Effects of Food Bioactive Compounds on Oxidative Stress and the Antioxidant Defense System in Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Context: *Type 2 diabetes mellitus (T2DM) is a global health problem characterized by chronic hyperglycemia, which disrupts the antioxidant defense system and increases reactive oxygen species (ROS). These changes contribute to the progression and complications of diabetes. As a result, therapies targeting redox balance, especially by enhancing endogenous antioxidant defenses, are being explored to prevent or reduce diabetic complications.*

Objective: *The present study aimed to systematically review the effects of bioactive food compounds on oxidative stress and the antioxidant defense systems in patients with T2DM.*

Data sources: *A comprehensive literature search was performed across multiple databases, including Medline, Embase, Web of Science, Scopus, and Cochrane CENTRAL.*

Data extraction: *The literature search included documents published from inception up to April 22, 2025, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Only randomized controlled trials (RCTs) that evaluated the effects of food bioactive compounds on the outcomes of interest were included. Meta-analyses were performed using R. The standardized mean difference (SMD) and corresponding 95% CI were used to represent the pooled effects.*

Data analysis: *We included 109 human RCTs. Our meta-analysis demonstrated that both alpha-lipoic acid (ALA) and vitamin D led to significant reductions in glycosylated hemoglobin (HbA1c) levels. Additionally, the analysis indicated that curcumin and vitamin D significantly decreased malondialdehyde (MDA) levels. Amino acids like N-acetylcysteine, L-citrulline, and an amino sulfonic acid derivative (2-aminoethanesulfonic acid [taurine]), enhanced antioxidant defenses and improved*

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glycemic control. Supplementation with zinc, selenium, and chromium was linked to better glycemic control and antioxidant status, including lower HbA1c and MDA, and higher total antioxidant capacity (TAC), glutathione (GSH), and antioxidant enzyme activity.

Conclusion: *Supplementation with food bioactive compounds such as vitamin E, vitamin D, curcumin, and ALA may help to regulate HbA1c levels and enhance antioxidant defenses in patients with T2DM, indicating significant clinical potential for diabetes management. However, further research is needed to confirm their clinical efficacy and to determine optimal dosing strategies.*

Systematic Review Registration: *PROSPERO registration No. CRD42024592055.*

Key words: diabetes mellitus, type 2, oxidative stress, antioxidant response elements, glycated hemoglobin A.

INTRODUCTION

Diabetes is a major global health challenge, ranking among the leading causes of death and disability worldwide.[1] Current estimates suggest that diabetes affects approximately 10% of the global population, with projections indicating a dramatic increase to 592 million cases by 2035[2] and potentially surpassing 1.3 billion by 2050.[3] The rising prevalence of type 2 diabetes mellitus (T2DM) is closely linked to modifiable factors, such as unhealthy dietary patterns, sedentary lifestyles, alcohol consumption, and tobacco use.[3,4] The major consequences of T2DM are an increased risk of developing cardiovascular, metabolic, and renal diseases.[1,3,5]

Type 2 diabetes mellitus is primarily characterized by pancreatic beta cell dysfunction and persistent hyperglycemia resulting from insulin resistance (IR).[6] Chronic hyperglycemia is known to disrupt the antioxidant defense system (ADS) and promote excessive reactive oxygen species (ROS), which play a central role in the progression and complications of diabetes.[7,8] The generation of ROS in T2DM is associated with several pathogenic pathways, including the polyol and hexosamine pathways, increased formation of advanced glycation end products (AGEs) and their receptors (RAGE), and activation of protein kinase C (PKC) isoforms.[9] These mechanisms collectively contribute to oxidative stress (OS), cellular damage, and the development of cardiovascular, metabolic, and renal complications.[5,10]

Biomarkers of OS, such as 8-iso prostaglandin F2α (8-iso-PGF2α), malondialdehyde (MDA), and 8-hydroxy-2′-deoxyguanosine (8-OHdG), are consistently elevated in individuals with T2DM, reflecting impaired antioxidant defenses.[11–13] The endogenous ADS comprises several enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidases (GPxs).[14]

The usual pharmacological treatments for patients with diabetes are mainly aimed at reducing the risk factors that favor the disease, such as obesity, metabolic syndrome, hyperglycemia, hyperlipidemia and hypertension, but do not focus on the mechanisms of development and progression of atherosclerosis induced by diabetes, which highlights the need for targeted, mechanism-based therapies.[15] Alternative therapeutic strategies aimed at directly or indirectly interfering with one or more specific ROS-producing enzymes, such as approaches designed to modulate the ADS, seem to be the most promising therapeutic options for diabetic complications.[9]

Emerging evidence suggests that food-derived bioactive compounds (BACs), including polyphenols, flavonoids, and other phytochemicals, may exert beneficial effects on OS by directly scavenging ROS and upregulating the endogenous ADSs.[16] Increased dietary intake of antioxidants has been associated with improved insulin sensitivity, better glycemic control, and reduced risk of T2DM.[17–19] Furthermore, certain BACs have demonstrated the ability to enhance intracellular glutathione (GSH) levels and protect against oxidative damage in diabetic conditions.[20]

Despite these promising findings, the effects of food BACs on OS and on both enzymatic and nonenzymatic ADSs in T2DM remain incompletely understood. In particular, the impact of these dietary compounds on insulin resistance and pancreatic beta cell function warrants further investigation. Therefore, this systematic review and meta-analysis of randomized controlled trials (RCTs) aimed to comprehensively synthesize the current scientific evidence regarding the effects of food BACs on OS and ADSs in patients with T2DM.

METHODS

Systematic Review Protocol

We conducted a systematic review and meta-analysis to assess the effects of food BACs on OS and the ADS in

individuals with T2DM, following international guidelines.[21,22] The review process was documented according to a pre-established protocol, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[23]

Data Sources, Search Strategy, and Screening Criteria

The research was conducted across 4 electronic databases: MEDLINE (PubMed), SCOPUS, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL). The literature search included documents published from the inception up to April 22, 2025. Only RCTs involving adult humans were included. Articles published in English, Spanish, French, German, Italian, and Portuguese were considered.

We included only human RCTs that evaluated the effects of food BACs on the outcomes of interest. MeSH terms and keywords related to both OS / the ADS and food BACs were used. The search strategy comprised 3 equations: The first included terms related to alterations in OS and the enzymatic and non-enzymatic ADS. The second identified food BACs that could affect oxidative status or antioxidant defenses, focusing on vitamins and related compounds, minerals, phenolic compounds, amino acids, and others. The third addressed T2DM, prediabetes, diabetes complications, insulin, and other glycemic control parameters.

All MeSH terms were also included as free-text keywords for the expanded search in the titles or abstracts. Search strategies were adapted for each database to maximize comparability. The complete search strategy (combining MeSH terms, keywords, and Boolean operators) is detailed in Supplementary Material (Text S1). Additionally, references from previous systematic reviews and other relevant reviews were checked to identify studies not captured in the original search.

Eligibility Criteria, Study Selection, and Screening Criteria

The inclusion and exclusion criteria were established by the PICOS criteria (Table 1). Original publications were included in the present systematic review when they fulfilled the following criteria: (1) RCTs, defined as trials properly controlled with placebo or non-exposure groups (parallel, cross-over, or double cross-over) in humans; (2) study populations comprising adults aged ≥19 years with T2DM diabetes diagnosed according to international criteria; (3) examined the effect of oral intake of any of the supplements based on previously defined food BACs; (4) studies with an intervention of at least 4 weeks; (5) the primary variables of interest (outcomes) reported alterations in HbA1c, in the OS, or in enzymatic and non-enzymatic ADS variables; and (6) studies published in English, Spanish, French, German, Italian, and Portuguese.

The exclusion criteria were as follows: (1) interventions with a mixture of food BACs for which the exact intake of the compounds was not specified; (2) herbal

Table 1. PICOS Criteria for Inclusion and Exclusion of Studies

Parameter	Inclusion criteria	Exclusion criteria
Population	Studies involving adults (aged ≥19 years) with T2DM	Studies involving: pregnant or lactating women, women with gestational diabetes; patients with type 1 diabetes; patients aged <19 years; and animal models
Intervention	Studies reporting the effect of oral intake of any of the supplements based on previously defined food BACs for at least 4 weeks	Mixture of food BACs for which the exact intake of the compounds was not specified; herbal or extract mixtures or herbal formulations in which the quantity of any BAC was not indicated
Comparison or control	RCTs properly controlled with placebo or non-exposure groups (parallel, cross-over, or double cross-over)	Studies with intravenous or parenteral administration of supplements; studies with treatment for less than 4 weeks
Outcomes	Alterations in HbA1c, OS, or enzymatic and non-enzymatic ADS variables	Studies lacking the listed outcomes
Study design	RCTs, defined as trials properly controlled with placebo or non-exposure groups (parallel, cross-over, or double cross-over) in humans	Studies that are not properly controlled RCTs; studies that are not published in English, Spanish, French, German, Italian, or Portuguese; animal or cell experiments, case reports, comments, letters, editorials, conference papers, unpublished articles, and literature with unavailable or uncovered data

Abbreviations: ADS, antioxidant defense system; BAC, bioactive compound; OS, oxidative stress; RCTs, randomized controlled trials; T2DM, type 2 diabetes mellitus.

or extract mixtures or herbal formulations in which the quantity of any BAC was not indicated; (3) non-clinical trials or RCTs conducted in pregnant or lactating women, women with gestational diabetes or patients with type 1 diabetes; (4) studies with intravenous or parenteral administration of supplements; (5) animal or cell experiments, case reports, comments, letters, editorials, conference papers, unpublished articles, and literature with unavailable or uncovered data; (6) studies with treatment of less than 4 weeks. Although omega-3 fatty acids were initially considered in the search strategy, they were subsequently excluded due to the large number of published reviews on this topic.

