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ORIGINAL ARTICLE

Meta-analysis of the anti-oxidative and anti-inflammatory effects of hypoglycaemic plant-derived medicines

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Abstract

Background The pivotal role of oxidative stress and inflammation in the pathophysiology of type 2 diabetes mellitus (T2DM) has been firmly established. However, the evidence concerning hypoglycaemic medicinal plants' antioxidant and anti-inflammatory effects remains inconclusive due to inconsistencies in prior studies. To address this gap, our study aims to perform a comprehensive systematic review and meta-analysis of randomized controlled trials (RCTs) to consolidate previous research findings in this field.

Methods We conducted a comprehensive search in the PubMed, Web of Science, Embase, Cochrane Library, and Scopus databases to identify relevant English randomized controlled trials (RCTs). Our study adhered to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines. All eligible studies that evaluated concurrently the antioxidative and anti-inflammatory effects of hypoglycaemic plant-derived supplements on type 2 diabetes mellitus (T2DM) were included in the meta-analysis. The meta-analysis itself was carried out using both fixed and random effects models to synthesize the findings from the selected studies.

Results Our study included 47 trials with a total of 2636 participants, both male and female, aged between 20 and 79 years, diagnosed with prediabetes, type 2 diabetes mellitus (T2DM), or metabolic syndrome. The meta-analysis revealed that plant-derived treatments, compared to placebos or other medicines, significantly improved oxidative stress (SMD = − 0.36, 95% CI − 0.64 to − 0.09), inflammation (SMD = − 0.47, 95% CI − 0.63 to − 0.31), total antioxidant capacity (SMD = 0.46, 95% CI 0.16–0.75), and antioxidant enzyme activity (SMD = 1.80, 95% CI 1.26–2.33). The meta-regression analysis showed that treatment duration exceeding 8 weeks significantly impacted the heterogeneity of the oxidative stress data.

Conclusions Several hypoglycaemic plant-based treatments appear to positively affect T2DM patients by concurrently lowering oxidative stress and inflammatory indicators and boosting antioxidant enzyme activity.

Clinical Trail Registry PROSPERO ID: CRD42021226147.

Keywords Type 2 diabetes mellitus · Inflammation · Oxidative stress · Plant-derived · Clinical trial · Systematic review

Abbreviations

Akt	Protein kinase B
CAT	Catalase
CI	Confidence interval
DBRCT	Double-blind, randomized controlled trial
GPx	Glutathione peroxidase
GSH	Reduced glutathione
hs-CRP	High-sensitivity C-reactive protein
IL-6	Interleukin-6
MD	Mean difference
MDA	Malondialdehyde
NF-κB	Nuclear factor kappa light chain-enhancer of activated B cells
NO	Nitric oxide
Nrf2	Nuclear factor erythroid 2-related factor 2
PI3K	Phosphatidyl inositol-3-kinase
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROSPERO	International Prospective Register of Systematic Reviews
SD	Standard deviation
SE	Standard error
SIRT	Sirtuin 3

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Extended author information available on the last page of the article

SMD	Standardized mean difference
SOD	Superoxide dismutase
T2DM	Type 2 diabetes mellitus
TAC	Total antioxidant capacity
TNF-α	Tumor necrosis factor-α
WHO	World Health Organization

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common chronic diseases, with a prevalence estimated to exceed 536.6 million patients and expected to reach 783.2 million patients by 2045 (Sun et al. 2022). The increasing prevalence of T2DM is attributed to an aging population, unhealthy lifestyle behaviors, and the increased prevalence rate of T2DM risk factors, particularly obesity (Chan et al. 2020). Diabetes is a multifactorial disease caused by the interaction of genetic and environmental factors. It is associated with high morbidity and mortality worldwide (Vassalle and Gaggini 2022). T2DM is characterized by chronic hyperglycemia due to insulin resistance, β-cell dysfunction, or both (Giacco and Brownlee 2010). Under hyperglycemic conditions, increased glucose uptake leads to elevated oxidative stress markers. Consequently, this rise in oxidative stress markers can trigger the activation of inflammatory markers like interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). The interplay between inflammatory and oxidative stress pathways may contribute to T2DM dysfunction and complications (Vassalle and Gaggini 2022). It has been suggested that reducing oxidative stress and inflammation may be a target for developing novel antidiabetic medications (Vassalle and Gaggini 2022).

Current medications for T2DM are often costly and associated with various side effects, including severe hypoglycemia (Vassalle and Gaggini 2022). As an alternative, herbal medicines offer a promising avenue for developing new treatments due to their widespread availability, affordability, and relatively safe profile (Thomford et al. 2018; Soltani et al. 2022). An excellent example is metformin, the first-line drug for T2DM, which originated from *Galega officinalis*, a herbal medicine utilized in Europe to manage diabetes (Bailey 2017). Current evidence suggests that various hypoglycaemic herbal medicines can significantly reduce inflammation and oxidative stress biomarkers in diabetes (Atkin et al. 2016; Ebrahimpour koujan et al. 2015; Ghafouri et al. 2020). Hence, plants offer a valuable resource for developing novel antidiabetic drugs due to their antioxidant and anti-inflammatory effects. Since there are inconsistent results regarding the use of herbal medicines with anti-inflammatory and antioxidant properties on T2DM (Adab et al. 2019; Alnajjar et al. 2020; Azimi et al. 2014; Basu et al. 2013), the current systematic review and meta-analysis were conducted to critically assess all the trials that simultaneously evaluated the antioxidative and anti-inflammatory activities of hypoglycaemic herbal medicinal on T2DM.

Methods

This systematic review and meta-analysis study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Page et al. 2021). It was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the ID: CRD42021226147. In addition, the ethics committee of the Endocrinology and Metabolism Research Institute of Tehran University of Medical Sciences has authorized this study (IR.TUMS.EMRI.REC.1397.046).

Search strategy

A comprehensive and systematic search was conducted through PubMed, Web of Science, Embase, Cochrane Library, and Scopus databases. The following keywords were used: (“herbal medicine”, “diabetes”, “inflammation”, “antioxidant”, the name of each oxidative or inflammatory biomarker, antioxidative enzyme, and their equivalents) to retrieve all clinical trials published in English from their inception to April 2022. In addition, the reference lists of all relevant articles were screened to find any eligible studies that might have been missed. The search strategy is available in Table S1.

Study selection and eligibility criteria

All clinical trials conducted in English that met the following criteria were included in this study: (1) evaluated the effect of extract or powder of hypoglycaemic herbal medicine simultaneously on oxidative and inflammatory biomarkers; (2) conducted on patients with prediabetes, T2DM, or metabolic syndrome; (3) compared the effectiveness of herbal medicines to no treatment, placebo, or conventional pharmacological treatments. Clinical trials on type 1 diabetes mellitus, preclinical studies, review articles, letters, thesis, and unpublished data were excluded. At least two independent researchers evaluated all studies according to inclusion/exclusion criteria during the screening phase. After removing duplicates, the publications’ titles, abstracts, and full text were evaluated to see whether they met the inclusion criteria. Any discrepancies at each screening step were discussed and resolved in consultation with the corresponding author.

