission of any eligible trials.

1.3. Study selection

Eligible studies were selected based on the following criteria: 1) investigation of the effects of fenugreek supplementation on T2DM; 2) clinical trials with a crossover or parallel design; 3) studies that included adult individuals; 4) designs that provide enough data to assess outcomes at baseline and post-intervention. When the same dataset is the basis for multiple papers, the most complete paper is selected. In addition, an additional arm in a clinical trial was regarded as a separate study. Studies that had the following characteristics were excluded: 1) investigations conducted on pregnant women, adolescents, and children; 2) studies with no control or placebo group; 3) trials that applied fenugreek along with other ingredients, and were unable to determine the single impact of fenugreek; 4) studies conducted *in vivo* or *in vitro*, seminars, conference abstracts, letters, books, reviews, or case reports.

1.4. Data extraction

The data from each of the eligible articles was extracted independently by two different authors (MV, AB). A principal investigator (MAF) examined any inconsistencies to attain a consensus. The studies included provided the following data: first author's name, publication date, country, and study design, duration of the study, mean age, sample size, gender, mean BMI, health status, fenugreek dosage, and main outcomes.

1.5. Quality assessment and certainty of evidence

To assess the quality of the included studies, the updated Cochrane risk-of-bias for randomized trials (RoB 2) method was utilized [32]. The RoB2 assessment considers various elements, including randomization, outcome measurement, missing outcome data, deviations from intended interventions, and reported result selection. If methodological errors are present in the study, each domain

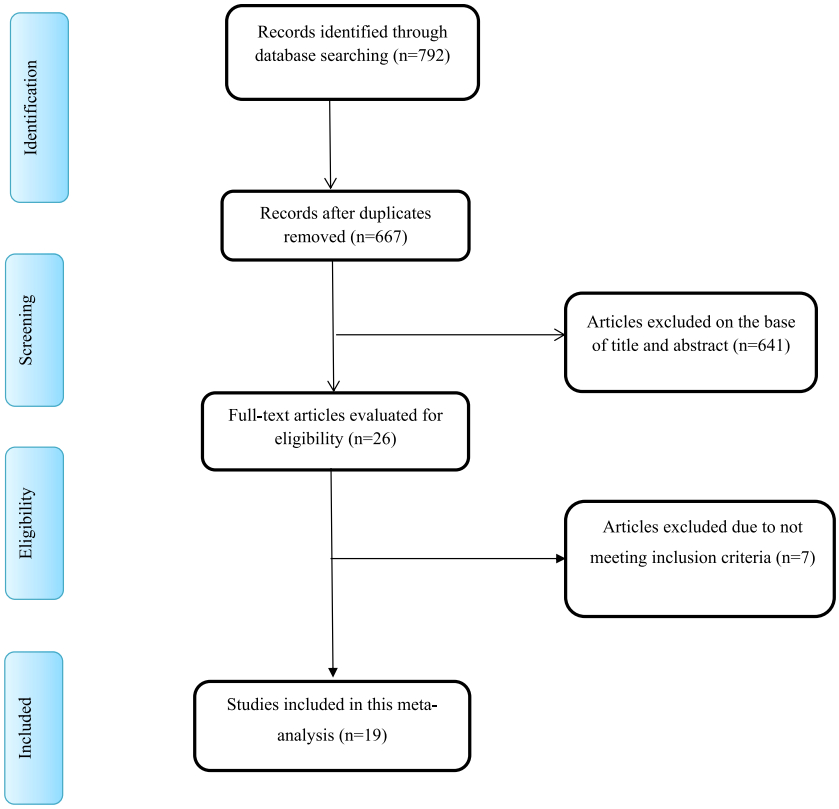

Fig. 1. Flow chart of the number of studies identified and selected into the meta-analysis.

receives a "high risk" score; conversely, a "low risk" score is assigned when no errors are detected, and an "unclear risk" score indicates insufficient data for assessment. Moreover, we applied the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) method to grade the overall certainty of evidence across studies [33,34].

1.6. Statistical analysis

Stata version 14 (Stata Corporation, College Station, Texas) was used to perform the statistical analysis of this meta-analysis, and a p-value <0.05 was considered statistically significant in all analyses. By using the means and standard deviations (SDs) reported for the control and intervention groups, the overall estimates were calculated [35]. To calculate the SD changes, the following formula was used: SD change = square root ([SD baseline]^2 + [SD final]^2 – [2R × SD baseline × SD final]), R = (SD1^2 + SD2^2 - SDchange^2)/(2 × SD1 × SD2) [35]. Additionally, we calculated the standard deviation (SD) using the formula: SD=SEM × $\sqrt{n}$, if only the standard error of the mean was available from the studies [36]. The data were analyzed using a random-effects model and presented as the weighted mean difference (WMD) along with the associated 95% confidence interval (CI). [37]. To evaluate heterogeneity among the included studies, we applied Cochran's Q test and the I^2 statistic, and substantial heterogeneity was indicated by $I^2 > 50$ % [32]. The sources of heterogeneity were identified by conducting subgroup analyses based on sample size, intervention duration, type of intervention, and participants' mean age. Furthermore, a sensitivity analysis was used to assess the influence of each trial on the overall effect size. Begg's, and Egger's test and visual inspection of funnel plots were used to evaluate publication bias. To correct for the publication bias, trim and fill were performed [38].