Three independent reviewers screened the titles and abstracts using the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). For accepted citations, 3 reviewers independently (A.H.-R., M.B., F.R.-O.) assessed the full manuscripts. Disagreements were resolved by a fourth reviewer (A.G.) and, if necessary, by group consensus. All screening was managed via the Covidence® online platform.

Data Extraction and Synthesis of Results

For eligible manuscripts, we developed a data extraction template. The following information was independently extracted from full-text articles: (1) Characteristics of the study (first author, publication year, and country); (2) Study description, sample size, and intervention (duration of the intervention, types of food BACs and dose and frequency of intervention; (3) Outcome variables: HBA1c, biomarkers of OS, and alterations in the ADS (enzymatic and non-enzymatic). Any discrepancies during data extraction were resolved by reviewers' consensus, although if a consensus could not be reached, a fourth reviewer adjudicated the decision.

Critical Appraisal: Risk-of-Bias Assessment and Synthesis

The Joanna Briggs Institute (JBI) offers a suite of critical appraisal tools that are freely available to anyone aiming to conduct a systematic review or critically appraise the literature.[24] For RCTs, the JBI critical appraisal tool was used to assess the risk of bias in the included studies. To evaluate the RCTs' risk of bias, 10 items were evaluated according to the JBI criteria: Selection and allocation, intervention, administration, outcome assessment, follow-up, and statistical analysis. Using the guidelines, each JBI item was categorized as "yes," "no," "unclear," or "not applicable."

Outcome Variables

The main outcomes considered were HbA1c and variables related to OS and ADS, such as MDA, plasma or blood levels of GSH, total serum antioxidant capacity (TAC), and blood activity of the SOD, CAT, GPxs and nitric oxide-related species (NOx) enzymes.

Statistical Analysis

Meta-analysis was performed when at least 5 studies of the same food BAC had evaluated the same outcome. The meta-analysis was carried out using R, version 4.4.2. A P value of $<.05$ was considered significant. The standardized mean difference (SMD) and its corresponding 95% CI (CI) for each study were used to estimate the pooled effects of the included studies for each continuous variable measured. To obtain the overall SMD, we applied a random-effects model that took both within- and between-study variations into account. I^2 statistics and Cochrane's Q test were used to assess heterogeneity among the studies. For the I^2 statistic, we considered I^2 values of $<25\%$, $25\%-<50\%$, $50\%-<75\%$, and $\geq 75\%$ as indicating low, moderate, high, and very high between-study heterogeneity, respectively. The random effect was applied to count effect sizes to provide more balance in individual study weights.

RESULTS

Characteristics of the Included Studies and the Screening Process

The initial screening process incorporated a total of 4202 studies, of which 2754 were deemed relevant and included in the subsequent analysis. Three independent reviewers screened the 2754 studies by title or abstract, and 2492 were evaluated as irrelevant. A total of 262 studies were screened for full-text review, and 82 of these were excluded for various reasons, including inappropriate study design or patient population, irrelevant intervention, incorrect exposure, irrelevant outcomes, or retracted studies. Ultimately, 180 studies were extracted, of which 71 did not meet the inclusion criteria. The final number of studies included in the current systematic review and meta-analyses was 109 (Figure 1).

The characteristics of the studies selected in the present systematic review and meta-analyses were collected, including the country, the year of publication, sample size, intervention, dose of food BAC, frequency, and main outcomes. The classification of studies was based on the type of intervention made in each study, and the studies were grouped into 5 different categories:

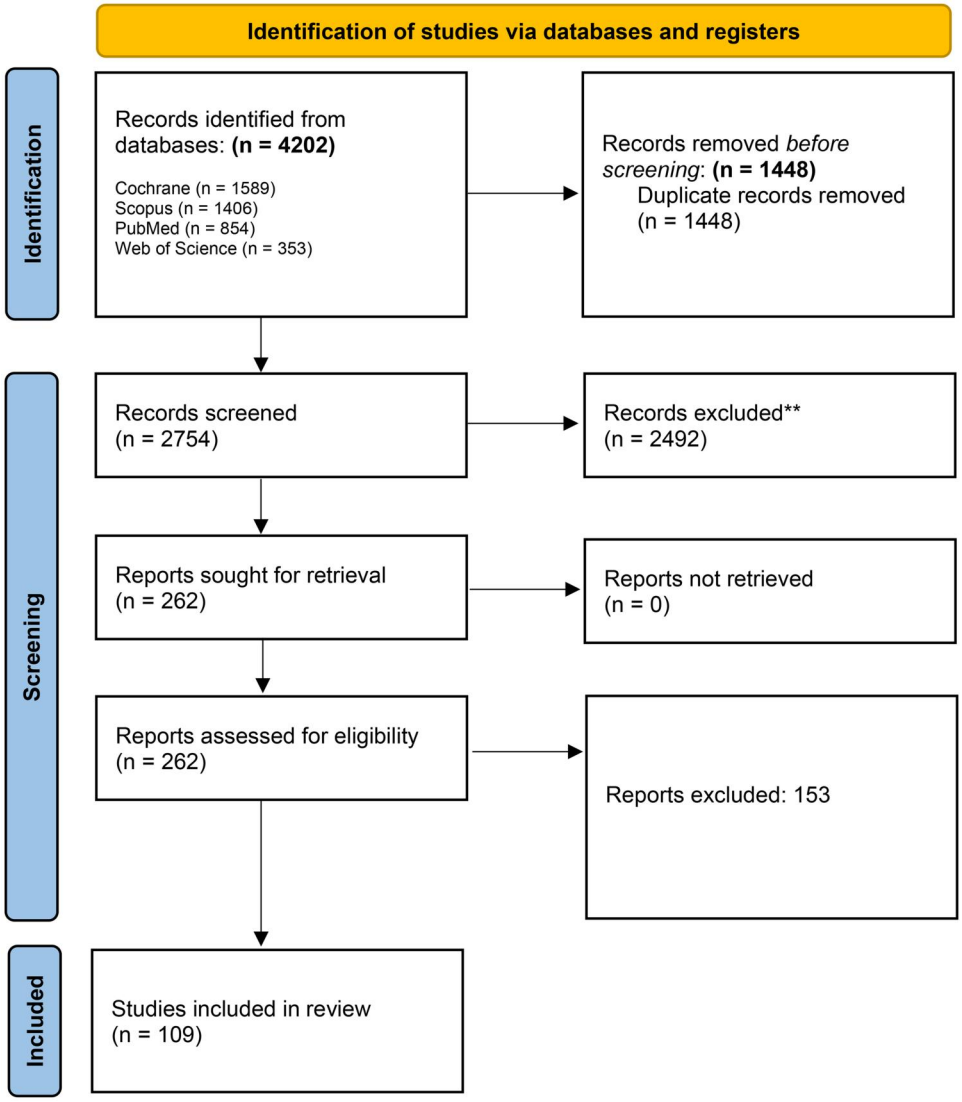

Figure 1. Flow Chart Showing Selection of Eligible Studies

Amino acids, vitamins and related compounds, minerals, phenolic compounds, and other BACs.

Amino Acids and Derivatives

Seven studies[25–31] reported the effects of amino acid supplementation in T2DM patients. This study collated results from multiple amino acid interventions, including N-acetylcysteine, L-citrulline, and the 2-aminoethanesulfonic acid (taurine) (Table 2).

N-Acetylcysteine. Two studies[27,29] reported results from N-acetylcysteine supplementation. In one study, participants received 600 mg/day for 8 weeks, which led to enhanced antioxidant activity, evidenced by increased levels of GPx, TAC, and SOD, along with a reduction in MDA. In the other study, 1200 mg/day was administered for 4 weeks, and this showed no effect of N-acetylcysteine on HbA1c levels but did result in increased levels of GSH.

L-citrulline. One study[25] showed a higher TAC and higher activity of NOx, and lower levels of MDA after L-citrulline supplementation.

Taurine. Four studies[25,26,28,30,31] reported results from taurine supplementation. The daily dose of taurine ranged from 1000 mg to 3000 mg, and the intervention period ranged from 2 to 3 months. The findings demonstrated that taurine supplementation enhanced the ADS, as evidenced by increased levels of SOD and TAC, and reduced levels of MDA. In addition, the findings of 1 study indicated a decrease in HbA1c levels following taurine supplementation. Conversely, 2 studies did not demonstrate a significant association between taurine intervention and substantial variation in HbA1c levels.

Table 2. Amino Acids and Derivatives

Author	Country	Year	Sample size	Intervention	Dose	Frequency	Outcomes	Outcomes direction
Azizi et al (2021)[b,25]	Iran	2021	54	L-citrulline	3 g/day	8 weeks	MDA; GPx; TAC; SOD	Null (SOD, GPx); higher is better (TAC); lower is better (MDA)
Chauncey et al (2003)[b,26]	United States	2003	45	Taurine	3000 mg	16 weeks	HbA1c	Null
De Mattia et al (1998)[b,27]	Italy	1998	15	N-acetyl-L-cysteine[a]	1200 mg/day	4 weeks	HbA1c; GSH	Null; higher is better
Esmaeili et al (2020)[b,28]	Iran	2020	46	Taurine	3000 mg/day	8 weeks	HbA1c	Lower is better
Heidari et al (2019)[29]	Iran	2019	90	N-acetylcysteine	600 mg/day	8 weeks	MDA; SOD; GPx; TAC	Lower is better; higher is better
Maleki et al (2020)[30]	Iran	2020	50	Taurine	3000 mg/day	8 weeks	SOD; MDA; TAC	Higher is better; lower is better; null
Moludi et al (2022)[31]	Iran	2022	120	Taurine	1 g/day	8 weeks	HbA1c; MDA: TAC	Null; lower is better; higher is better

[a]Cross-over group.
[b]Sponsorship.
Abbreviations: GPx, glutathione peroxidase; GSH, glutathione; Hba1c, hemoglobin A1C; MDA, malondialdehyde; SOD, superoxide dismutase; TAC, total antioxidant capacity.