Quality assessment of included studies

Methodological quality assessment of each included study was independently performed by at least two researchers using the modified Jadad checklist (Oremus et al. 2001). Clinical trials with a score < 3 were rated as poor quality. In addition, the risk of bias for each study was assessed using the Cochrane Risk of Bias tool (Higgins et al. 2011), where the domains were judged as "low-risk, high-risk, or unclear".

Data extraction

From the included studies, the following data were extracted: (1) Study characteristics, such as author name, year of publication, study design, and duration of intervention; (2) Patient characteristics, such as age, gender, number of patients in each group, and underlying disease; (3) Specific information regarding the interventions, such as herbal medicine name, intervention modality, dosage, and duration of treatment, as well as type of intervention for the control group, including placebo, standard pharmacological treatments, or no treatment; and (4) Primary outcomes (measurements of antioxidative and anti-inflammatory biomarkers) and secondary outcomes (total antioxidant capacity and antioxidant enzymes activity).

Statistical analysis

All data were extracted from the included studies using mean difference (MD) and standard deviation (SD) for both the intervention and control groups. When the standard error (SE) or confidence interval (CI) was reported, it was transformed into SD. Using standard statistical formulas, the SD of change was calculated based on the baseline and final SDs (Higgins et al. 2019). Clinical and methodological heterogeneity was statistically evaluated using the chi-square and I^2 tests, and $P < 0.1$ was considered statistically significant (Ioannidis 2008). To determine the pooled effect of the herbal medicine, random- or fixed-effect methods were employed to conduct the meta-analysis based on the level of heterogeneity between studies.

Furthermore, a random-effect meta-regression analysis was performed to evaluate the impact of influencing factors (Higgins et al. 2011). Forest plots were used to show the findings of the meta-analysis schematically. STATA software, version 14.0 (StataCorp, College Station, TX, USA), was used for all analyses.

Results

General results

Out of 6209 studies, 47 clinical trials were eligible for inclusion in the meta-analysis (Fig. 1). A total of 2636 participants, including men and women aged between 20 and 79 years, were included in these studies. Forty-four studies were conducted on patients with T2DM, two on metabolic syndrome patients, and one on patients with prediabetes. The design of most studies was a double-blind, randomized controlled trial (DBRCT) in which the use of a sole plant was compared to a placebo. Some of the herbal medicines used include turmeric, bilberry, *M. officinalis*, garlic, cardamom, cinnamon, ginger, saffron, pomegranate, *Camellia sinensis*, *Cichorium intybus*, *Crataegus laevigata*, silymarin, *Rheum ribes*, *Nigella sativa*, *Anethum graveolens*, grape, or blueberry. Details of the included studies and characteristics of the participants are shown in Table 1. The quality score of most studies was ≥ 3. The quality assessment results based on the modified Jadad checklist and the Cochrane risk of bias assessment are presented in Tables 1 and 2, respectively.

Meta-analyses of the main outcomes

Total change in oxidative stress biomarkers, including malondialdehyde (MDA), nitric oxide (NO), and F2-isoprostane, was assessed in 30 studies (68 data), which pooled data showed a significant reduction with a standardized mean difference (SMD) of − 0.36 and 95% CI − 0.64 to − 0.09 ($P < 0.001$) in a random-effect meta-analysis (I^2: 91.9%), Fig. 2.

Total change in inflammatory biomarkers, including high-sensitivity C-reactive protein (hs-CRP), TNF-α, IL-6, and CRP, was measured in 45 studies (98 data) and showed a significant reduction ($P < 0.001$) with an $SMD = -0.47$ and 95% CI − 0.63 to − 0.31 in the random-effect meta-analysis (I^2: 85.4%), Fig. 3.

Meta-analyses of the secondary outcomes

Total antioxidant capacity (TAC) was measured in 27 studies (28 data). It was significantly ($P = 0.002$) improved with an SMD = 0.46 and 95% CI 0.16–0.75 in a random-effect meta-analysis (I^2: 86.9%), Fig. S1.

The activity of antioxidant enzymes, including catalase (CAT), superoxide dismutase (SOD), glutathione (GSH), and glutathione peroxidase (GPX), was assessed in 14 studies (37 data). The pooled results showed a significant ($P < 0.001$) increase in total activity (SMD = 1.80, 95% CI 1.26–2.33), in the random-effect meta-analysis (I^2: 94.9%), Fig. S2.

Subgroup analyses

In subgroup analyses, a significant change was observed in oxidative stress biomarkers, including MDA and NO (SMDs = − 0.96 and 1.01, 95% CIs − 1.30 to − 0.63 and 0.63 to 1.40, respectively). However, the change was not