2. Results

2.1. Study selection

The literature search flowchart is presented in Fig. 1. 792 papers were obtained from various databases through our systematic search, of which 125 were duplicates and 641 were irrelevant based on the screening of their titles and abstracts. The pre-specified criteria for inclusion were met by only 19 out of the 26 studies that were evaluated in detail. After reviewing the full texts of the remaining 26 studies, we excluded seven studies based on the following criteria: absence of a true control group (n = 3), conference abstract only (n = 2), and co-administration of fenugreek supplement with other interventions (n = 2). Among the studies analyzed, 15 studies investigated the impact of fenugreek on FPG, 11 studies reported data on HbA1c, two studies were on insulin, two studies were on HOMA-IR, eight studies were on TC, eight studies were on TG, eight studies were on HDL-C, seven studies were on LDL-C, five studies were on BMI, and three studies were on BW.

2.2. Study characteristics

Table 1 contains a summary of the general characteristics of eligible trials. These studies, which were published between 1992 and 2023, included individuals aged between 18 and 70 years. The clinical trial included a total of 1612 participants, with 807 in the intervention group and 805 in the control group. Studies were carried out in India [13,22,25,39–47], Iran [10,23,48], Ethiopia [24], China [49], Bangladesh [50], and Egypt [26]. Different clinical trials had varying dosage ranges of fenugreek (extract or powder), ranging from 25 to 50,000 mg/day, and duration of intervention ranged between 4 and 24 weeks. While most of the studies were carried out on both genders, one trial was performed on females [48]. Fig. 2 displays the results of the quality assessment of the chosen trials. According to the RoB2 assessment, six trials had a low risk of bias, whereas others were of lower quality because one or more domains were at unclear or high risk of bias. After assessing the certainty of the evidence using the GRADE protocol (Supplementary Table 2), it was determined that the effect evaluations of LDL-C, TG, BMI, and HDL-C were of high quality. The evidence regarding FPG, HbA1c, and TC was identified as moderate quality due to significant limitations in publication bias. Additionally, due to significant limitations in imprecision, BW was considered to be of moderate quality.

2.3. FPG

In 15 trials with 22 treatment arms, which involved a total of 1337 patients, the impact of fenugreek consumption on FPG was evaluated. In comparison to the placebo group, administering fenugreek significantly decreased FPG levels (WMD: 20.32 mg/dl; 95 % CI: 26.65 to −13.99; $P < 0.001$; $I^2 = 94.3$ %; $P < 0.001$) (Supplementary Fig. 1a). To recognize potential sources of heterogeneity, we performed a subgroup analysis based on sample size, intervention duration, fenugreek dosage, intervention type, and age. In studies that involved a sample size ≥50, trials that used fenugreek powder, studies that prescribed <10 g/d fenugreek, and studies with a duration of fewer than eight weeks, fenugreek supplementation led to a more significant decrease in FPG (Supplementary Table 3).

2.4. HbA1c

The impact of fenugreek consumption on HbA1c levels was investigated in 11 eligible studies, which comprised 13 effect sizes. The combined effect sizes showed that fenugreek consumption led to a substantial reduction in HbA1c levels compared to placebo (WMD: 0.54 %; 95 % CI: 0.80 to −0.28; $P < 0.001$; $I^2 = 88.2$ %; $P < 0.001$) (Supplementary Fig. 1b). Subgroup analysis demonstrated that the heterogeneity could be explained by sample size, dose, and type of intervention. Additionally, a significant reduction in HbA1c was

Table 1
Characteristics of included studies in the meta-analysis.