Vitamins and Related Compounds

A total of 48 studies[32–80] were included in the vitamins and related compounds group. The most prevalent interventions involved vitamin supplements, with most studies focusing on the supplementation of vitamin C, vitamin D, and vitamin E (Table 3).

Vitamin E. Fifteen studies[32,34,35,37,39–46,48–50] demonstrated the effects of vitamin E supplementation in patients with T2DM. The daily vitamin E dosage administered to diabetic patients ranged from 200 mg to 1632 mg throughout 1 to 12 months. The results indicated that vitamin E supplementation led to a favorable improvement in glycemic control, as evidenced by a significant reduction in HbA1c levels, as also shown by our meta-analysis (SMD −0.22, 95% CI −0.42; −0.02) (Figure 2A).

Additionally, the intervention increased ADS markers (SOD, CAT, GPx, and TAC), while decreasing oxidant markers (MDA and lipid peroxidation). Furthermore, data were collected on multiple vitamin E isoforms. Three studies demonstrated the outcomes of alpha-tocopherol supplementation, identifying reduced levels of MDA, lipid peroxidation, and HbA1c, and augmented levels of TAC and SOD activity. In contrast, delta-tocopherol supplementation was investigated in another study, which reported enhanced glycemic control, as indicated by a reduction in HbA1c levels. Moreover, a reduction in OS, as indicated by a decrease in MDA levels, was observed.

Vitamin D. Thirteen studies[33,36,38,47,53–57,59,61–63] evaluated the use of vitamin D supplementation in patients with T2DM. Vitamin D doses were categorized as either daily or weekly. Five studies reported daily doses of vitamin D ranging from 400 IU to 2000 IU, with a duration of 12 weeks. The findings demonstrated that daily vitamin D supplementation resulted in increased antioxidant marker levels (TAC, GSH), decreased OS marker levels (MDA and lipid oxidation), and improved glycemic control as reflected by reduced HbA1c levels. Indeed, the meta-analysis revealed that vitamin D supplementation significantly lowered HbA1c (SMD −0.37, 95% CI −0.56; −0.18) (Figure 2B), and MDA levels (SMD −0.45, 95% CI −0.77; −0.12) in T2DM patients (Figure 2C).

Vitamin C. Seven studies[58,60,64,65,67,75,78] investigated the effects of vitamin C supplementation in patients with T2DM. The intervention period ranged from 6 weeks to 12 weeks, during which time the patients received daily doses of vitamin C ranging from 60 mg to 1000 mg. Four studies assessed glycemic status by measuring HbA1c levels, which decreased following vitamin C supplementation in 3 studies. Furthermore, ADS markers (TAC, GSH, and NO) increased, while OS markers (MDA and lipid oxidation) decreased after the intervention.

Folic Acid. One study[65] investigated the effect of folic acid supplementation in T2DM patients. This study found that a daily dose of 5 mg over 8 weeks enhanced

Table 3. Vitamins and Related Compounds

Author	Country	Year	Sample size	Intervention	Dose	Frequency	Outcomes	Outcomes direction
Anand et al (2011)[32]	India	2011	74	Vitamin E	600 mg/day	12 weeks	SOD; CAT; GPx; HbA1c	Higher is better; lower is better
Baumgartner et al (2017)[a,34]	Netherlands	2017	20	Vitamin E[b]	804 mg/day	4 weeks	MDA; HbA1c; GSH/GSSG	Null
Ble-Castillo et al (2005)[a,35]	Mexico	2005	34	Vitamin E Alpha-tocopherol	800 IU/day	6 weeks	MDA; HbA1c; Gpx; SOD; TAC	Null; null higher is better
Fuller et al (1996)[37]	United States	1996	28	Vitamin E (RRR-alpha-tocopheryl acetate)[b]	1632 mg/day	8 weeks	HbA1c	Lower is better
Haghighat et al (2014)[39]	Iran	2014	44	Vitamin E (tocotrienols)	200 mg/day	8 weeks	NO	Null
Hejazi et al (2014)[81]	Iran	2015	30	Vitamin E	400 IU/day	6 weeks	MDA	Lower is better
Mahjabeen et al (2021)[41]	Pakistan	2021	110	Vitamin E (delta-tocotrienol)	250 mg/day	24 weeks	HbA1c; MDA	Lower is better
Park et Choi (2002)[42]	South Korea	2002	98	Vitamin E (alpha-tocopherol)	200 mg/day	8 weeks	Lipid peroxidation	Lower is better
Rafraf et al (2016)[43]	Iran	2016	83	Vitamin E	400 IU/day	8 weeks	HbA1c, TAC	Lower is better; higher is better
Reaven et al (1995)[44]	United States	1995	21	Vitamin E	1600 IU/day	10 weeks	HbA1c; MDA	Null; lower is better
Sampson et al (2001)[45]	United Kingdom	2001	70	Vitamin E (alpha-tocopherol)	400 IU/day	8 weeks	Lipid oxidation	Null
Tan et al (2019)[46]	Malaysia	2019	54	Vitamin E-tocotrienol-rich	400 mg/day	12 weeks	HbA1c; MDA	Null
Winterbone et al (2007)[48]	United Kingdom	2007	19	Vitamin E K(alpha-tocopherol)	1200 IU/day	4 weeks	HbA1c	Null
Wu et al (2007)[49]	Australia	2007	55	Vitamin E (alpha-tocopherol)	500 mg/day	6 weeks	SOD; GPx	Null
Zitouni et al (2020)[50]	United Kingdom	2020	170	Vitamin E	400 IU/day	12 months	GPx	Higher is better
Barzegari et al (2018)[a,33]	Iran	2018	50	Vitamin D	50 000 IU/week	8 weeks	TAC; SOD; CAT; GPx; MDA	Null
Cojic et al (2021)[a,36]	Serbia	2021	130	Vitamin D	14 000–50 000 IU/2 weeks	24 weeks	HbA1c; MDA	Lower is better; null
Gu et al (2022)[38]	China	2022	178	Vitamin D[b]	400 IU	12 weeks	GSH	Higher is better
Wenclewska et al (2019)[47]	Polonia	2019	92	Vitamin D	2000 IU/day	12 weeks	HbA1c	Lower is better
Eftekhari et al (2013)[a,52]	Iran	2013	70	Vitamin D	Calcitriol (0.25 μg 1,25-dihydroxy-cholecalciferol)	12 weeks	MDA	Lower is better
Hoseini et al (2022)[53]	Iran	2022	48	Vitamin D	50 000 IU/week	8 weeks	GSH; TAC; SOD; CAT; GPx; NO; MDA	Higher is better; lower is better

(continued)

Table 3. Continued

Author	Country	Year	Sample size	Intervention	Dose	Frequency	Outcomes	Outcomes direction
Imanparast et al (2020)[54]	Iran	2020	92	Vitamin D	50 000 IU/week	16 weeks	MDA; TAC	Lower is better; higher is better
Johny et al (2022)[55]	India	2022	59	Vitamin D	60 000 IU/week	24 weeks	HbA1c; SOD; GSH; NO	Null; higher is better
Qasemi et al (2021)[56]	Iran	2021	44	Vitamin D	2000 IU/day	12 weeks	Lipid oxidation	Lower is better
Razzaghi et al (2017)[58]	Iran	2017	60	Vitamin D	50 000 IU/2 weeks	12 weeks	HbA1c; MDA	Lower is better
Shab-Bidar et al (2015)[60]	Iran	2015	100	Vitamin D	1000 IU/day	12 weeks	GSH; TAC; MDA; HbA1c	Higher is better; lower is better; Null
Tamadon et al (2018)[61]	Iran	2018	60	Vitamin D	50 000 IU/2 weeks	12 weeks	HbA1c; MDA; TAC	Null; lower is better; higher is better
Yiu et al (2013)[63]	Hong Kong	2013	100	Vitamin D	5000 IU/day	12 weeks	HbA1c; SOD	Null
Ragheb et al (2020)[57]	Egypt	2020	53	Vitamin C	500 mg/day	8 weeks	HbA1c; MDA; SOD	Null
Salama et al (2021)[59]	Egypt	2021	55	Vitamin C	1 g/day	12 weeks	HbA1c	Lower is better
Sanguanwong et al (2016)[63]	Thailand	2016	100	Vitamin C	1000 mg/day	8 weeks	MDA; TAC	Lower is better; higher is better
El-Aal et al (2018)[64]	Palestine	2018	40	Vitamin C, vitamin E and vitamin C plus vitamin E	1 g/day of vitamin C: 800 mg/day of vitamin E; 1 g/day of vitamin C + 800 mg/day of vitamin E)	12 weeks	HbA1c; GSH	Lower is better; higher is better
Boonthongkaew et al (2021)[66]	Thailand	2021	24	Vitamin C[c]	1000 mg/day	6 weeks	MDA; NO	Lower is better; higher is better
Fenercioglu et al (2010)[a,74]	Turkey	2010	114	Vitamin C	60 mg/day	12 weeks	HbA1c; MDA; GSH; TAC	Lower is better; higher is better
Tessier et al (2009)[77]	Canada	2009	36	Vitamin C	0.5 g/day and 1 g/day	12 weeks	GSH	Higher is better
Fakhrabadi et al (2014)[67]	Iran	2014	70	Coenzyme Q10[b]	200 mg/day	12 weeks	HbA1c; TAC	Null; higher is better
Fallah et al (2019)[68]	Iran	2019	60	Coenzyme Q10[b]	120 mg/day	12 weeks	TAC; NO; GSH; MDA	Higher is better; null (GSH, MDA)
Gholami et al (2018)[69]	Iran	2018	68	Coenzyme Q10[b]	100 mg/day	12 weeks	MDA	Lower is better
Hamilton et al (2009)[70]	Australia	2009	23	Coenzyme Q10[b]	200 mg/day	12 weeks	Lipid oxidation	Null
Hernández-Ojeda et al (2012)[71]	Mexico	2012	49	Coenzyme Q10 (ubiquinone)[b]	400 mg/day	12 weeks	Lipid peroxidation	Lower is better