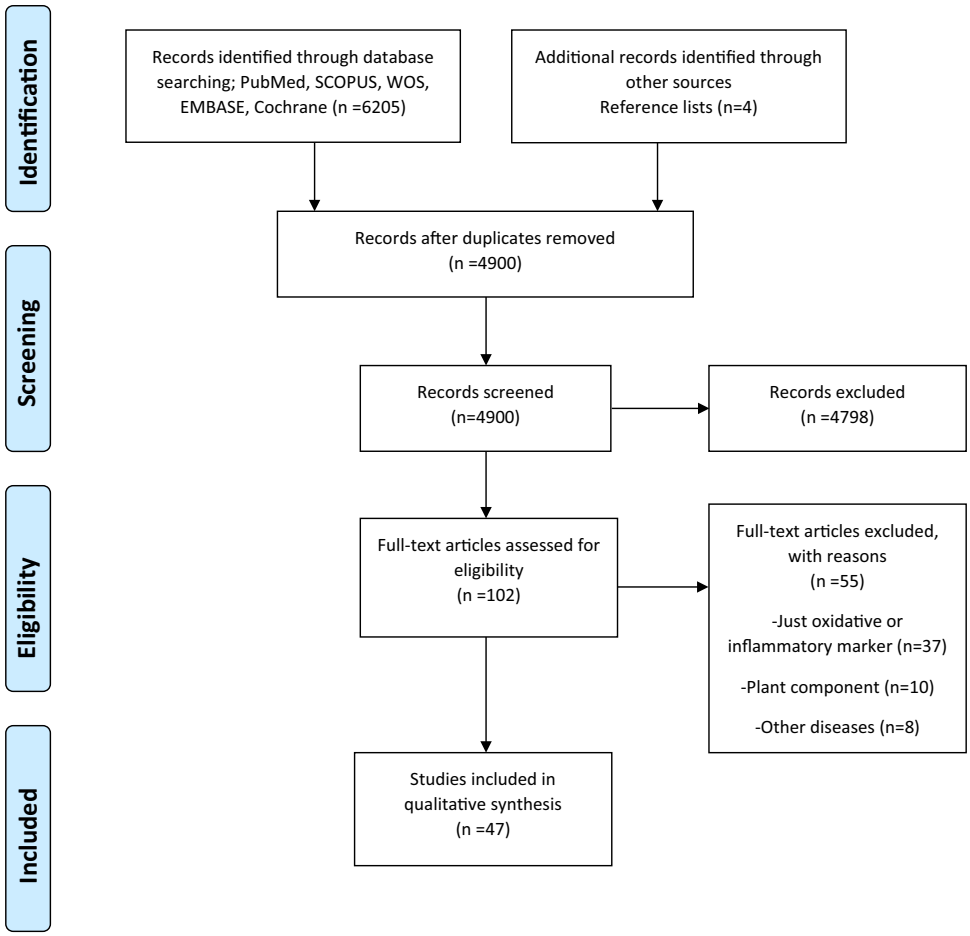

Fig. 1 Flow diagram of the study selection processes

significant ($P \geq 0.05$) for F2-isoprostane (SMD = − 0.67 95% CI − 1.42 to 0.09). Regarding the inflammatory biomarkers, subgroup analyses showed significant changes for hs-CRP and TNF-α (SMDs = − 0.64 and − 0.71, 95% CIs − 0.84 to − 0.44, and − 1.18 to − 0.24, respectively). On the other hand, the change for IL-6 and CRP were not significant ($P \geq 0.05$) (SMDs = − 0.14 and 0.25, 95% CIs − 0.28 to 0.005 and − 0.01 to 0.52, respectively).

Except for CAT (SMD = 0.24, 95% CI − 0.19 to 0.67), the subgroup analysis antioxidant enzyme revealed a significant increase in SOD (SMD = 2.29, 95% CI 0.97–3.62) and a significant decrease in GSH (SMD = 1.44, 95% CI 0.79–2.10) and GPX (SMD = 3.29, 95% CI 0.79–5.79).

Additional subgroup analyses were performed to assess the effect of the herbal medicines on primary and secondary outcomes compared to placebo/non-placebo treatment in the control group and also based on the duration of intervention; ≤ 8 weeks vs. > 8 weeks. The details of the analyses are shown in Table S2.

Meta-regression test

A meta-regression analysis was performed to determine the sources of the heterogeneity. The results of this analysis demonstrated that the type of treatment in the control groups (placebo/non-placebo) and the duration of the intervention (≤ 8 weeks vs. > 8 weeks) were not the sources of heterogeneity observed in the results of primary and secondary outcomes. However, biomarkers of oxidative stress were significantly affected by the duration of the intervention (coefficient = 1.31 for > 8 weeks, $P = 0.027$).

Discussion

The present meta-analysis demonstrated a simultaneous and significant reduction in oxidative stress and inflammatory biomarkers, along with a noteworthy increase in TAC and antioxidant enzyme activity.

Table 1 Characteristics of controlled trials included to the study

	References	Country	Design	Participants, age (case/control) (years), sex	Intervention		Dose/Duration (weeks)	Results	Quality assessment (modified Jadad score)
					Case (*n*)	Control (*n*)			
1	Adab et al. (2019)	Iran	Parallel DBRCT	75 hyperlipidemic T2DM, 54.76 ± 6.6/5.66 ± 8.64 years, M: 36, F: 39	Turmeric capsules (*n* = 39)	Placebo (*n* = 36)	One 700-mg turmeric capsule three times a day for 8 weeks	Non-sig. change in hs-CRP, TAC within and between groups	7
2	Alnajjar et al. (2020)	UK	Cross-over DBRCT	16 Overweight, postmenopausal with/without T2DM, 62 ± 7 years, M: 6, F: 10	Anthocyanin-enriched bilberry extract (*n* = 16)	Placebo (*n* = 16)	3 capsules, 0.47 g/day for 3 weeks	Non-sig. change in TNF-α, hs-CRP, FRAP	5
3	Asadi et al. (2019)	Iran	DBRCT	62 T2DM, 53.90 ± 6.28/52.77 ± 7.83 years, M: 34, F: 28	Hydroalcoholic extract of *M. officinalis* (*n* = 31)	Placebo (*n* = 31)	700 mg/day for 12 weeks	↓Sig. hs-CRP Non-sig. change TAC	7
4	Atkin et al. (2016)	UK	Cross-over DBRCT	26 T2DM, 61 ± 8 years, M: 17, F: 9	Aged garlic extract (kyolic) (*n* = 26)	Placebo (*n* = 26)	1200 mg/day for 4 weeks	Non-sig. change total glutathione, TAS, hs-CRP, lipid hydroperoxides	5
5	Azimi et al. (2014)	Iran	Parallel SBRCT	204 T2DM, aged ≥ 30 years, overweight, not on insulin but taking metformin or glibenclamide, M: 79, F: 125	One of cardamom (*n* = 40), cinnamon (*n* = 42), ginger (*n* = 42), saffron (*n* = 41) + 3 glasses of black tea	Black tea (*n* = 39)	3 g cardamom, or 3 g cinnamon, or 3 g ginger, or 1 g saffron, + 3 glasses of black tea for 8 weeks	↓Sig. hs-CRP by all groups except cardamon ↓Sig. F2-isoprostane just by ginger Non-sig. diff. between groups for all above measures	5
6	Basu et al. (2013)	USA	Before–after trial	8 obese T2DM and nine healthy non-T2DM, 52.4 ± 13.3/47.1 ± 6.3 years, M: 2, F: 15	Pomegranate polyphenol extracts (*n* = 8)	Pomegranate polyphenol extracts (*n* = 9)	One capsule twice a day (each capsule: 753 mg polyphenols) for 4 weeks	↓Sig. MDA only in T2DM Non-sig. effect on CRP, lipid oxidation	3
7	Bazyar et al. (2021)	Iran	Parallel DBRCT	44 T2DM, 51.57 ± 6.79/52.61 ± 7.22 years, M: 21, F: 23	Epigallocatechin-3-gallate (EGCG) of *Camellia sinensis* leaves (*n* = 22)	Placebo (*n* = 22)	300 mg/day for 8 weeks	↑Sig. TAC Non-sig. change in IL-6	6

Table 1 (continued)