First Author	Year	Location	Sample size (intervention/ control)	Gender	Mean Age		Mean BMI		Design	Supplement	Comparator	Dose g/d	Duration (week)	Main results
					Case	Control	Case	Control						
Hadi et al. (10)	2020	Iran	48(24/24)	m/f	47.7	47.4	30.02	30.02	RCT	SP + antidiabetic drugs and nutritional recommendations	Control (antidiabetic drugs and nutritional recommendations)	15	8	FBS ↓, BP ↔
Sundaram et al. (13)	2021	India	80(40/40)	m/f	NR	NR	NR	NR	RCT	SP + metformin	Control (metformin)	0.025	4	HbA1c ↓, FBS ↓
Ranade et al. (22)	2017	India	60(30/30)	m/f	48	46.22	25.23	26.02	RCT	Seed + antidiabetic drugs	Anti-diabetic drugs	10	24	FBS ↓, HbA1c ↓
Hassani et al. (23)	2019	Iran	63(31/32)	m/f	50.19	52.81	27.43	28.21	RDBPC	SP + NT	Placebo (wheat flour) + NT	10	8	FBS ↓, HbA1c ↓, BMI ↓, WC ↓
Geberemeskel et al. (24)	2019	Ethiopia	95(49/46)	m/f	NR	NR	NR	NR	RCT	TFGSP	Nothing	0.05	4	TG ↓, TC ↓, LDL ↓, HDL ↑
Zargar et al. (25)	1992	India	25(11/14)	m/f	40–60	40–60	NR	NR	Control trial	SP	Nothing	20	6	FBS ↓, HbA1c ↔
Shakour et al. (26)	2003	Egypt	40(20/20)	m/f	25–45	25–45	NR	NR	RCT	boiled seeds + regular diabetic diet	Regular diabetic diet)	15	4	FBS ↔, TC↔, LDL ↔, TG ↔, HDL ↔
Suchitra et al. (39)	2015	India	60(30/30)	m/f	50.37	50.1	NR	NR	RCT	seed	Nothing	30	8	HbA1c ↓
Kaur et al. (40)	2016	India	60(30/30)	m/f	52.97	53.23	25.17	25.91	RCT	SP + Metformin	Control (Metformin)	3	12	FBS ↓, HbA1c ↓, BMI ↔, weight ↔
Gupta et al. (41)	2001	India	25(12/13)	m/f	49.16	52.83	26.55	26.86	RDBPC	SE (Hydro alcoholic)	Placebo (unclear)	1	8	FBS ↓, HbA1c ↔, TC↔, LDL ↔, TG ↓, HDL ↔
Bordia et al. (42)	1997	India	60(30/30)	m/f	NR	NR	NR	NR	RCT	SP	Placebo (unclear)	5	12	TC ↓, TG ↓, HDL ↔
Verma et al. (43)	2019	India	154(77/77)	m/f	25–60	25–60	NR	NR	RDBPC	TFGSE	Placebo (di calcium phosphate)	1	12	FBS ↓, HbA1c↓
Khan et al. (44)	2018	India	90(40/50)	m/f	18–70	18–71	31.2	28.4	RCT	Sprouted seed	Anti-diabetic drugs	50	6.4	FBS ↓, BMI ↓, BP ↓, Weight ↓
Kandhare et al. (45)	2018	India	78(38/40)	m/f	51.48	51.42	26.08	26.36	RDBPC	SE	Placebo (microcrystalline cellulose)	2.1	12	FBS ↓, HbA1c ↓, TC ↑, LDL↑, TG ↔, HDL ↔
Hota et al. (46)	2023	India	204(102/102)	m/f	53.03	52.22	26.7	26.2	RDBPC	TFGSE	Placebo (unclear)	1	12	HbA1c ↓, FBS ↔, HOMA-IR

(*continued on next page*)

Table 1 (*continued*)

First Author	Year	Location	Sample size (intervention/ control)	Gender	Mean Age		Mean BMI		Design	Supplement	Comparator	Dose g/d	Duration (week)	Main results
					Case	Control	Case	Control						
														↔, Insulin ↔
Kumar et al. (47)	2015	India	45(21/24)	m/f	40–60	40–60	NR	NR	control trial	SP	Regular diabetic diet except fenugreek	20	8	FBS ↓, HbA1c ↔, TG ↓, TC ↓, LDL ↓, HDL ↑
Gholaman et al. (48)	2018	Iran	20(10/10)	f	44.2	44.2	33.11	32.86	RDBPC	Seed + yoghurt	Placebo (yoghurt)	15	8	FBS ↓, Insulin ↔, HOMA-IR ↔, TC ↔, LDL ↓, TG ↔, HDL ↑, BMI ↔, weight ↔, PBF ↔
LU FR et al. (49)	2008	China	69(46/23)	m/f	54.8	53.7	24.69	24.70	RDBPC	SP	Placebo (Chinese yam)	6.3	12	FBS ↓, HbA1c ↓, BMI ↔
Moosa et al. (50)	2006	Bangladesh	30(15/15)	m/f	30–65	30–65	NR	NR	Control trial	SP + usual anti-diabetic treatment	Control + usual anti-diabetic treatment	50	6	TG ↓, TC↓, LDL ↓, HDL ↔

RDBPC, randomized double-blind placebo-controlled; RTBPC, randomized triple-blind placebo-controlled; RCT, randomized controlled trial; TFGSP, Trigonella foenum-graecum seed powder; TFGSE, Trigonella foenum-graecum seed extract; SE, seed extract; SP, seed powder, T2DM, Type 2 Diabetes, NIDDM, Non-insulin-dependent diabetes mellitus; ET, exercise training; NT, nutrition training; BMI, body mass index; PBF, percent body fat; CAD, coronary artery disease; M, male; F, female; FBS, fasting blood sugar; HbA1c, hemoglobin A1C; TC, total cholesterol, LDL, low-density lipoprotein, TG, triglyceride; HDL, high-density lipoprotein; BP, blood pressure; WC, waist circumference; NR, not reported. ↓ significant reduction; ↑ significant increase; ↔ not changed significantly.