(continued)

Table 3. Continued

Author	Country	Year	Sample size	Intervention	Dose	Frequency	Outcomes	Outcomes direction
Hodgson et al (2002)[72]	Australia	2002	74	Coenzyme Q10	200 mg/day	12 weeks	HbA1c	Lower is better
Hosseinzadeh-Attar et al (2013)[73]	Iran	2013	64	Coenzyme Q10	200 mg/day	12 weeks	HbA1c	Lower is better
Playford et al (2003)[75]	Australia	2003	80	Coenzyme Q10	200 mg/day	12 weeks	HbA1c	Lower is better
Rodríguez-Carrizalez et al (2016)[76]	Mexico	2016	60	Coenzyme Q10	400 mg/day	24 weeks	HbA1c; MDA	Null; lower is better
Yen et al (2018)[78]	China	2018	50	Coenzyme Q10 (liquid ubiquinone)[b]	100 mg/day	12 weeks	HbA1c; CAT; GPx	Lower is better; higher is better
Zarei et al (2018)[79]	Iran	2018	68	Coenzyme Q10	100 mg/day	12 weeks	CAT; TAC	Higher is better
Aghamohammadi et al (2011)[65]	Iran	2011	68	Folic acid	5 mg/day	8 weeks	MDA; TAC	Lower is better; higher is better
El-Kady et al (2022)[80]	Egypt	2022	70	Nicotinamide	1000 mg/day	12 weeks	MDA	Null

[a]Sponsorship.
[b]Parallel group.
[c]Cross-over group.
Abbreviations: CAT, catalase; GPx, glutathione peroxidase; GSH, glutathione; GSSG, glutathione disulfide (oxidized glutathione); Hba1c, hemoglobin A1C; MDA, malondialdehyde; NO, nitric oxide; SOD, superoxide dismutase; TAC, total antioxidant capacity.

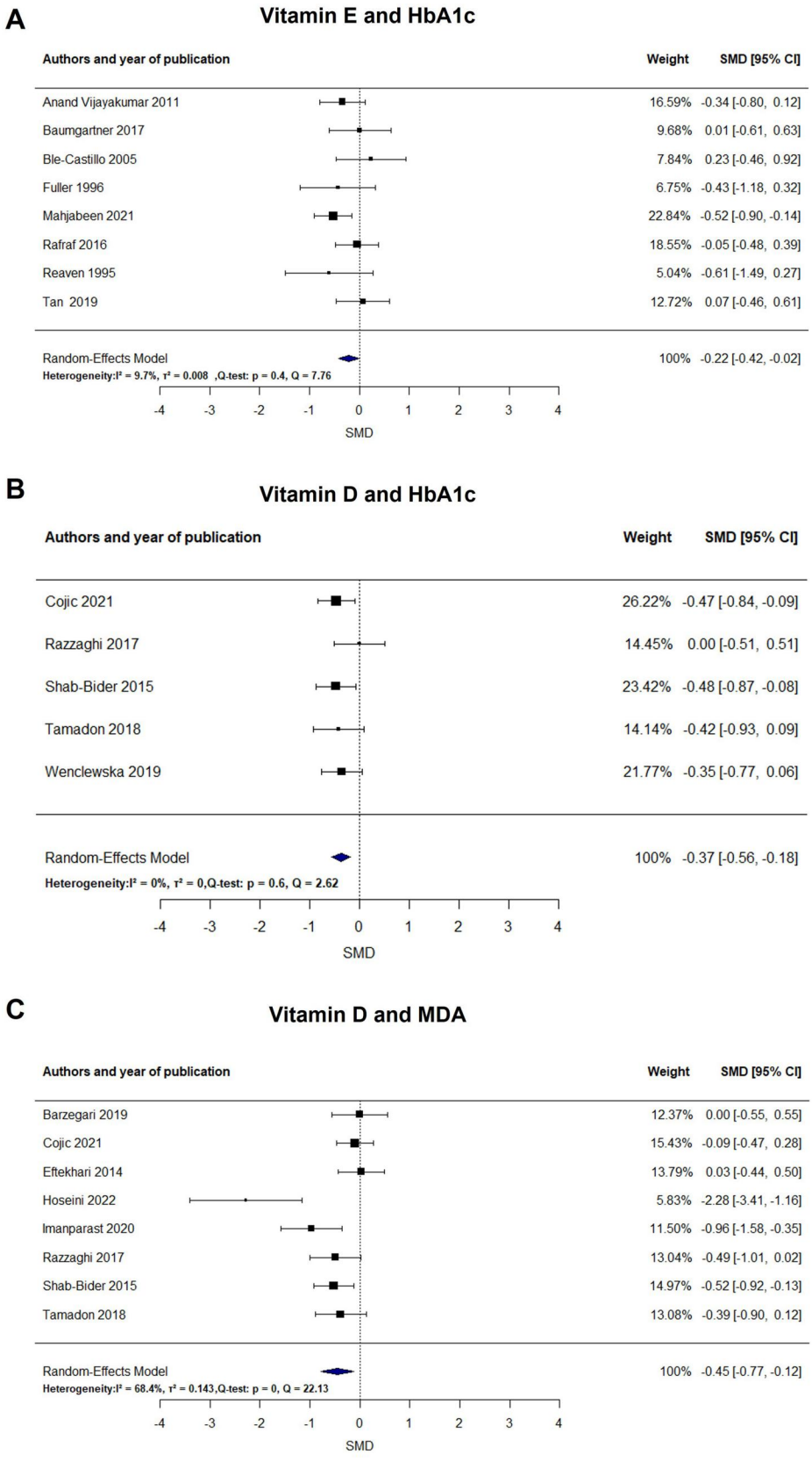

Figure 2. Forest Plot of a Meta-Analysis Describing the Effect of (A) Vitamin E Supplementation on Hba1c Levels, (B) Vitamin D Supplementation on Hba1c Levels, and (C) Vitamin D Supplementation on MDA Levels in T2DM Patients. SMD, standardized mean difference

the ADS markers (higher TAC levels), while reducing OS markers (lower MDA levels).

Coenzyme Q10. The impact of coenzyme Q10 supplementation in T2DM patients was examined in 1 studies.[67–73,75,76,78,79] Daily doses of coenzyme Q10 ranged from 100 mg to 400 mg over intervention periods of either 12 or 24 weeks. Three studies demonstrated that coenzyme Q10 supplementation improved glycemic control, as evidenced by reduced HbA1c levels, while 2 studies did not report any significant variation. Increased ADS (CAT, TAC, NO, GPx) were reported in 4 studies, and decreased OS markers (MDA and lipid peroxidation) were observed in 3 studies.

Mineral Compounds

We identified 13 studies[81–93] that investigated the supplementation of mineral compounds in T2DM patients (Table 4).

Zinc (Zn). Zinc supplementation was examined in 3 studies.[87,88,90] The daily dose of zinc ranged from 30 mg for 24 weeks, to 50 mg for 12 weeks, and 60 mg for 8 weeks. The findings indicated that zinc supplementation led to enhanced glycemic control, decreased OS, and increased ADS. This was evidenced by reductions in HbA1c and MDA levels, as well as increases in GSH and TAC levels.

Selenium (Se). Selenium supplementation was the most prevalent, being reported in 4 studies.[82,83,85,91] The dosage of selenium administered ranged from 200 µg to 960 µg per day for a period of 8 to 12 weeks. The implementation of selenium resulted in reductions in HbA1c and MDA levels, as well as increases in NO, plasma TAC, and plasma GSH in diabetic patients.

Chromium (Cr). Finally, 4 studies[81,84,86,92] demonstrated that chromium supplementation (200 µg/day for 12 weeks and 1000 µg/day for 6 months) was associated with reduced levels of MDA and HbA1c, as well as with increased levels of TAC, CAT, and GPx activities.

Phenolic Compounds

A total of 31 studies[94–124] were included in the phenolic compounds group (Table 5).

Curcuminoids. Ten studies[95,99,100,102,105,107,109,110,112,113] examined the effects of curcuminoid-dipheruloyl quinone derivatives supplementation in T2DM patients. The dosage of curcuminoids administered ranged from 80 mg to 2100 mg daily, with the intervention period lasting from 2 to 12 months. The results from 6 studies demonstrated that diabetic patients experienced enhancements in the ADS, as evidenced by elevated levels of TAC, GSH, and NO. Moreover, we performed a meta-analysis including 6 studies that met the inclusion criteria, which reported a significant reduction in the OS marker MDA and lipid oxidation (SMD −0.60, 95% CI −1.14; −0.06) (Figure 3). Furthermore, a decline in HbA1c levels was observed following curcuminoid supplementation.