	References	Country	Design	Participants, age (case/control) (years), sex	Intervention		Dose/Duration (weeks)	Results	Quality assessment (modified Jadad score)
					Case (*n*)	Control (*n*)			
8	Chan et al. (2021)	China	Cross-over DBRCT	20 T2DM, 55.8 ± 9.5 years, M: 9, F: 11	Bilberry extract capsule, 350 mg in each capsule (*n* = 10)	Placebo (*n* = 10)	Two capsules twice daily, 4 weeks, separated by a 6-week washout period	Non-sig. change in GPx, SOD, FRAP, hs-CRP, (urine) U8OG	6
9	Chandra et al. (2020)	India	Parallel DBRCT	100 T2DM, 46 ± 11.42/48 ± 9.8 years, M: 55, F: 45	Aqueous extract of *Cichorium intybus* seeds (270.5 mg) extract (*n* = 51)	Placebo (*n* = 49)	One capsule twice a day, 12 weeks	↑Sig. GSH, SOD, CAT ↓Sig. MAD, TNF-α, IL-1β	6
10	Dalli et al. (2011)	Spain	Parallel DBRCT	45 T2DM with chronic CHD, 61.3 ± 8.3/60.4 ± 8.2 years, M: 38, F: 7	*Crataegus laevigata* (*n* = 24)	Placebo (*n* = 21)	400 mg, 3 times a day for 24 weeks	Non-sig. change in hs-CRP, MDA	6
11	Darmian et al. (2022)	Iran	Parallel SBRCT	42 Hyperlipidemic T2DM female, 45–60 years	Aerobic training (AT) + turmeric supplementation (TS) (*n* = 11), TS (*n* = 11)	Placebo + AT (*n* = 10), placebo + control (*n* = 10)	3 capsules (700 mg turmeric in 1cap-sule)/day, 8 weeks	Within-group analysis: ↑Sig. GSH, TAC ↓Sig. MDA, hs-CRP in AT + TS, AT, TS groups Between-group analysis: Significantly higher effects in AT + TS vs. AT, TS	6
12	Ebrahimi et al. (2019)	Iran	DBRCT	80 T2DM, 55.2 ± 7.3/53 ± 10.6 years, M: 36, F: 44	Saffron (*n* = 20)	Placebo (*n* = 20)	100 mg twice/day for 12 weeks	↓Sig MDA Non sig. changes in TAC, hs-CRP, TNF-α	5
13	Ebrahimpour koujan et al. (2015)	Iran	Parallel TBRCT	40 T2DM, 25–50 years, M: 20, F: 20	Silymarin tablets (*n* = 20)	Placebo (*n* = 20)	140 mg/3 times/day after meals for 6.4 weeks	↑Sig. SOD, GPX, TAC ↓Sig. hs-CRP, MDA	7
14	Fallahzadeh et al. (2012)	Iran	Parallel DBRCT	56 T2DM with macroalbuminuria, 30–70 years, M: 26, F: 30	Silymarin tablets (*n* = 28)	Placebo (*n* = 28)	140 mg/3 times/day for 12 weeks	↓Sig. TNF-α, MDA Non-sig. change in TGFβ	7

Table 1 (continued)

	References	Country	Design	Participants, age (case/control) (years), sex	Intervention		Dose/Duration (weeks)	Results	Quality assessment (modified Jadad score)
					Case (*n*)	Control (*n*)			
15	Ghafouri et al. (2020)	Iran	Parallel three-arm, DBRCT	60 T2DM, 20–79 years, both sexes: unknown numbers	Aqueous extract (*n* = 20) or ethanolic extract (*n* = 20) of *Rheum ribes*	Placebo (*n* = 20)	Three 450-mg capsules/day for 6 weeks	↓Sig. hs-CRP in both groups ↓Sig. MDA by ethanolic extract Non-sig. change in MDA by aqueous extract ↓Sig. MDA between group analysis by aqueous extract vs. placebo	6
16	Grabež et al. (2022)	Bosnia and Herzegovina	Parallel DBRCT	60 overweight T2DM, 57.87 ± 6.08/ 56.93 ± 6.67, M: 30, F: 30	Pomegranate peel extract (*n* = 30)	Placebo (*n* = 30)	250-mg capsule/ twice/day for 8 weeks	↑Sig. TAC ↓Sig. hs-CRP, IL-6, TNF-α, TBARS	6
17	Hadi et al. (2018)	Iran	Parallel DBRCT	43 T2DM, 51.4 ± 9.2/56.0 ± 3.4 years, F: 43	*Nigella sativa* oil extract capsule (*n* = 23)	Placebo (*n* = 20)	Two 500-mg capsules/day for 8 weeks	↑Sig. SOD, CAT ↓Sig. MDA Non-sig. change in CAT, MDA between groups Non-sig. change within- and between groups in TNF-α, IL-1B, NO	6
18	Haidari et al. (2020)	Iran	Parallel DBRCT	42 T2DM, 50.66 ± 8.22/ 50.42 ± 8.61 years, M: 12/ F: 30	*Anethum graveolens* (*n* = 21)	Placebo (*n* = 21)	Three 1-g capsules/3 times/day after each meal for 8 weeks	Within and between analysis ↑Sig. TAC ↓Sig. MDA Non-sig. change in hs-CRP	8

Table 1 (continued)

	References	Country	Design	Participants, age (case/control) (years), sex	Intervention		Dose/Duration (weeks)	Results	Quality assessment (modified Jadad score)
					Case (*n*)	Control (*n*)			
19	Hemmatabadi et al. (2009)	Iran	Parallel DBRCT	61 T2DM, 51.9 ± 6.2/51.4 ± 5.4 years, M: 30, F: 31	Samelil (ANGI-PARS™) is derived from *Melilotus officinalis* (*n* = 31)	Placebo (*n* = 30)	100 mg of ANGI-PARS capsules twice/day for 12 weeks	↓Sig. serum Deoxyguanosine Non-sig. change in CRP, TNF-α, TBARS, FRAP	6
20	Javid et al. (2019)	Iran	DBRCT	42 T2DM, 52.81 ± 6.44/51.62 ± 5.95, M:1 9, F: 23	Ginger (*n* = 21)	Placebo (*n* = 21)	2 g/day for 8 weeks	↓Sig IL-6, hs-CRP, TNF-α ↑Sig SOD, GPx ↑Sig GPx between groups Non-sig. changes in CAT	7
21	Kanellos et al. (2014)	Greece	RCT	48 T2DM, 63.7 ± 6.3/63 ± 8.5, M: 25, F: 23	Corinthian raisins (CR) equal to two fruit servings (*n* = 26)	Usual dietary habits (*n* = 22)	36 g/day for 24 weeks	↑Sig. TAC Non-sig. changes in hs-CRP, IL-6, TNF-α	5
22	Kar et al. (2009)	London, UK	CRCT	32 T2DM, 61.8 ± 6.36, M: 16, F: 16	Grape seed extract (*n* = 32)	Placebo (*n* = 32)	300 mg twice/day for 4 weeks	Non-sig. changes in TAOS ↑Sig. GSH ↓Sig. hs-CRP	4
23	Kazemi et al. (2017)	Iran	DBRCT	80 prediabetes, 48.3 ± 10.4/47.5 ± 10.3 years, F: 80	Cardamom (*n* = 40)	Placebo (*n* = 40)	3.0 g for 8 weeks	↑Non-sig. TNF-α, TAC, SOD, GR, IL-6 ↓Sig. hs-CRP, MDA	7
24	Kempf et al. (2010)	Germany	SBCT	47 T2DM, 54.0 ± 9.0, M: 11, F: 36	Coffee (before–after) (*n* = 47)		First month refrained from coffee Second month: 4 cups/day (1 cup = 150 ml) Third month: 8 cups/day	↓Sig. IL-18, 8-isoprostane Non-sig. changes IL-6, CRP, NO	2