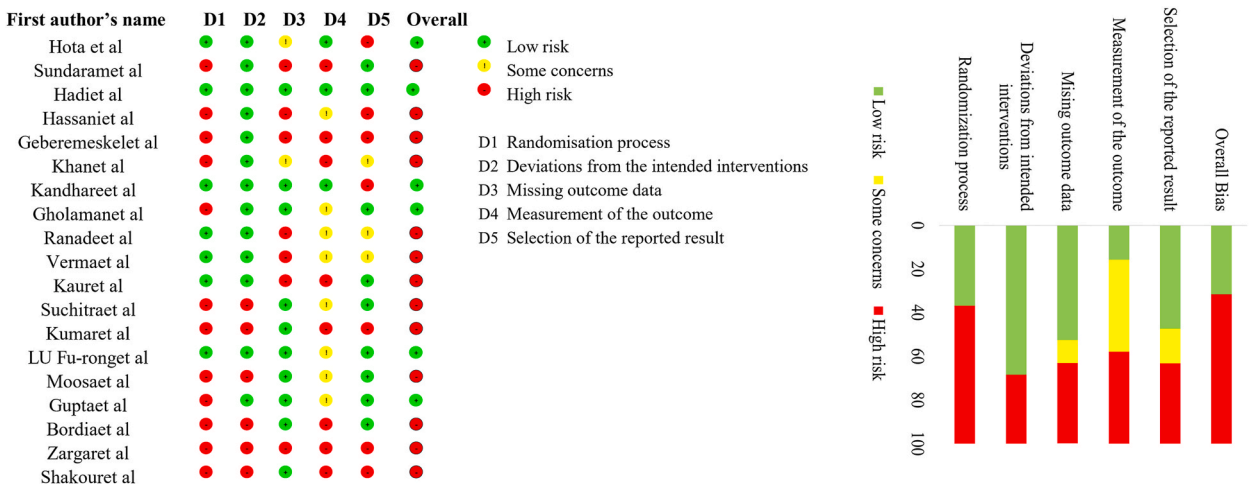

Fig. 2. Quality assessment (A summary of the risk of bias according to the updated Cochrane risk-of-bias for randomized trials (RoB 2)). Each study's risk of bias was divided into three categories based on these items: low risk, some concerns, and high risk.

observed subsequent to fenugreek intake in the subgroup administered a fenugreek dosage of less than 10 g/d, in trials with a sample size of fewer than 50, in trials with duration <8 weeks, and with the intervention involving fenugreek powder (Supplementary Table 3).

2.5. HOMA-IR

In two studies with three treatment arms, fenugreek supplementation was investigated for its effect on HOMA-IR and demonstrated a significant impact on decreasing HOMA-IR levels (WMD: 0.36; 95 % CI: 0.67 to −0.05; P = 0.024; I^2 = 0.00 %; P = 0.850) (Supplementary Fig. 1c). Any subgroup analysis was not possible due to the limited number of available trials.

2.6. Insulin

Fenugreek supplementation was evaluated in two trials with three treatment arms to assess its impact on insulin levels. No significant effects on insulin levels were observed when compared to the control group, according to the pooled estimate from the random-effects model (WMD: 0.37 mU/ml; 95 % CI: 0.83 to 0.09; P = 0.115; I^2 = 75.1 %; P = 0.018) (Supplementary Fig. 1d). The analysis of subgroups was not conducted due to the limited number of available data.

2.7. TG

The effect of fenugreek consumption on TG levels was studied in eight trials, which consisted of 12 treatment arms in total. The pooled estimate from the random-effects model showed no significant effects on TG levels after fenugreek consumption compared to the control group (WMD: 31.54 mg/dL; 95 % CI: 66.35 to 3.27; P = 0.076; I^2 = 99.5 %; P < 0.001) (Supplementary Fig. 2a). To recognize potential sources of heterogeneity, we performed a subgroup analysis based on sample size, intervention duration, fenugreek dosage, intervention type, and age. These analyses revealed that fenugreek supplementation led to a substantial reduction in serum TG concentrations in studies conducted on patients aged ≥45 years, clinical trials that administered ≥10 g/d fenugreek, with a sample size <50, intervention with powder type of fenugreek, and those with duration ≥8 weeks (Supplementary Table 4).

2.8. TC

The impact of fenugreek consumption on TC levels has been studied in eight studies with 12 effect sizes. According to the pooled estimate from the random-effects model, fenugreek had a significant effect on decreasing TC levels (WMD: 33.10 mg/dL; 95 % CI: 64.31 to −1.88; P = 0.038; I^2 = 99.5 %; P < 0.001) (Supplementary Fig. 2b). Between-study heterogeneity was attributed to age and intervention type based on subgroup analysis. In addition, interventions involving fenugreek seed and powder types, individuals with age ≥45 years, dosages of ≥1 g, intervention duration ≥8 weeks, and trials with <50 sample size exhibited a substantial and potent reduction effect on TC levels compared to other subgroups (Supplementary Table 4).