Resveratrol. Seven studies[96–98,101,104,106,108] investigated resveratrol (a stilbenoid) supplementation in T2DM patients. The dosage of resveratrol administered ranged from 200 mg to 1000 mg, with intervention durations spanning 2 to 6 months. The results showed reductions in both HbA1c and MDA levels following resveratrol supplementation in 4 studies and 3 studies, respectively. Furthermore, it was observed that the levels of TAC, NO, and GSH, as well as the activities of the antioxidant enzymes SOD, CAT, and GPx, were elevated in diabetic patients who received resveratrol supplementation.

Epigallocatechin-3-Gallate. Epigallocatechin-3-gallate implementation[94] in diabetic patients (600 mg/day for 6 weeks) reported better ADS capacity (higher TAC levels).

Quercetin. One RCT parallel-group study[122] (500 mg/day for 32 weeks) showed decreasing levels of HbA1c in diabetic patients after quercetin (a flavonol) intervention.

Rutin. Rutin—the glycoside combining the flavonol quercetin and the disaccharide rutinose—supplementation[116] in T2DM patients (1000 mg/day for 12 weeks) showed better glycemic status (lower HbA1c levels), lower MDA levels, and higher TAC levels.

Hesperidin. Hesperidin (a flavonoid) supplementation[115] (500 mg/day for 6 weeks) improved TAC levels of diabetic patients.

Anthocyanin. Anthocyanin (a flavonoid) supplementation[103,111] (320 mg/day for 24 weeks and 280 mg/day for 8 weeks) in T2DM patients led to higher levels of TAC and lowered HbA1c levels.

Baicalin. Baicalin (a flavone) supplied[114] to T2DM patients (2400 mg/day for 24 weeks) lowered HbA1c levels and enhanced SOD and GPx activities.

Table 4. Minerals Compounds

Author	Country	Year	Sample size	Intervention	Dose	Frequency	Outcomes	Outcomes direction
Cheng et al (2024)[82]	Taiwan	2024	68	Cr yeast chromium (III)	1000 μg/day	24 weeks	SOD; GPx; CAT; HbA1c	Null, lower is better
Faghihi et al (2014)[83]	Iran	2014	60	Selenium	200 μg/day	12 weeks	HbA1c	Lower is better
Farrokhian et al (2016)[a,84]	Iran	2016	60	Selenium	200 μg/day	8 weeks	NO; TAC; GSH; MDA	Higher is better; lower is better
Farrokhian et al (2020)[a,85]	Iran	2020	64	Chromium picolinate	200 μg/day	12 weeks	MDA; TAC	Lower is better; higher is better
Faure et al (2004)[a,86]	France	2004	56	Selenium supplementation	960 μg/day	12 weeks	MDA; SOD	Null; higher is better
Jain et al (2012)[87]	United States	2012	74	CDNC	400 μg/day	12 weeks	HbA1c	Null
Momen-Heravi et al (2017)[88]	Iran	2017	60	Zinc	220 mg zinc sulfate (50 mg elemental zinc)/day	12 weeks	HbA1c; TAC; GSH; MDA	Lower is better; higher is better; higher is better; lower is better
Nazem et al (2019)[89]	Iran	2019	70	Zinc gluconate	60 mg/day	8 weeks	HbA1c	Lower is better
Rashvand et al (2019)[90]	Iran	2019	96	Choline, magnesium[b]	0.94 g/day, 500 mg/day	8 weeks	HbA1c	Null
Roussel et al (2003)[91]	Tunisia	2003	56	Zinc	30 mg/day	24 weeks	HbA1c	Lower is better
Salimian et al (2022)[92]	Iran	2022	60	Selenium	200 μg/day	24 weeks	GSH	Higher is better
Usharani et al (2017)[93]	India	2017	96	PPC	400 μg/day	12 weeks	GSH; MDA; NO; HbA1c	Higher is better; lower is better
Paolisso et al (1994)[94]	Italy	1994	9	Magnesium[c]	4.5 g/day	4 weeks	Lipid oxidation	Null

[a]Sponsorship.
[b]Parallel group.
[c]Cross-over group.
Abbreviations: CAT, catalase; CDNC, chromium dicocysteinate; GPx, glutathione peroxidase; GSH, glutathione. Hba1c, hemoglobin A1C; MDA, malondialdehyde; NO, nitric oxide; PPC, proprietary chromium complex; SOD, superoxide dismutase; TAC, total antioxidant capacity.

Table 5. Phenolic Compounds

Author	Country	Year	Sample size	Intervention	Dose	Frequency	Outcomes	Outcomes direction
Amini et al (2024)[95]	Iran	2024	60	Curcumin	1000 mg/day	12 weeks	MDA; SOD; TAC	Lower is better; higher is better
Darmian et al (2022)[100]	Iran	2022	42	Turmeric	2100 mg capsules	8 weeks	MDA; GSH; TAC	Lower is better, higher is better
Hodaei et al (2019)[102]	Iran	2019	53	Curcumin	1500 mg/day	10 weeks	HbA1c; MDA; TAC	Null
Jiménez-Osorio et al (2016)[103]	Mexico	2016	101	Curcumin	320 mg/day	8 weeks	Lipid peroxidation; TAC	Lower is better; higher is better
Pratama et al (2021)[106]	Indonesia	2021	67	Curcumin	2 g/day	8 weeks	NO	higher is better
Pratama et al (2020)[108]	Indonesia	2020	67	Curcumin	2 g/day	8 weeks	TAC	higher is better
Shafabakhsh et al (2020)[110]	Iran	2020	60	Nano-curcumin	80 mg/day	12 weeks	MDA; NO; TAC	Lower is better; higher is better
Shafabakhsh et al (2020) (A)[111]	Iran	2020	60	Curcumin	1000 mg/day	12 weeks	GSH; TAC; MDA	Higher is better; lower is better
Usharani et al (2008)[113]	India	2008	67	Curcumin[b]	300 mg/day	8 weeks	MDA	Lower is better
Yaikwawong et al (2024)[114]	Thailand	2024	227	Curcumin	1550 mg/day	12 months	HbA1c	Lower is better
Bhatt et al (2012)[a,97]	India	2012	57	Resveratrol	250 mg/day	24 weeks	MDA; HbA1c; SOD; CAT; GPx	Lower is better, higher is better
Bo et al (2016)[a,98]	Italy	2016	192	Resveratrol	500 mg/day; 40 mg/day	24 weeks	HbA1c	Null
Bo et al (2018)[a,99]	Italy	2018	128	Resveratrol	500 mg/day; 40 mg/day	24 weeks	HbA1c; TAC	Null; higher is better
García-Martínez et al (2023)[101]	Mexico	2023	97	Resveratrol[b]	500/1000 mg/day	24 weeks	HbA1c; TAC	Lower is better; higher is better
Mahjabeen et al (2022)[105]	Pakistan	2022	110	Resveratrol[b]	200 mg/day	24 weeks	HbA1c, MDA	Lower is better
Sattarinezhad et al (2019)[108]	Iran	2019	60	Resveratrol[b]	500 mg/day	12 weeks	NO; SOD; GSH; MDA; HbA1c	Higher is better; lower is better
Seyyrdebrahimi et al (2018)[109]	Iran	2018	48	Resveratrol	800 mg/day	8 weeks	TAC; SOD	Higher is better
Bazyar et al (2021)[96]	Iran	2021	50	EGCG	600 mg (2 tablets)	8 weeks	TAC	Higher is better
Li et al (2015)[104]	China	2015	58	Anthocyanin	320 mg/day	24 weeks	TAC	Higher is better
Teparak et al (2025)[112]	Thailand	2025	60	Anthocyanin	280 mg/day	8 weeks	Hba1c	Lower is better
Yang et al (2019)[115]	China	2019	95	Baicalin	2400 mg/day	24 weeks	HbA1c; SOD; GPx	Lower is better; higher is better

(continued)

Table 5. Continued

Author	Country	Year	Sample size	Intervention	Dose	Frequency	Outcomes	Outcomes direction
Homayouni et al (2017)[116]	Iran	2017	64	Hesperidin	500 mg/day	6 weeks	TAC	Higher is better
Bazyar et al (2023)[117]	Iran	2023	50	Rutin	1 g/day	12 weeks	HbA1c, TAC, MDA	Lower is better, higher is better
Behrouz et al (2021)[118]*	Iran	2021	50	Crocin	30 mg/day	12 weeks	MDA	Null
Braxas et al (2019)[119]*	Iran	2019	60	Genistein	108 mg/day	12 weeks	HbA1c; MDA; TAC	Lower is better, higher is better
Ghadimi et al (2021)[120]	Iran	2021	44	Ellagic acid[b]	180 mg/day	8 weeks	HbA1; MDA; TAC; GPx; SOD	Lower is better, higher is better
Hussain (2007)[121]	Iraq	2007	59	Silymarin	200 mg/day	16 weeks	HbA1c	Lower is better
Lirussi et al (2002)[122]	Italy	2002	42	Silibin-beta-cyclodextrin (IBI/S)	135 mg/day	24 weeks	HbA1c; MDA	Lower is better
Mantadaki et al (2024)[123]	Greece	2024	100	Quercetin[b]	500 mg/day	32 weeks	HbA1c	Lower is better
Vaz et al (2018)[124]	Brazil	2018	60	Green tea extract (polyphenols)	1120 mg	20 weeks	SOD; HbA1c; CAT; GPx	Higher is better; null
Hokayem et al (2013)[125]	France	2013	38	Grape polyphenols	2 g/day	9 weeks	CAT; Gpx; GSH; SOD	Null

[a]Sponsorship.
[b]Parallel group.
Abbreviations: CAT, catalase; EGCG, epigallocatechin-3-gallate; GPx, glutathione peroxidase; GSH, glutathione; Hba1c, hemoglobin A1C; MDA, malondialdehyde; NO, nitric oxide; SOD, superoxide dismutase; TAC, total antioxidant capacity.