Table 1 (continued)

	References	Country	Design	Participants, age (case/control) (years), sex	Intervention		Dose/Duration (weeks)	Results	Quality assessment (modified Jadad score)
					Case (*n*)	Control (*n*)			
25	Kim et al. (2018)	Texas	DBRCT	37 MetS, 46.6 ± 11.5/2.0 ± 14.4 years, M: 11, F: 26	Açaí (*Euterpe oleracea* Mart.) berries beverage (*n* = 19)	Placebo (*n* = 18)	Containing 1139 mg/l gallic acid equivalents of total polyphenolics for 12 weeks	↓Sig. 8- isoprostane Non-sig. change TNF-α, hs-CRP, IL-6	5
26	Kim et al. (2012)	Korea	Parallel DBRCT	62 Glucose intolerance and T2DM, 35–79 years, 94, 31 F/62 M, 47/47	Ginseng roots + mulberry leaf water extract + Banaba leaf water extract (*n* = 32)	Placebo (*n* = 30)	6 g/day for 24 weeks	↓Sig. OX-LDL ↓Non-sig. hs-CRP	6
27	Kooshki et al. (2020)	Iran	DBRCT	50 T2DM, 52.30 ± 9.43/55.91 ± 8.98 years, M: 16, F: 34	*Nigella sativa* oil (*n* = 27)	Placebo (*n* = 23)	1000 mg/day for 8 weeks	↓Sig. hs-CRP, MDA	6
28	Legiawati et al. (2020)	Indonesia	DBRCT	106 T2DM, 52–54 years, M: 25, F: 81	*Centella asiatica* (CA) oral + CA topical (*n* = 53)	Placebo oral + placebo topical (*n* = 53)	CA Oral, 2 × 1.100 mg + CA topical 1% ointment twice a day for 4 weeks	↑Sig. SOD ↑Non-sig. IL-1α	6
29	Musolino et al. (2020)	Italy	DBRCT	60 T2DM with NAFLD, 40–61 years, sex (UN)	Oral bergamot polyphenolic fraction (BPF) (*n* = 20), OR *Cynara cardunculus* (CyC) (*n* = 20)	Placebo (*n* = 20)	Oral BPF (300 mg/day), OR CyC (300 mg/day for 16 weeks	↑Non-sig. GPx, SOD ↓Non-sig. MDA, TNF-α	6
30	Nair et al. (2017)	US	DBRCT	27 MetS, 55 ± 2/59 ± 3 years, M: 9, F: 18	Blueberry (*n* = 15)	Placebo (*n* = 12)	45 g/day for 6 weeks	↓Sig. ROS, gene expression of TNF-α, IL-6 ↓Non-sig. IL-12	7
31	Neyestani et al. (2010)	Iran	CT	45 T2DM, 57.0 ± 7.9/55.4 ± 8.3 years, M: 16, F: 29	Black tea extract (BTE), *n* = 23	BTE once: 150 ml/day (*n* = 22)	BTE: Week 1: 150, week 2: 300, week 3: 450, week 4: 600 ml/day/week	↑Sig. TAC, GSH ↑Non-sig. SOD ↓Sig. MDA, CRP	2
32	Nigam and Nambiar (2019)	India	RCT	60 T2DM, 51.35 ± 9.13 years, M: 25, F: 35	*Aegle marmelos* leaf juice (*n* = 30)	Non-intervention (*n* = 30)	20 g/100 ml 8.5 weeks	↑Sig. FRAP ↓Sig. CRP	1

Table 1 (continued)

	References	Country	Design	Participants, age (case/control) (years), sex	Intervention		Dose/Duration (weeks)	Results	Quality assessment (modified Jadad score)
					Case (*n*)	Control (*n*)			
33	Park et al. (2020)	Korea	DBRCT	61 T2DM, 59:3 ± 8:79/59:7 ± 7:22 years, M: 36, F: 25	Korean red ginseng (*n* = 30)	Placebo (*n* = 31)	3 g/day for 24 weeks	Non-sig. changes in hs-CRP, IL-6, TNF-α	8
34	Pingali et al. (2020a)	India	DBRCT	80 T2DM, 30–65 years, M: 46, F: 34	Aqueous extract of *Azadirachta indica* leaves and twigs (*n* = 60)	Placebo (*n* = 20)	125, 250, 500 mg/twice daily/12 weeks	↓Sig MDA, hs-CRP, IL-6, TNF-α ↑Sig. GSH, NO	8
35	Pingali et al. (2020b)	India	Parallel DBRCT	60 T2DM, 30–65 years, M: 39, F: 21	*T. chebula* (*n* = 40)	Placebo (*n* = 20)	250, 500 mg twice daily for 12 weeks	↑Sig. GSH, NO ↓Sig. MDA, hs-CRP	8
36	Ricklefs-Johnson et al. (2017)	US	RCT	17 T2DM, 59.7 ± 7.9/58.5 ± 9.4 years, M: 9, F: 8	Ground flaxseed (*n* = 9)	Placebo (*n* = 8)	28 g/day for 8 weeks	↑Sig. NO Non-sig. changes in CRP and TNF-α ↓Sig. TBARS	5
37	Sakhaei et al. (2021)	Iran	DBRCT	60 Diabetic nephropathy, 52.00 ± 1.05/52.00 ± 7.20 years, M: 22, F: 38	*Hibiscus sabdariffa* Linnaeus. (*n* = 30)	Placebo (*n* = 30)	425 mg/twice daily for 8 weeks	↑Sig. TAC ↓Sig. CRP	7
38	Sanaei et al. (2015)	Iran	Parallel DBRCT	42 T2DM, 33–74 years, both sexes (UN)	Polyherbal: StemFlo, and StemEnhance (*n* = 22)	Placebo (*n* = 20)	508-mg StemFlo (enzyme blend nattozime, serrazime, papain, bromelain, Protease 6.0, Protease 4.5, Indian gooseberry fruit, citrus bioflavonoid, black-currant extract, mangos, teen fruit and rind, cats claw bark, and turmeric root extract) and 180 StemEnhance (500 mg *Aphanizomenon flos-aquae* extract per capsule)/12 weeks	Non-sig. changes in IL-6, TNF-α, MDA, CRP	7

Table 1 (continued)