2.9. HDL-C

The combined results from eight studies with 12 effect sizes demonstrated a significant increase in serum HDL-C levels when

compared to the placebo (WMD: 5.68 mg/dL; 95 % CI: 3.51 to 7.85; P < 0.001; I^2 = 87.4 %; P < 0.001) (Supplementary Fig. 2c). Subgroup analysis showed that heterogeneity might be explained by intervention type. According to subgroup analysis, trials with a sample size <50, durations ≥8 weeks, intervention dosage of ≥10 g/d, participants with age <45 years, and seed types of fenugreek had a notable and substantial increasing effect on HDL-C compared to other subgroups (Supplementary Table 4).

2.10. LDL-C

The effect of fenugreek consumption on LDL-C was studied in seven trials with 11 treatment arms. In general, the quantitative meta-analysis showed that fenugreek consumption resulted in a significant reduction in serum LDL-C levels among patients with T2DM when compared to the control group (WMD: 29.14 mg/dL; 95 % CI: 55.45 to −2.83; P = 0.030; I^2 = 99.0 %; P < 0.001) (Supplementary Fig. 2d). The heterogeneity could be explained by intervention type, as demonstrated by the subgroup analysis. In these analyses, we realized that fenugreek administration has a more impressive reduction in LDL-C in the subgroup of seed and powder type of fenugreek, with a sample size of <50, fenugreek dosage ≥10 g/d, duration of intervention ≥8 weeks, and in participants aged ≥45 years old (Supplementary Table 4).

2.11. BMI

The impact of fenugreek supplementation on BMI was evaluated in seven treatment arms across five eligible articles. According to the pooled outcomes from the random-effects model, fenugreek resulted in a significant decrease in BMI compared to the control group (WMD: 0.73 kg/m^2; 95 % CI: 1.40 to −0.07; P = 0.031; I^2 = 86.6 %; P < 0.001) (Supplementary Fig. 3a). The heterogeneity observed might be explained by sample size, type of intervention, and age of subjects, as demonstrated by the subgroup analysis. According to these analyses, we discovered that the effect of fenugreek supplementation on BMI was significant in trials that treated fenugreek powder, dosages of ≥10 g/d, in trials on participants with a mean age of ≥45 years, with a sample size of ≥50, and both intervention duration (<8 weeks and ≥8 weeks).

2.12. Weight

Fenugreek supplementation was found to have no significant effect on BW compared to the control group, according to the combination of four estimates from three studies (WMD: 2.55 kg; 95 % CI: 6.46 to 1.36; P = 0.201; I^2 = 96.1 %; P < 0.001) (Supplementary Fig. 3b). The heterogeneity observed might be explained by sample size, duration of intervention, type of intervention, and age of subjects, as demonstrated by the subgroup analysis. Fenugreek supplementation led to a significant reduction in BW in trials that prescribed ≥10 g/d fenugreek, <8 weeks of duration, sample size ≥50, ≥45 years old subjects, and in studies with fenugreek powder.

2.13. Sensitivity analysis

The sensitivity analysis performed on BW, FPG, HbA1c, fasting insulin, and HDL-C demonstrated that the overall estimates were not influenced by the exclusion of any study. However, the impact of fenugreek on BMI was sensitive to the trials by Hassani et al. [23] (WMD: 0.78; 95 % CI: 1.62 to 0.06), Khan et al. [44] (WMD: 0.35; 95 % CI: 0.73 to 0.02), and Kaur et al. [40] (WMD: 0.75; 95 % CI: 1.56 to 0.04), HOMA-IR was sensitive to the studies by Hota et al. [46] (WMD: 0.31; 95 % CI -0.67 to 0.05), Gholaman et al. [48] (WMD: 0.35; 95 % CI: 0.74 to 0.02), TG was sensitive to the study by Kumar et al. [47] (WMD: 18.05; 95 % CI: 26.75 to −9.35), TC was sensitive to the studies by Moosa et al. [50] (WMD: 35.05; 95 % CI: 75.01 to 4.90), and Shakour et al. [26] (WMD: 32.64; 95 % CI: 65.62 to 0.33), and LDL-C was sensitive to the studies by Geberemeskel et al. [24] (WMD: 28.67; 95 % CI: 58.13 to 0.78), and Shakour et al. [26] (WMD: 27.63; 95 % CI: 56.03 to 0.75) **(Supplementary Fig. 4 a-j)**.

2.14. Publication bias

Publication bias tests were performed based on Begg's test, Egger's test, and visual inspection of the funnel plots. There was no evidence of publication bias from clinical trials assessing the effect of fenugreek on BW (P = 0.308; P = 0.336), BMI (P = 0.548; P = 0.359), fasting insulin (P = 0.296; P = 0.369), TG (P = 0.064; P = 0.747), HDL-C (P = 0.537; P = 0.226), and LDL-C (P = 0.640; P = 0.361). In contrast, significant publication bias was observed for FPG (P = 0.024; P = 0.001), HOMA-IR (P = 0.296; P = 0.047), HbA1c (P = 0.044; P = 0.033), and TC (P = 0.047; P = 0.636). Therefore, we did the trim-and-fill method and found no interference in the effects of fenugreek on FPG and HOMA. However, the results of trim and fill analysis with four imputed studies showed that fenugreek had more robust impact on reducing HA1C (WMD: 0.66; 95 % CI: 1.01 to −0.32) and TC (WMD: 47.27; 95 % CI: 71.87 to −22.66) levels after considering publication bias **(Supplementary Fig. 5 a-j)**.