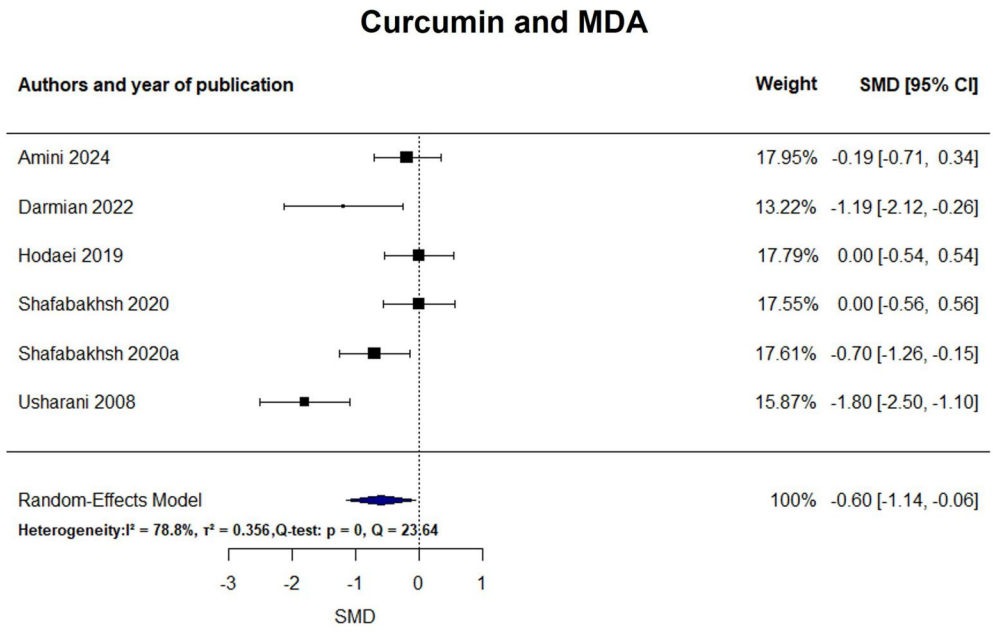

Figure 3. Forest Plot of a Meta-Analysis Describing the Effect of Curcumin Supplementation on MDA Levels in T2DM Patients. MDA, malondialdehyde

Silymarin. Silymarin—a mixture of flavonolignans—supplied[120] to diabetic patients (200 mg/day for 16 weeks) reported lower levels of HbA1c.

Silybin-beta-cyclodextrin. Silybin-beta-cyclodextrin supplied[121] to diabetic patients (135 mg/day for 24 weeks) resulted in lower levels of HbA1c and MDA.

Genistein. Genistein (an isoflavone) supplementation[118] in T2DM patients (108 mg/day for 12 weeks) resulted in lower plasma MDA and HbA1c levels and increased TAC levels.

Polyphenols. Three studies[119,123,124] reported on the effects of polyphenol interventions in patients with T2DM. Polyphenols derived from ellagic acid (180 mg/day for 8 weeks) were associated with lower HbA1c and MDA levels, and higher TAC, GPx, and SOD levels. In contrast, supplementation with grape polyphenols (2 g/day for 9 weeks) did not result in any changes in ADS markers. However, polyphenols derived from green tea extract (1120 mg/day for 20 weeks) led to increased SOD and CAT levels and a reduction in HbA1c levels.

Other Bioactive Compounds

A total of 11 studies[34,125–134] were incorporated into this category of other food BACs, as they did not correspond with the previously established groups (Table 6).

Alpha-lipoic-acid. Nine studies[34,125–128,131–134] demonstrated the outcomes of alpha-lipoic acid (ALA) supplementation in patients diagnosed with T2DM. The dosage of ALA administered to diabetic patients ranged from 300 mg to 1800 mg daily, with intervention durations ranging from 8 to 24 weeks. The main outcome reported was HbA1c, which was shown to decrease by almost 1 point (SMD −0.99, 95% CI −1.68; −0.3) following ALA implementation (Figure 4). Furthermore, OS markers such as MDA and lipid oxidation were found to be reduced by ALA supplementation. Conversely, ALA supplementation enhanced the ADS in T2DM patients, as evidenced by increased levels of TAC and activities of GPx and SOD.

Ursodeoxycholic Acid. Ursodeoxycholic acid—a biliary acid—supplementation[130] increased levels for some of the ADS biomarkers, such as GSH and the activity of SOD.

Risk-of-Bias Assessment

Risk of bias was assessed for each study included in this systematic review based on the JBI checklist. For RCTs, 10 items were evaluated. Most of the studies were scored as having a high risk of bias for items 4, 5, and 6. The items in question pertain to the potential repercussions of whether participants were blinded, the individuals responsible for delivering the treatment, and the assessors evaluating the outcomes. Therefore, this information was missing in most of the studies. Only 18 of 109

Table 6. Other Bioactive Compounds

Author	Country	Year	Sample size	Intervention	Dose	Frequency	Outcomes	Outcomes direction
Baumgartner et al (2017)[34]*	Netherlands	2017	20	ALA[b]	600 mg/day	4 weeks	MDA; HbA1c; GSH/GSSG	Null
Baziar et al (2020)[126]	Iran	2020	70	ALA	1200 mg/day	8 weeks	Lipid oxidation	Lower is better
Derosa et al (2016)[127]*	Italy	2016	105	ALA, L-carnosine, zinc, and vitamins of group B	600 mg/day of ALA, 165 mg/day of L-carnosine, 7.5 mg/day of zinc, and vitamins of group B	12 weeks	HbA1c; MDA; SOD; GPx	Lower is better; higher is better
Hamid et al (2022)[128]	Egypt	2022	60	ALA	600 mg/day	24 weeks	HbA1c	Lower is better
Hasti et al (2021)[129]	Iran	2011	58	ALA	300 mg/day	8 weeks	GPx	Lower is better
Ostadmohammadi et al (2022)[132]	Iran	2022	60	ALA	600 mg/day	12 weeks	MDA; TAC	Lower is better; higher is better
Porasuphatana et al (2012)[133]	Thailand	2012	38	ALA	330, 600, 900, 1200 mg/day	24 weeks	HbA1c	Lower is better
Surapaneni et al (2018)[134]	India	2018	40	ALA	1800 mg/day	12 weeks	HbA1c	Lower is better
Udupa et al (2012)[135]	India	2012	104	ALA, EPA, DHA, Vitamin E	300 mg/day ALA, 180 mg/day EPA, 120 mg/day DHA, 400 mg Vitamin E	12 weeks	HbA1c	Lower is better
Khosravi et al (2022)[130]	Iran	2022	42	Sodium butyrate	600 mg/day	6 weeks	HbA1c	Null
Lakic et al (2024)[131]	Bosnia and Herzegovina	2024	60	Ursodeoxycholic acid (bile acid)	1500 mg/day	8 weeks	GSH; SOD	Higher is better

Abbreviations: ALA, alpha-lipoic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GPx, glutathione peroxidase; GSH, glutathione; GSSG, glutathione disulfide (oxidized glutathione); Hba1c: hemoglobin A1C; MDA, malondialdehyde; SOD, superoxide dismutase; TAC, total antioxidant capacity.

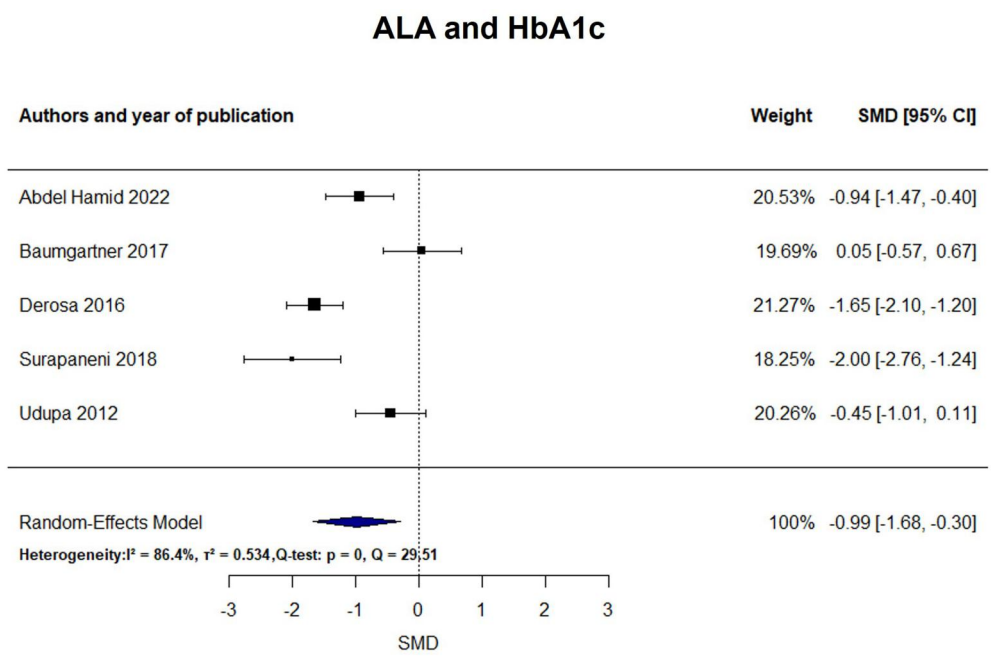

Figure 4. Forest Plot of a Meta-Analysis Describing the Effect of ALA Supplementation on Hba1c Levels in T2DM Patients. ALA, alpha-lipoic acid

studies included in this systematic review were scored as having all items with a low risk of bias. We found them in the vitamin group, phenolic compounds group, and other BAC group (Figures S1–S5).