	References	Country	Design	Participants, age (case/control) (years), sex	Intervention		Dose/Duration (weeks)	Results	Quality assessment (modified Jadad score)
					Case (*n*)	Control (*n*)			
39	Maithili Karpaga Selvi et al. (2015)	India	RCT	60 T2DM, 35–55 years, 60 M	Turmeric + metformin (*n* = 30)	Metformin (1000 mg/day) (*n* = 30)	2000 mg/day for 4 weeks	↑Sig. glutathione, TAC, ↓Sig. MDA, hsCRP Non-sig. change in GPX, CAT	7
40	Shahbazian et al. (2019)	Iran	DBRCT	68 T2DM, (placebo: 52.4 ± 13, case: 53.5 ± 9.9) years, M: 19, F: 45	Saffron (*n* = 32)	Placebo (*n* = 32)	15 mg/(two pills/day for 12 weeks	↑Sig. IL-6, TNF-α, ↑Non-sig. IL-10, hs-CRP, TAC ↓Non-sig. MDA	7
41	Shidfar et al. (2015)	Iran	DBRCT	45 T2DM, (placebo: 47.1 ± 8.31, case: 45.2 ± 7.64), both sexes (UN each number)	Ginger (*Zingiber officinale*) (*n* = 22)	Placebo (*n* = 23)	3 g/day for 12 weeks	Within and between groups ↑Sig. TAC ↓Sig. MDA, CRP	8
42	Soleimani et al. (2017)	Iran	Parallel DBRCT	60 T2DM with grade 3 DFU, 58.8 ± 11.2/59.9 ± 9.2 years, M: 30, F: 30	Flaxseed oil + conventional treatment (*n* = 30)	Placebo + conventional treatment (*n* = 30)	1000 mg of flaxseed oil/day for 12 weeks	↑Sig. TAC, GSH ↓Sig. hs-CRP Non-sig. change in NO, MDA	6
43	Somanah et al. (2012)	Republic of Mauritius	RCT	87 Neo-diabetic, 25–60 years, M: 44, F: 43	Fermented papaya (*n* = 40)	Water (*n* = 47)	6 g FPP®/day for 14 weeks	↓Sig. CRP within and between groups Non-sig. change in TAS	7
44	Taghizadeh et al. (2017)	Iran	DBRCT	60 Diabetic nephropathy, 45–85 years, F: 46, M: 14	Mulberry extract (*n* = 30)	Placebo (*n* = 30)	300 mg/day/BD/12 week	↑Sig. NO, total glutathione ↑Non-sig. TAC ↓Sig. hs-CRP, ↓Non-sig. MDA	8
45	Tavakoly et al. (2018)	Iran	RCT	48 T2DM, 49.63 ± 6.43, F: 22, M: 26	Fenugreek (*Trigonella foenum-graecum*) seed + routine drugs (*n* = 24)	Routine drugs (*n* = 24)	15 g/day for 6 weeks	↑Sig. SOD ↓Sig. hs-CRP Non-sig. change in TAC, IL-6, GPX, TNF-α	10

Table 1 (continued)

	References	Country	Design	Participants, age (case/control) (years), sex	Intervention		Dose/Duration (weeks)	Results	Quality assessment (modified Jadad score)
					Case (n)	Control (n)			
46	Usharani et al. (2014)	India	DBRCT	30 T2DM, 18–65 years, 30, F: 4, M: 26	*Phyllanthus emblica* ($n=10$), *Withania sommifera* ($n=10$)	Combination ($n=10$)	500 mg/BD/12 weeks	↓Sig. NO, GSH, CRP, MDA	5
47	Usharani et al. (2013)	India	DBRCT	80 T2DM, 30–60 years, F: 27, M: 53	*Phyllanthus emblica* extract ($n=40$)	Placebo or placebo + atorvastatin ($n=40$)	250 or 500 mg/BD for 12 weeks	↑Sig. NO, GSH ↓Sig. MDA, hs-CRP	5

DBRCT double-blind randomized controlled trials, *TBRCT* triple-blind randomized controlled trials, *GPx* glutathione peroxidase, *SOD* superoxide dismutase, *U8OG* urinary 8-oxoguanine, *hs-CRP* high-sensitivity C-reactive protein, *FRAP* ferric-reducing/antioxidant power (plasma total antioxidant power), *DFU* diabetic foot ulcer

Recognizing the escalating global prevalence of T2DM and the limited accessibility of conventional antidiabetic medications, the World Health Organization (WHO 2013) advocates for the utilization of accessible and indigenous natural products. Consequently, the use of herbal medicines is on the rise in both developed and developing countries (WHO 2013), underscoring the need for a scientific evaluation of their efficacy and safety (WHO 2013). It is essential to note that meta-analysis studies rank as the highest level of evidence-based medicine, contributing valuable scientific insights (Howick et al. 2022). Our meta-analysis revealed that when a placebo was administered to the control group, the effect size was more significant, suggesting that a standard trial design yields a more reliable effect. A standard trial design eliminates the effect of chance on the trial outcomes through randomization, blinding, and placebo (Ahmad et al. 2021).

Curcuma longa L. root (turmeric), the rhizome of *Zingiber officinale* Roscoe (ginger), stigmas of *Crocus sativus* L. (saffron), *Vaccinium* spp. fruits (bilberry), fruit extract of *Punica granatum* L. (pomegranate extract), *Nigella sativa L.* oil extract, and *Elettaria cardamomum* (L.) Maton (cardamom) were the extensively studied herbal medications in this study. Remarkably, these medicinal plants are commonly used as spices or food additives in daily culinary practices, suggesting their safety even over prolonged periods. Utilizing herbal medicines as spices or food additives could pave the way for functional foods, offering a promising approach to harnessing food as a medicine without the risk of adverse effects or non-adherence, which often presents a significant barrier to conventional pharmacological therapies (Nieto 2020).

Plant-derived supplementations contain numerous bioactive compounds responsible for their pharmacological effects. Therefore, it is valuable to identify these bioactive compounds and investigate their pharmacological effects alone or in combination to determine synergistic, additive, or antagonistic effects (Soltani et al. 2022). On the contrary, each active compound within herbal medicine may exhibit its beneficial effects by acting through distinct pathways. This implies that herbal medicines containing multiple active compounds can simultaneously exert therapeutic effects through multiple pathways. This may make the combination of the active compounds of a herb more effective than using a single ingredient (Yuan et al. 2017). Therefore, it is necessary to apply modern pharmacological science in studying the beneficial effects of polyherbal medicine.