3. Discussion

This study evaluated the effects of fenugreek supplementation on metabolic parameters in T2DM patients. A pooled analysis of 19 studies including 1612 patients examined the impact of fenugreek on lipid profile, glycemic control, and anthropometric measures. Fenugreek supplementation demonstrated significant beneficial effects on HOMA-IR, FPG, HbA1c, LDL-C, TC, HDL-C, and BMI. However, fenugreek did not significantly improve TG, insulin levels, or BW in the overall analysis. Subgroup analyses revealed that

fenugreek powder at doses ≥10 g/day and in patients aged ≥45 years significantly reduced TG levels and BW.

According to glycemic control, our meta-analysis revealed that fenugreek supplementation significantly reduced FPG by 20.32 mg/dL, glycated hemoglobin by 0.54 %, and HOMA-IR by 0.36 in patients with T2DM. In consistence with our results, the meta-analysis by Gong et al. showed similar benefits on glycemic levels with fenugreek supplementation [7]. Their meta-analysis of 12 RCTs revealed significant decreases in fasting plasma glucose (FPG) and HbA1c after administration of fenugreek. The consistent glycemic parameters improvements seen in both meta-analyses provide corroborating quantitative evidence for the use of fenugreek to improve diabetes control. Regarding glycemic parameters control, our subgroup analysis revealed that lower fenugreek doses (<10 g/day) resulted in greater reductions in both FPG and HbA1c in comparison to higher doses (≥10 g/day).

In contrast to the findings of this study, the meta-analysis by Shabil et al. reported different results for FPG [27]. Their analysis of 14 RCTs with 894 total participants found a non-significant reduction in FPG levels after administration of fenugreek supplementation. However, they found a substantial reduction in HbA1c levels, in line with our HbA1c findings. The reasons for the discordant FPG findings between the two studies are unclear, but may be related to differences in study populations, or inclusion criteria. Notably, the current meta-analysis included 15 trials assessing FPG effects and had a larger overall sample size (n = 1247) compared to their analysis (n = 894), providing greater statistical power to detect significant FPG changes [27].

In our study, the decrease in FPG levels with the lower dose of fenugreek was 33.10 mg/dL compared to 18.12 mg/dL with a high dose. For HbA1c, the decrease with the lower dose was 0.76 % versus 0.12 % with the high dose. This inverse association between fenugreek dose and glycemic efficacy has not been reported before, as previous reviews like Shabi et al. did not examine dose-response relationships through subgroup analyses [27]. The reasons for higher glucose-reduction effects at lower doses are unclear but could relate to changes in glucose homeostasis or saturation of active compounds at higher intakes. These novel dose-response insights suggest lower fenugreek doses may optimize glycemic benefits, but confirmatory dose-ranging studies are still needed. We also found that shorter trial duration (<8 weeks) increased reductions in both FPG and HbA1c levels compared to longer trial duration (≥8 weeks), indicating potential attenuation of efficacy over time. However, sustained efficacy needs to be verified in long-term trials. Again, the influence of duration has not been characterized previously due to the lack of subgroup stratification in earlier reviews [27,29,51,52]. The evidence suggests that fenugreek can improve hyperglycemia through its insulin-stimulating, immunomodulatory, and antioxidant effects. The favorable effects of fenugreek in diabetes are attributed to four bioactive components, including furostanol saponins, 4-hydroxyisoleucine, diosgenin, and fiber [53], which could improve insulin signaling by reducing oxidative stress and inflammation [54]. Saponins, and polyphenols available in fenugreek may also reduce hepatic gluconeogenesis based on preclinical studies [55].