DISCUSSION

The present systematic review and meta-analyses report the effects of BACs on OS and the ADS in patients with T2DM from human RCTs. The studies were grouped into amino acids, vitamins and related compounds, minerals, phenolic compounds, and other BACs. We found that ALA and vitamin D significantly improved the HbA1c levels, while vitamin E and C showed a trend toward lower HbA1c, as evidenced by our meta-analysis. Moreover, the meta-analysis showed that curcumin and vitamin D significantly improved MDA levels. Supplementation with amino acids such as N-acetylcysteine, L-citrulline, and the 2-aminoethanesulfonic acid, taurine, generally enhanced the ADS and, in some cases, improved glycemic control. Zinc, selenium, and chromium supplementation were associated with improved glycemic control and enhanced antioxidant status, including reduced HbA1c and MDA levels and increased TAC and GSH, and the activities of several antioxidant enzymes. Other phenolics, such as quercetin, rutin, anthocyanin, baicalin, and polyphenols from ellagic acid and green tea, also improved antioxidant capacity and glycemic outcomes in various studies. Ursodeoxycholic acid increased antioxidant biomarkers such as GSH and SOD activity.

Amino Acids and Derivatives

We reported results from RCT studies examining the effect of amino acid supplementation in individuals with T2DM. We collected results from several amino acids, including N-acetylcysteine, L-citrulline, and the 2-aminoethanesulfonic acid, taurine.

Taurine reverses T2DM-associated depletion by restoring mitochondrial electron transport chain function through incorporation into mitochondrial tRNA, enhancing glucose-stimulated insulin secretion through transcription factor upregulation, preventing pancreatic β-cell senescence, and improving endothelial dysfunction and arterial stiffness through nitric oxide bioavailability.[135] Multiple studies investigated taurine supplementation, and findings regarding glycemic control were inconsistent. Only 1 study showed a reduction in HbA1c variation,[28] while 2 studies reported no significant change.[26,31] However, the findings were more consistent for the ADS and OS markers, with studies showing increased levels of TAC and SOD and decreased levels of MDA in patients with T2DM.[25,30,31]

Although taurine is a relatively well-studied amino sulfonic acid, a growing body of evidence underscores its critical physiological roles in T2DM. Reduced serum taurine levels have been linked to various OS–related disorders, suggesting its importance in cellular redox balance. Moreover, taurine participates in neuromodulation and contributes to the maintenance of intracellular calcium homeostasis. Collectively, these findings highlight taurine's multifaceted function as an

antioxidant, neuromodulator, detoxifying agent, and regulator of calcium signaling in human health.[135] Clinically, taurine administration has been demonstrated to be effective in the treatment and prevention of a wide range of conditions associated with OS. These include but are not limited to hepatotoxicity and hepatic disorders, renal disorders, epilepsy and other seizure disorders, cardiomyopathy, cystic fibrosis, alcoholism, Alzheimer's disease, growth retardation, retinal degeneration, and diabetes mellitus.[136–138]

Although our systematic review demonstrated only marginal effects of taurine supplementation on HbA1c, likely reflecting the small number of available trials, a separate meta-analysis based on patients with diabetes reported a statistically significant decrease in HbA1c levels (WMD −0.41 [95% CI: −0.74, −0.09], $P = .01$).[139]

A previous systematic review and meta-analysis of RCTs examined the effect of taurine treatment in patients with metabolic syndrome.[140] Compared with controls, the taurine-supplemented group exhibited significant reductions in key glycemic markers—fasting blood glucose, HbA1c, and fasting insulin levels. Together with our findings, these results support a potential role for taurine in improving glycemic control via several mechanisms: Lower hepatic glucose production,[141] potentiation of insulin signaling,[142] and preservation of pancreatic β-cell viability and function.[143] However, future studies should further investigate the effects of taurine supplementation on HbA1c, both a reliable marker of chronic glycemic exposure and a strong predictor of long-term diabetes complications, in larger and more diverse cohorts, to clarify its role in sustained glycemic control.[144]

N-Acetylcysteine functions as a glutathione precursor that restores depleted intracellular antioxidant pools, directly scavenges ROS through its thiol group, and preserves pancreatic β-cell function by protecting against OS–induced apoptosis, islet fibrosis, and mitochondrial dysfunction in high-glucose and high-fat diet conditions.[29] Two studies reported that N-acetylcysteine lowered MDA, SOD/GPx, and TAC and increased the GSH ratio in patients with T2DM. These results are relevant, since N-acetyl-L-cysteine reduces VCAM-1 expression by decreasing OS.[27]

L-Citrulline functions as a natural arginase inhibitor and precursor to L-arginine through the citrulline-to-arginine recycling pathway, increasing nitric oxide bioavailability by decreasing arginase-mediated L-arginine consumption, thereby preventing arginase-induced vascular endothelial dysfunction while simultaneously enhancing pancreatic β-cell insulin secretion, skeletal muscle glucose uptake, and adipose tissue lipolysis.[145] L-citrulline is a non-essential and nonprotein amino acid in humans.[145] The diet is a poor source of L-citrulline; the main source is endogenous synthesis from glutamine, but it can also be synthesized from arginine and proline.[146] Only 1 study has reported a higher TAC and lower MDA after L-citrulline supplementation in patients with T2DM, which suggests it could be a promising nutritional intervention for preventing cardiovascular risk. However, further studies are needed.

Vitamins and Related Compounds

A total of 48 studies were included in the vitamins and related compounds group. The most prevalent interventions involved vitamin supplements, with most studies focusing on supplementation with vitamin E, vitamin D, and vitamin C.

Vitamin E acts primarily as a lipid-soluble peroxyl radical scavenger that terminates chain reactions by donating electrons from its phenolic group to neutralize lipid peroxyl radicals. All naturally occurring vitamin E forms, including α-, β-, γ-, δ-tocopherol and α-, β-, γ-, δ-tocotrienol, share similar antioxidant properties.[147] Vitamin E supplementation has been shown to attenuate diabetes-associated microvascular complications and may also confer protective effects against macrovascular disease.[148] Notably, it has been demonstrated that dietary vitamin E intake is associated with a 13% reduction in the incidence of T2DM.[149] Moreover, high-dose vitamin E supplementation has been shown to reduce HbA1c in both insulin-dependent and non-insulin-dependent diabetic patients.[150,151] Conversely, some clinical trials in non-insulin-dependent diabetic patients have reported no significant effects of vitamin E supplementation on serum protein glycation, HbA1c, fasting blood glucose, or serum lipid profiles.[37,152] Additionally, a systematic review from 2011 assessing vitamin E supplementation in patients with T2DM found no overall benefit for glycemic control in unselected cohorts. However, subgroup analyses suggested that individuals with poor baseline glycemic control or low circulating vitamin E levels might experience reductions in HbA1c following supplementation.[148] Our meta-analysis of 8 RCTs demonstrated that vitamin E supplementation in T2DM patients was associated with a modest but statistically significant reduction in HbA1c (SMD, –0.22; 95% CI –0.42 to –0.02). None of the cited studies examined the relationship between dietary lipid intake and vitamin E bioavailability or absorption. These results suggest that vitamin E may confer a favorable effect on long-term glycemic control. However, to establish its safety profile and clinically meaningful benefits, especially over extended periods, larger and longer-duration trials are needed.

Increased OS is a key driver in the pathogenesis and progression of diabetes and its complications. In our review of RCTs evaluating vitamin E supplementation, most studies reported enhancements in the ADS, specifically, increases in TAC, SOD activity, and CAT activity, accompanied by reductions in MDA concentrations. These results corroborate earlier findings that vitamin E attenuates lipid peroxidation and lowers MDA levels in diabetic patients.[153]

Patients with T2DM frequently exhibit reduced serum 25-hydroxyvitamin D concentrations, and vitamin D supplementation has been proposed as a strategy to mitigate diabetes risk.[154,155] The active form of vitamin D, 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), exerts its effects primarily through the vitamin D receptor (VDR) pathway and increases insulin sensitivity, reduces pro-inflammatory cytokine production, and inhibits apoptosis in pancreatic β-cells through upregulation of anti-apoptotic proteins.[156] Observational studies consistently report an inverse association between baseline serum 25-hydroxyvitamin D concentrations and the subsequent risk of developing T2DM.[155,157,158] Furthermore, data from recent large-scale randomized trials have indicated a trend toward a lower incidence of new-onset T2DM among participants receiving vitamin D supplementation compared with placebo.[159,160] In the present meta-analysis, we evaluated the effect of vitamin D supplementation on HbA1c levels in patients with T2DM. Five RCTs met our predefined inclusion criteria, and the pooled estimates demonstrated a significant reduction in HbA1c following vitamin D treatment (SMD −0.37; 95% CI −0.56; −0.18). These findings are consistent with previous observations and support the potential of vitamin D supplementation to enhance long-term glycemic control in T2DM patients.