Terpenoids, carotenoids, and phenolic compounds such as phenolic acid, flavonoids, and stilbenoids were the primary active compounds detected in these hypoglycaemic plant-derived medicines. These bioactive compounds could exert their pharmacological effects through attenuation of oxidative stress, inhibition of inflammation, protection of

Table 2 Cochrane risk of bias item for each included trial

Study (Author, year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Adab et al. (2019)	L	U	L	U	L	L	L
Alnajjar et al. (2020)	U	L	L	U	L	L	H
Asadi et al. (2019)	L	L	L	L	L	L	L
Atkin et al. (2016)	U	U	L	U	L	L	L
Azimi et al. (2014)	L	L	U	U	L	L	H
Basu et al. (2013)	H	H	H	U	L	L	H
Bazyar et al. (2021)	L	U	L	U	L	L	U
Chan et al. (2021)	L	U	L	U	L	L	L
Chandra et al. (2020)	U	U	L	U	L	L	U
Dalli et al. (2011)	L	U	L	U	L	L	L
Darmian et al. (2022)	L	U	L	U	L	L	H
Ebrahimi et al. (2019)	L	L	U	L	L	L	L
Ebrahimpour Koujan et al. (2015)	L	L	L	L	L	L	L
Fallahzadeh et al. (2012)	L	L	L	L	L	L	L
Ghafouri et al. (2020)	L	U	L	U	L	L	L
Grabež (2022)	L	U	L	U	L	L	L
Hadi et al. (2018)	L	U	L	U	U	L	U
Haidari et al. (2020)	L	U	L	U	L	L	L
Hemmatabadi et al. (2009)	U	U	U	U	U	L	U
Javid et al. (2019)	L	L	L	L	L	L	L
Kanellos et al. (2014)	L	H	H	L	L	L	L
Kar et al. (2009)	H	U	L	H	H	U	H
Kazemi et al. (2017)	L	L	L	L	L	L	L
Kempf et al. (2010)	L	L	L	L	L	L	L
Kim et al. (2018)	U	U	L	L	L	L	U
Kim et al. (2012)	L	U	L	L	U	L	L
Kooshki et al. (2020)	L	L	L	H	H	L	L
Legiawati et al. (2020)	L	L	U	L	L	H	L
Musolino et al. (2020)	L	L	L	H	L	U	L
Nair et al. (2017)	L	L	L	L	H	H	L
Neyestani et al. (2010)	H	H	H	U	H	H	H
Nigam and Nambiar (2019)	U	H	H	L	H	U	U
Park et al. (2020)	L	L	L	L	L	H	L
Pingali et al. (2020a)	L	L	L	L	L	L	L
Pingali et al., (2020b)	L	L	L	L	L	L	L
Ricklefs-Johnson et al. (2017)	L	H	U	L	L	L	L
Sakhaei et al. (2021)	L	L	L	L	L	L	L
Sanaei et al. (2015)	L	L	U	L	L	L	L
Maithili Karpaga Selvi et al. (2015)	L	U	H	U	L	U	L
Shahbazian et al. (2019)	L	U	L	L	L	L	L
Shidfar et al. (2015)	L	L	L	L	U	L	L
Soleimani et al. (2017)	L	L	L	L	L	L	L
Somanah et al. (2012)	U	U	H	H	U	U	U
Taghizadeh et al. (2017)	L	L	L	L	L	L	L
Tavakoly et al. (2018)	L	L	H	L	L	L	L
Usharani et al. (2014)	U	U	U	H	L	L	U
Usharani et al. (2013)	L	U	L	L	U	L	L

H high risk of bias, *L* low risk of bias, *U* unclear or unrevealed risk of bias

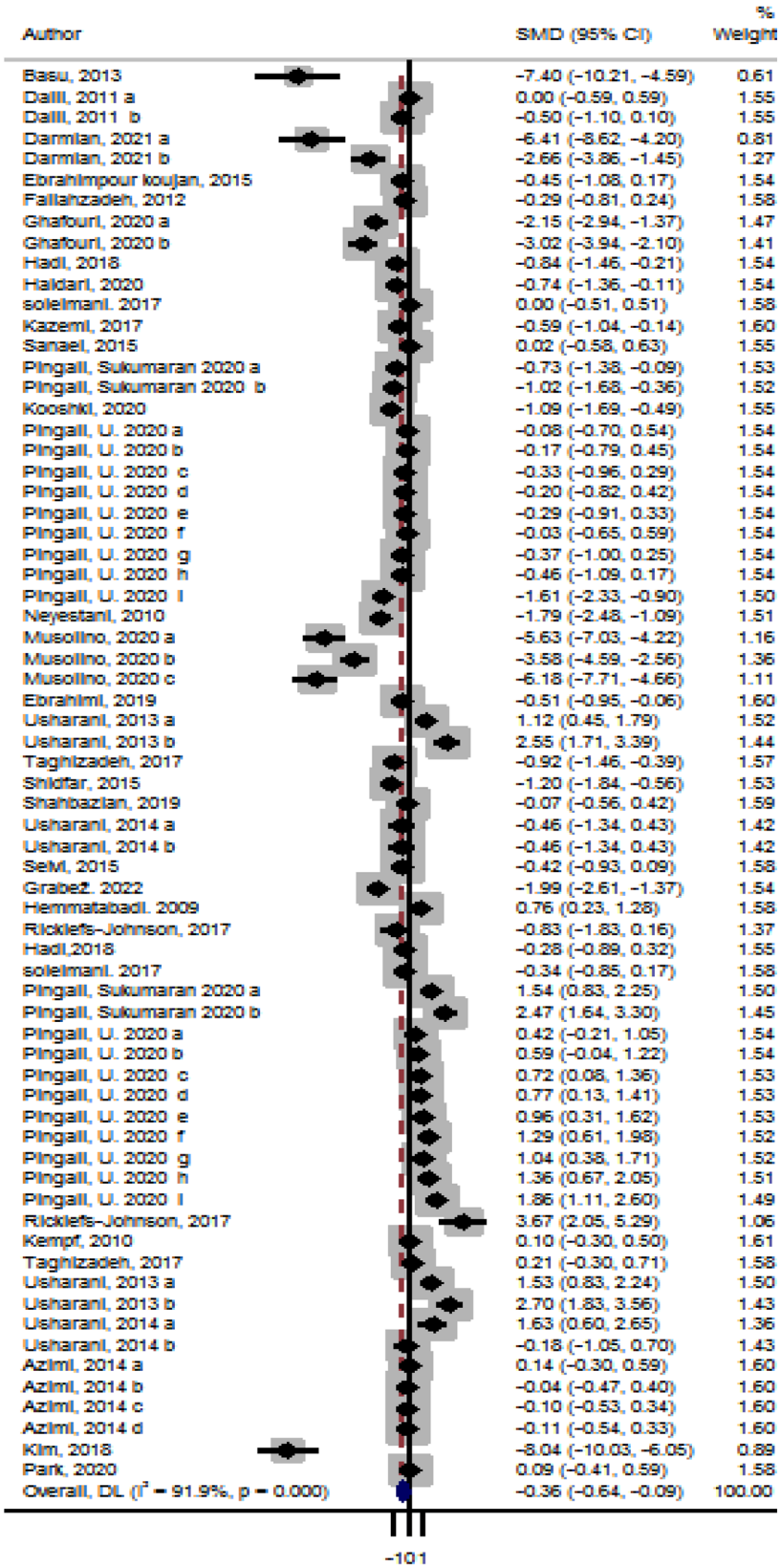

Fig. 2 Forest plot of oxidative stress' biomarkers in the random-effect meta-analysis