According to lipid profile, fenugreek supplementation significantly reduced total cholesterol by 33.1 mg/dL and LDL-C by 29.14 mg/dL, along with increasing HDL-C by 5.68 mg/dL in patients with T2DM. The meta-analysis by Heshmat-Ghahdarijani et al. examined the effects of fenugreek on the lipid profile and had similar findings to our study regarding HDL-C, LDL-C, TC, and TG levels. However, their meta-analysis had a smaller overall sample size compared to our work. Specifically, their analysis included 281 participants in the fenugreek supplementation groups, whereas our meta-analysis had a larger sample of 807 participants receiving fenugreek [28]. Considering the effect sizes are smaller compared to our analysis, likely due to smaller trial sample sizes, the directions of effect are consistent. The similar results between the two meta-analyses provide stronger quantitative evidence for the lipid-lowering potential of fenugreek. Another meta-analysis by Askarpour et al. focused on both lipid and anthropometric effects, including 12 RCTs with 560 total participants [56]. This meta-analysis found significant improvements in HDL-C, TG, and TC, but non-significant changes in LDL-C following fenugreek supplementation administration. Although this meta-analysis had a larger sample size compared to Heshmat-Ghahdarijani et al.'s study, the effect sizes were still smaller than what we observed, potentially related to differences in studied populations (adults generally vs diabetes patients) [56]. Nonetheless, the beneficial effects on TC, TG, and HDL-C further support the hypolipidemic effects of fenugreek. Our meta-analysis, along with Heshmat-Ghahdarijani et al. and Askarpour et al., provides strong evidence from RCTs that fenugreek supplementation can significantly improve lipid profile by lowering TC, TG, and LDL-C levels while increasing protective HDL-C levels [28,56]. The effects seem to be most prominent in patients with underlying metabolic conditions like diabetes based on our analysis. Our subgroup analysis on lipid profile revealed that higher fenugreek doses (≥10 g/day) and longer trial duration (≥8 weeks) resulted in greater improvements among all parameters, including TG, TC, HDL-C, and LDL-C. For example, HDL-cholesterol increased by 4.98 mg/dL with the high dose of fenugreek versus 3.49 mg/dL with the lower dose. TG declined by 17.93 mg/dL with a short duration versus 44.38 mg/dL with a long duration of trial. These results indicate a potential dose- and duration-dependent relationship, where higher intakes and sustained treatment are needed to optimize lipid profile effects. In contrast to our study, the meta-analyses by Heshmat-Ghahdarijani et al. did not perform any subgroup analysis for lipid outcomes based on dose or duration [28]. Therefore, our study is one of the first studies suggesting potential non-linear associations between fenugreek dose and duration of trial and lipid profile. However, the high residual heterogeneity shows these preliminary trends need verification through further RCTs using systematic dose escalation and treatment periods. Further studies are still required to confirm optimal dosing and treatment duration with fenugreek for the management of dyslipidemia. The lipid-lowering effects of fenugreek supplementation that were observed in this study may be due to several bioactive constituents. Fenugreek contains high levels of soluble fiber and saponins such as diosgenin, which can decrease cholesterol absorption and inhibit cholesterol synthesis in the liver by binding bile acids [57,58]. Moreover, fenugreek also has antioxidant effects and reduces lipid peroxidation, which can contribute to the beneficial effects on dyslipidemia [59]. However, the exact mechanisms mediating the lipid-lowering effects of fenugreek in humans still need further elucidation through mechanistic studies.

In the field of anthropometric measurements regarding BW and BMI, our analysis did not find a significant effect of fenugreek consumption on BW (−2.55 kg, 95 % CI: 6.46 to 1.36) based on 3 small RCTs. However, we found a small but significant reduction in BMI of −0.73 kg/m2 (95 % CI: 1.40 to −0.07) among 5 clinical trials. Similarly, the study by Askarpour et al. found no statistically

significant changes in BW or BMI after administration of fenugreek supplementation among 12 and 6 RCTs, respectively [56]. The non-significant BW effects may be related to the limited RCT data and only 3 clinical trials evaluated BW in our analysis. The small BMI reduction we observed requires further study as well, especially in patients with obesity where metabolic benefits may be greater. Indeed, the existing evidence does not support a major weight loss effect with administration of fenugreek supplementation. High-quality randomized clinical trial data in larger samples are required to fully elucidate the anthropometric effects of fenugreek supplementation.

For anthropometric measures, our subgroup analysis suggested potentially greater BMI reduction with higher fenugreek doses administration ($\geq$10 g/day), and longer trial duration ($\geq$8 weeks), but the overall BW effects remained non-significant. For example, BMI reduction by 0.75 kg/m2 in studies with doses $\geq$10 g/day compared to 0.51 kg/m2 with doses $<$10 g/day. The meta-analysis by Askarpour et al. did not perform any subgroup analysis based on dose or duration for their BMI data [56]. Therefore, we are unable to directly compare our anthropometric dose-response findings with previous meta-analyses [56].

The limited yet modest positive effects of fenugreek on BMI may be attributed to several potential mechanisms, including available soluble fiber and expansion in the gut to promote feelings of fullness and satiety, which may reduce food intake and subsequently BW [60]. Fenugreek can also decrease gastric emptying and carbohydrate absorption to decrease postprandial glucose spikes that can negatively affect BW [54]. However, some recent studies have paradoxically shown BW gain with fenugreek administration with mineral absorption and glycogen storage increment [61], indicating the necessity of further evaluation to determine the exact effect of fenugreek on BW.

Recent studies have reported several potential side effects of fenugreek supplementation. The most common adverse effect is gastrointestinal distress, including nausea, diarrhea, and dyspepsia [62]. In a randomized controlled trial by Bordia et al. (1997), around 20 % of subjects taking a fenugreek seed extract reported gastrointestinal symptoms such as flatulence, diarrhea, and stomachache. Allergic reactions have also been documented in some individuals [63].). It is hypothesized that the high content of protein antigens in fenugreek may trigger immunoglobulin E-mediated hypersensitivity reactions in sensitized people [64]. Additionally, the coumarin content of fenugreek has raised concerns about possible hepatotoxicity and anticoagulant activity [62]. While isolated cases of hemorrhage and necrosis after massive fenugreek ingestion have been reported in preclinical studies, controlled trials to date have not found evidence of hepatotoxicity or significant anticoagulant effects at the lower therapeutic doses commonly used [65].