Experimental studies indicate that vitamin D exerts antioxidant effects by inhibiting free-radical generation, attenuating lipid peroxidation, and preventing oxidative modification of proteins, lipids, and nucleic acids.[161] Given these antioxidative actions, vitamin D supplementation has been proposed as a therapeutic strategy in T2DM to bolster endogenous antioxidant defenses and mitigate OS–driven complications.[162] In our systematic review, most studies assessing the effects of vitamin D supplementation reported reductions in MDA levels, an established biomarker of lipid peroxidation, alongside increases in key antioxidant markers, including TAC, SOD, GSH, and CAT. These findings align with a recent meta-analysis demonstrating that vitamin D supplementation significantly lowers MDA levels, further supporting its role in enhancing antioxidant defense in individuals with T2DM.[163]

Vitamin C supplementation has also been proposed as a potential adjunct therapy for improving glycemic control and attenuating OS in individuals with T2DM. Indeed, vitamin C is a potent water-soluble antioxidant that scavenges ROS and reduces mitochondrial-derived OS, and as an essential cofactor for 15 mammalian enzymes involved in collagen synthesis, carnitine biosynthesis, iron absorption, and neurotransmitter production in diabetic patients.[164] A recent systematic review and meta-analysis assessed the certainty of the available evidence, concluding that long-term (≥12 weeks) and high-dose (≥1000 mg/day) vitamin C supplementation may significantly improve glycemic parameters, highlighting its potential role in diabetes management.[165] In line with these findings, the present systematic review provides evidence that vitamin C supplementation in patients with T2DM leads to reductions in HbA1c and MDA levels, alongside increases in key antioxidant markers such as SOD, TAC, and CAT. Notably, vitamin C treatment was associated with decreased MDA concentrations, indicating a reduction in lipid peroxidation and overall OS. Nevertheless, a recent review concluded that vitamin C does not result in a decrease in MDA.[166] The absence of MDA reduction may be attributable to either the dosage or the duration of supplementation.[167–169]

Coenzyme Q10 restores mitochondrial electron transport chain function by transferring electrons from complexes I and II to complex III, enhancing ATP synthesis, reducing superoxide production at the electron transport chain, and improving β-cell glycerol-3-phosphate dehydrogenase activity. Moreover, Coenzyme Q10 is a potent lipid-soluble antioxidant that scavenges ROS and activates the Nrf2/Keap1/HO-1/NQO1 antioxidant signaling pathway.[170] The present study also examined the effect of coenzyme Q10 on diabetic patients, as evidenced by the results of several studies. Inconsistent findings were observed for HbA1c, as coenzyme Q10 supplementation did not improve glycemic control. Conversely, further evidence was identified pertaining to its impact on the ADS and OS. A substantial body of research has indicated that the administration of coenzyme Q10 to patients diagnosed with T2DM has been associated with an enhancement in the levels of TAC, SOD, CAT, and GPxs, accompanied by a decrease in MDA. Research has indicated that individuals diagnosed with T2DM exhibit reduced levels of coenzyme Q10 in comparison with those not afflicted with the condition. This observation suggests the potential for coenzyme Q10 supplementation to exert a favorable influence on metabolic markers and to concomitantly attenuate OS markers.[171–173] It can thus be concluded that exogenous coenzyme Q10 supplements have the potential to ameliorate the OS-induced

abnormalities in mitochondrial function, consequently enhancing glycemic control in patients diagnosed with T2DM.[174]

Minerals

A total of 13 studies were included in the analysis to examine the effects of mineral compounds on patients with T2DM. The minerals that were examined included zinc, selenium, chromium, and magnesium.

Zinc is an essential cofactor for SOD, one of the primary endogenous antioxidant enzymes that catalyzes the dismutation of superoxide anion (O_2^-) to hydrogen peroxide and molecular oxygen. Zinc also functions as a critical cofactor for insulin biosynthesis, storage, and secretion through zinc transporter proteins.[170] The present study demonstrated that mineral supplementation exerts a beneficial effect, as evidenced by the observation of reduced HbA1c levels and elevated antioxidant marker levels, including TAC, GSH, and SOD. In contrast, no substantial enhancements in MDA levels were observed in patients with T2DM following mineral treatment. The present findings are consistent with those of a previous systematic review, which reported that zinc supplementation may enhance glycemic control by reducing HbA1c levels in T2DM patients.[175] In addition, zinc has been shown to play a protective role against OS.[176] Nevertheless, a further systematic review of selenium supplementation in patients with T2DM revealed that there is an absence of definitive evidence to suggest that selenium treatment improves glycemic control.[177] Selenium is a cofactor of GPxs, which reduces lipid peroxidation and inflammation. The observed effects after selenium supplementation are relevant, since it could improve insulin signaling, by enhancement of the antioxidant status (SOD, GSH), and glycemic control (HbA1c).[178] Regarding chromium, 1 study reported that chromium picolinate supplementation improved the TAC and decreased the MDA levels in patients with T2DM, which could improve metabolic health and reduce cardiovascular risk.

Phenolic Compounds

Among phenolic compounds, relevant results were observed from studies that evaluated the effect of curcuminoid supplementation on diabetic patients. Polyphenols contain multiple aromatic rings with hydroxyl groups that enable direct ROS scavenging and Nrf2-ARE pathway activation. They inhibit ROS production, enhance endogenous antioxidant enzyme activity (SOD, CAT, GPx), increase GSH levels, and suppress pro-inflammatory NF-κB signaling.[179,180] Our meta-analysis demonstrated a substantial decrease in MDA levels following curcumin treatment. Following these findings, elevated levels of antioxidant markers, including GSH, SOD, and TAC, were also reported. As the predominant form of curcuminoids, curcumin exhibits a broad spectrum of pharmacological effects, encompassing antioxidant, anti-inflammatory, antibacterial, antiviral, antifungal, and antitumor properties.[181,182] The results of experimental and clinical studies have indicated that curcumin supplementation exerts a beneficial effect on glycemic status.[183] Indeed, a recent systematic review confirmed that curcumin supplementation also had beneficial effects on glycemic status.[180] Other phenolics, such as quercetin, rutin, anthocyanin, baicalin, and polyphenols from ellagic acid and green tea, also improved antioxidant capacity and glycemic outcomes in various studies. Ursodeoxycholic acid increased antioxidant biomarkers such as GSH and SOD activity. None of the studies revealed robust evidence that individual phenolic compounds such as curcumin, resveratrol, ellagic acid, hesperidin, or polyphenol mixtures interfere with the absorption or bioavailability of micronutrients or BACs in patients with T2DM.

Other Bioactive Compounds

Alpha-lipoic acid is a potent antioxidant, and it is a mitochondrial energy metabolism cofactor in the pyruvate dehydrogenase complex and α-ketoglutarate dehydrogenase complex, enabling NADH oxidation and ATP synthesis, while simultaneously activating the PI3K/Akt pathway.[184] A meta-analysis was performed on 5 articles investigating the effects of ALA on HbA1c in diabetic patients, as part of the BACs group. It was reported that, following ALA treatment, T2DM patients exhibited enhanced glycemic control, accompanied by a substantial decline in HbA1c levels. Furthermore, a positive association was observed between ALA and antioxidant markers, including higher levels of TAC, SOD, and GPx, as well as lower levels of MDA and of the products of lipid oxidation. ALA is regarded as a potent antioxidant, exerting its antioxidant effects by eradicating free radicals and chelating metal ions. In addition, ALA has been observed to interact with other antioxidants, such as ascorbic acid and vitamin E, and to enhance intracellular glutathione levels.[184,185] ALA has gained considerable attention for its potential in the management of diabetic complications, largely attributable to its antioxidant properties. A recent systematic review and meta-analysis demonstrated that ALA supplementation significantly reduced HbA1c. Despite the noteworthy findings, it was proposed that the consequences of ALA supplementation were not clinically

significant, as its impact was deemed to be marginal and unimportant.[186]

Strengths and Limitations

Our systematic review has several notable strengths. The review was prospectively registered, included a comprehensive literature search with a rigorous search and selection strategy, and all screenings and assessments were performed in duplicate. We also aimed to interpret our results and provide practical clinical guidance for healthcare professionals, especially nutrition professionals, who work with adults with T2DM. Notably, this systematic review uniquely reports on 110 studies, all of which are human RCTs with at least 4 weeks of treatment. The risk of bias was relatively low throughout the body of literature. Moreover, we were able to perform multiple meta-analyses, which frequently included 5 or more studies, thereby increasing the statistical power of our findings. There is a relatively wide age range across studies (30–70 years), and most participants were middle-aged to older adults, which is representative of the typical T2DM population. There were also several limitations to our systematic review and meta-analysis. We found high heterogeneity between the studies, due to methodological differences including dose, duration of treatment, sample size, and outcomes assessed. Owing to this heterogeneity, we were only able to conduct subgroup meta-analysis for 2 outcomes (HbA1c and MDA), and we could not perform meta-analysis for each of the individual BACs.

CONCLUSION

To date, this is the first systematic review and meta-analysis to comprehensively report on the effects of BAC supplementation on OS and ADS in T2DM patients. Our findings indicate that the BACs vitamin E, vitamin D, curcuminoids, and ALA may contribute to improved glycemic control. Additionally, these BACs were observed to have positive effects on the ADS and to mitigate oxidant stress. From a clinical perspective, these results highlight the potential benefits of incorporating BAC supplementation into the management of diabetes, which may ultimately enhance patients' quality of life and life expectancy. However, further studies are needed to determine whether these treatments should be considered a primary strategy for combating OS and T2DM. Finally, as the optimal duration and dosage of supplementation remain heterogeneous across studies, additional research is required to clarify these aspects and to address current gaps in the evidence.

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Supplementary Material

Supplementary Material is available at *Nutrition Reviews* online.

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Conflicts of Interest

None declared.

Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon request.

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