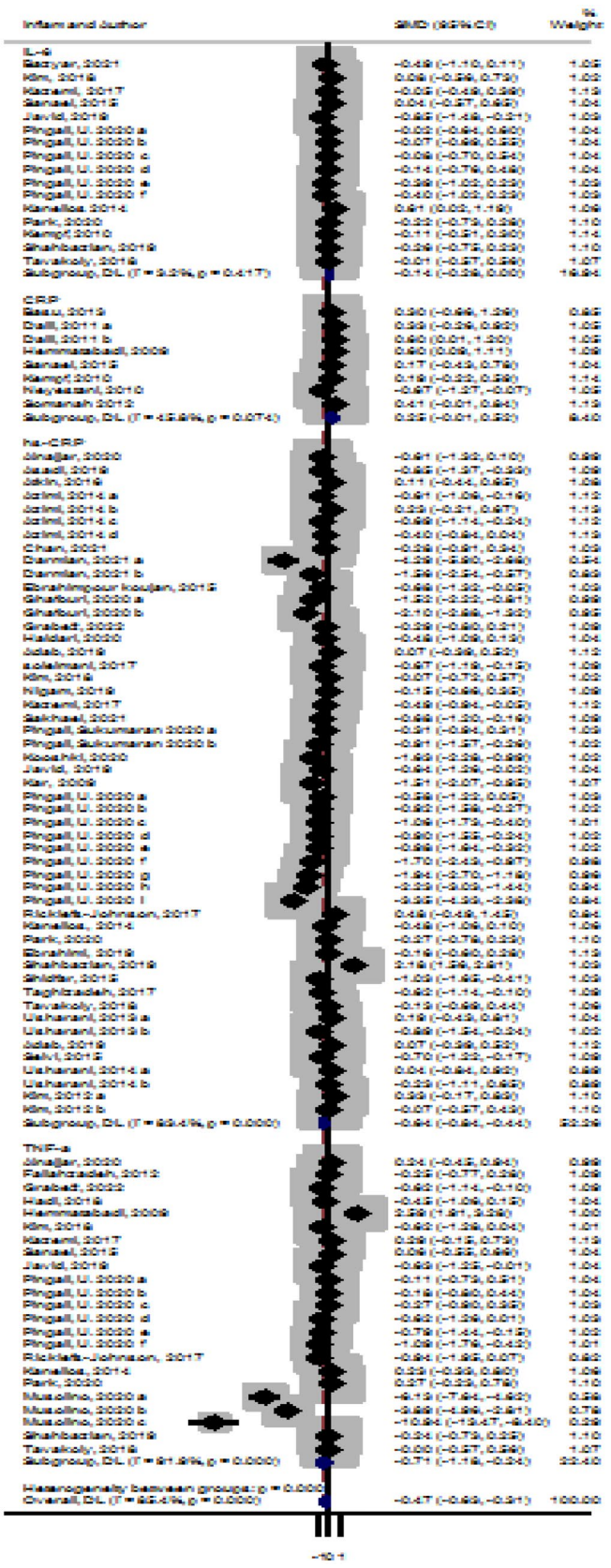

Fig. 3 Forest plot of total inflammatory biomarkers in the random-effect meta-analysis

pancreatic beta cells, activation of insulin signaling, stimulation of insulin secretion, and beneficial effects on glucose metabolism (Smitha Grace et al. 2019; Sun et al. 2020; Zhang and Tsao 2016).

A randomized controlled trial (Maithili Karpaga Selvi et al. 2015) investigated the efficacy of turmeric, with curcumin as its main bioactive compound, as an adjuvant to conventional therapy in T2DM patients. This study showed that consuming four 500-mg capsules daily along with metformin had more beneficial effects than taking metformin alone. It effectively reduced oxidative stress and inflammatory biomarkers and increased TAC without any significant effect on antioxidant enzymes, possibly due to its short duration (4 weeks). Turmeric exerts protective anti-inflammatory effects by inhibiting the synthesis of proinflammatory cytokines and mediators such as cyclooxygenase-2, prostaglandins, and leukotrienes (Maithili Karpaga Selvi et al. 2015). The antioxidant effects of curcumin are mediated by scavenging free radicals, inhibiting the production of lipid peroxides, increasing TAC, the expression of antioxidant enzymes, and enhancing Sirtuin 3 (SIRT3) activity (Bankowski et al. 2022). However, several meta-analysis studies have separately reported curcumin's anti-inflammatory and antioxidant effects (Bengmark 2006; Derosa et al. 2016; Gorbi et al. 2021). In another study (Shidfar et al. 2015), in a DBRCT, the effect of daily intake of 3 g of ginger, in which phenolic and terpenoid compounds are its main bioactive compounds, on glycemic control, oxidative stress, and inflammatory biomarkers in a 12-week trial had been investigated. Their results showed a significant reduction in MDA and CRP and a significant increase in TAC. The potential mechanism of the antioxidative effect of ginger is induced via activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway. The underlying mechanisms of its anti-inflammatory effects are the inhibition of phosphatidyl inositol-3-kinase (PI3K)/ protein kinase B (Akt) and the nuclear factor kappa light chain-enhancer of activated B cells (NF-κB) signaling pathways (Mao et al. 2019). Some of its antioxidative and anti-inflammatory effects include reducing free radicals, lipid peroxidation, and nitrosative stress levels, accelerating gene expression, increasing the level and activity of antioxidant enzymes, and reducing proinflammatory cytokines. In a recently published meta-analysis, the beneficial effects of ginger supplementation on hs-CRP, IL-6, and TNF-α levels in T2DM have been shown. These results align with our findings (Mohammad et al. 2021).

Based on our knowledge, the current meta-analysis is the first study that assessed the simultaneous antioxidative and anti-inflammatory effects of plant-derived anti-diabetic medicines on T2DM. The main strength of this review is that most of the included studies are randomized, double-blind, controlled trials with low levels of bias. However, we had several limitations. There was high heterogeneity across studies due to differences in plant species, dosage, duration of interventions, and methods of measuring oxidative stress and inflammatory biomarkers. Moreover, there were differences between the sources of each herb, the part of the plant used, their geographical area, and their preparation method (bulk, powder, or extract), which have been found to cause heterogeneity between the studies (Ahmad et al. 2021).

Conclusions

Some hypoglycaemic plant-based treatments have a positive effect on T2DM patients by concurrently reducing the serum level of oxidative stress and inflammatory indicators and boosting antioxidant enzyme activity. Further research is warranted to explore the antioxidative and anti-inflammatory effects of hypoglycaemic plant-derived medicines, which would enhance our understanding of their active ingredients and shed light on their therapeutic and adverse effects. To achieve this, well-designed trials with substantial sample sizes should be conducted, employing gold-standard methods for measuring and reporting outcomes, allowing for a comprehensive assessment of their impact through comparative data analysis.

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Data availability The data supporting this study's findings are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval Neither ethics approval nor participant consent was required, as this study was based solely on the summary results of previously published articles. Individual patient data were not obtained or accessed.

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