This systematic review and meta-analysis of fenugreek supplementation in T2DM patients builds on several recent reviews examining this topic [7,27–29,51]. Our findings were largely consistent with the meta-analyses by Gong et al. [7], Shabil et al. [27], Heshmat-Ghahdarijani et al. [28], and Askarpour et al. [56], which also found significant improvements in glycemic control and lipid markers with fenugreek. However, our meta-analysis expands on these earlier reviews in several ways. In this regard, we included a larger number of trials assessing glycemic indices or lipid profiles - 15 trials compared to 5–14 trials in prior reviews. Also, our overall sample size was larger (n = 1612) versus 560 to 1247 patients in previous analyses [7,27,28,56]. The enhanced statistical power from our larger dataset allowed for more precise estimates and subgroup analyses not performed before to explore heterogeneity.

Additionally, our meta-analysis specifically examined fenugreek effects on parameters like LDL-C, BMI, and BW in T2DM patients. We also conducted more detailed subgroup and sensitivity analyses than prior reviews to elucidate sources of heterogeneity. In summary, while consistent with previous findings, this meta-analysis provides a more comprehensive and higher-powered analysis of fenugreek supplementation in T2DM.

3.1. Implications for practice

The findings from this meta-analysis have important implications regarding the clinical application of fenugreek for patients with T2DM. Our results overall support the use of fenugreek supplements as an adjunct therapy alongside standard medications and lifestyle changes to improve glycemic control and dyslipidemia. Fenugreek appears to be safe and reasonably well-tolerated, making it an attractive option for many patients. The evidence indicates benefits are sustainable with long-term consistent use for at least 8–12 weeks. However, patients should be monitored for potential side effects.

3.2. Implications for research

While the therapeutic effects of fenugreek are well-established, we believe our updated quantitative synthesis provides value by strengthening the evidence base with new RCT data and identifying optimal regimens for diabetes management. However, the high residual heterogeneity indicates further research is still needed to determine the ideal dosage, duration, and formulations of fenugreek to maximize benefits on glycemic control and cardiovascular risk factors.

3.3. Study strengths and limitations

The present study is the most comprehensive meta-analysis exploring the effect of fenugreek supplementation on T2DM biomarkers. This systematic review and meta-analysis, when contrasted with earlier reviews [5,29], stands out due to its rigorous adherence to the PROSPERO-registered protocol and its evaluation of a broader range of outcomes. Furthermore, the number of included trials in our study was more than other studies (19 vs. 10 [29] and 13 [5] studies). The inclusion of recent studies and subgroup analyses in our meta-analysis provided further insights into potential sources of heterogeneity that were not examined in previous studies, which was the main advantage of our study. Despite these advantages, our study also has some limitations that should be considered. First of all, substantial heterogeneity was present among studied clinical trials, although subgroup analyses were

conducted. Residual confounding factors likely remain and their effects were not elucidated in this meta-analysis. Second, small sample sizes and the short duration of many included clinical trials limited the robustness of this study. Third, publication bias was detected for some outcomes in this review. Considering all advantages and disadvantages and with some available inconsistencies between meta-analyses, we can surmise that our study presents the most comprehensive synthesis of fenugreek's therapeutic potential in patients with T2DM to date.

4. Conclusion

Our findings indicate that fenugreek might have a substantial positive effect on FPG, HbA1c, LDL-C, TC, HDL-C, HOMA-IR, and BMI, and it could be endorsed as part of a healthy diet. Our findings reinforce the evidence from prior reviews supporting glycemic control and lipid profile improvements with the administration of fenugreek supplements. Further rigorously designed RCTs are critically required to optimize fenugreek dosing, treatment duration, and formulations for diabetes management.

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Ethical consideration

The study protocol was approved and registered by the ethics committee of Tabriz University of Medical Sciences (IR.TBZMED.VCR.REC.1402.319). The protocol of the current study has been registered in the PROSPERO system (CRD42023467126).

Data availability statement

Data will be made available on request the corresponding author (Mahdieh Abbasalizad-Farhangi, E-mail address: abbasalizad_m@yahoo.com)

CRediT authorship contribution statement

Mahdi Vajdi: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Nooshin Noshadi:** Writing – original draft. **Atefeh Bonyadian:** Writing – original draft. **Sahar Golpour-hamedani:** Writing – original draft. **Beitullah Alipour:** Writing – review & editing, Validation, Formal analysis, Data curation. **Fatemeh Pourteymour Fard Tabrizi:** Writing – review & editing, Writing – original draft, Validation, Methodology, Data curation. **Mahdieh Abbasalizad-Farhangi:** Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Formal analysis, Data curation. **Gholamreza Askari:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e36649.

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