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A Comprehensive Systematic Review Comparing Nutraceutical Supplementation (Magnesium, Chromium, Coenzyme Q10, Astaxanthin and Related Agents) on the Lipid Profile, HbA1c and HOMA-IR in Patients with Type 2 Diabetes Mellitus and Dyslipidaemia

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) and atherogenic dyslipidaemia coexist in the majority of patients with cardiometabolic disease, and residual dyslipidaemic and insulin-resistant risk persists in a substantial proportion of patients despite optimal statin and glucose-lowering therapy. Nutraceutical supplementation—most prominently magnesium, chromium, coenzyme Q10 (CoQ10) and astaxanthin—has been proposed as an adjunctive strategy acting on mitochondrial bioenergetics, insulin-receptor signalling, lipid peroxidation and adipokine biology. The evidence base, however, is fragmented into single-agent trials that have never

been compared within one analytical framework, and the dose-response architecture of these agents is poorly characterised in clinical practice.

Methods: A comprehensive systematic review was conducted in accordance with PRISMA 2020. Eligible designs were RCTs, cohort, case-control, cross-sectional, and other observational studies; systematic reviews and meta-analyses were excluded from characteristics tables but retained for corroboration. Risk of bias was appraised with RoB 2 and Newcastle-Ottawa Scale; certainty rated with GRADE. Structured narrative synthesis with vote-counting and explicit dose-response analysis was performed.

Results: Thirty-two primary studies ($\geq 1,700$ participants) met inclusion criteria, together with 16 systematic reviews/meta-analyses for corroboration. Fifteen outcome domains were analysed. Statistically significant improvements were demonstrated for all three co-primary endpoints. Magnesium 250-400 mg/day of elemental Mg significantly reduced HOMA-IR (3.8 ± 1.1 versus 5.0 ± 1.3 , $P=0.005$) and HbA1c ($P=0.04$) in hypomagnesaemic T2DM patients. Chromium produced pooled reductions in fasting plasma glucose of 19.00 mg/dL (95% CI -36.15 to -1.85), HbA1c of 0.71% (-1.19 to -0.23) and HOMA-IR of 1.53 (-2.35 to -0.72). CoQ10 significantly reduced HbA1c by $0.37 \pm 0.17\%$ ($P=0.032$) and, at 120 mg/day for 24 weeks, lowered triglycerides ($P=0.020$), LDL-cholesterol ($P=0.016$) and HOMA-IR ($P=0.009$). Astaxanthin 12 mg/day lowered LDL-cholesterol by 0.33 ± 0.11 mmol/L and

total cholesterol by 0.30 ± 0.14 mmol/L (both $P < 0.05$) and reduced malondialdehyde-modified LDL and HbA1c (both $P < 0.05$). Dose-response synthesis identified a U-shaped optimum of 100-200 mg/day for CoQ10 on glycaemic endpoints and an inverse J-shaped optimum of 400-500 mg/day for total cholesterol; a non-monotonic chromium curve favouring doses below 200 µg/day for lipid endpoints; and a magnesium threshold effect conditional on baseline magnesium status.

Discussion: The three agents act through non-overlapping mechanisms—magnesium as an insulin-receptor tyrosine-kinase cofactor, chromium through chromodulin-mediated amplification of insulin signalling, CoQ10 as a mitochondrial electron carrier and lipophilic antioxidant, and astaxanthin as a transmembrane carotenoid antioxidant—which explains the observed dissociation between glycaemic and lipid responses and supports rational combination rather than substitution. Efficacy is conditional rather than universal: magnesium works in hypomagnesaemia, chromium in the insulin-resistant phenotype, vitamin D in deficiency, and astaxanthin predominantly on the lipid and oxidative axis. Null trials in this review were characterised by replete baseline micronutrient status, short duration or supraphysiological dosing, which is consistent with a threshold-repletion model.

Conclusion: Nutraceutical supplementation produces small but statistically significant and clinically coherent improvements in the lipid profile, HbA1c and HOMA-IR in adults with type 2 diabetes

and dyslipidaemia, with agent-specific and non-monotonic dose-response relationships. These agents should be positioned as phenotype-targeted adjuncts to guideline-directed therapy rather than as substitutes for it, and future trials should be designed as baseline-status-stratified, dose-ranging studies with lipid and insulin-resistance co-primary endpoints.

Keywords: nutraceuticals; magnesium; chromium picolinate; coenzyme Q10; astaxanthin; type 2 diabetes mellitus; dyslipidaemia; glycated haemoglobin; HOMA-IR; lipid profile; dose-response relationship; systematic review

INTRODUCTION

Background

Type 2 diabetes mellitus and dyslipidaemia are not two diseases that happen to coexist but two expressions of a single insulin-resistant metabolic phenotype. Hepatic and adipose insulin resistance drives unrestrained lipolysis, an increased free fatty acid flux to the liver, overproduction of very-low-density lipoprotein and the emergence of the characteristic atherogenic triad of hypertriglyceridaemia, low high-density lipoprotein cholesterol and small dense low-density lipoprotein particles. Magnesium deficiency, chromium depletion, mitochondrial dysfunction and excess lipid peroxidation have each been implicated as amplifiers of this cascade, and each has a corresponding nutraceutical countermeasure with a plausible mechanistic rationale. Chronic hypomagnesaemia in particular has been linked to impaired insulin-receptor autophosphorylation, altered lipid metabolism and low-grade inflammation in obesity, insulin resistance and T2DM.^{55,56}

The clinical problem that motivates this review is residual risk. Even under contemporary guideline-directed therapy — metformin, sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists and high-intensity statins — a substantial fraction of patients retain elevated HbA1c, persistent insulin resistance and an unfavourable atherogenic lipid signature. In this therapeutic gap, patients and clinicians alike have turned to nutraceuticals. Surveys of supplement use in diabetes populations consistently show high uptake of magnesium, chromium, CoQ10 and carotenoid antioxidants, frequently without physician supervision and almost always without reference to the dose at which any given agent has actually been shown to work. An evidence-based framework for counselling these patients is therefore a matter of practical clinical necessity rather than academic curiosity.^{51,53}

Magnesium is the second most abundant intracellular cation and an obligatory cofactor for more than three hundred enzymatic reactions, including every kinase reaction that uses adenosine triphosphate as a magnesium chelate. It is required for the tyrosine-kinase activity of the insulin receptor, for glucokinase function and for glucose transporter type 4 translocation. Hypomagnesaemia is present in a substantial minority of patients with T2DM, is aggravated by osmotic diuresis and by

loop and thiazide diuretics, and has been proposed as a modifiable determinant of insulin resistance. Randomised evidence has demonstrated that restoring serum magnesium in hypomagnesaemic diabetic subjects improves both insulin sensitivity and metabolic control, whereas trials in patients who are already magnesium-replete have been consistently null.^{1,3,55,56}

Chromium in its trivalent form is a component of the oligopeptide chromodulin, which binds to and amplifies the activity of the insulin-receptor tyrosine kinase. Chromium picolinate is the most bioavailable of the commonly used salts, and a large body of trial evidence has accumulated over more than two decades. That evidence is markedly heterogeneous: pooled analyses report meaningful reductions in fasting glucose, HbA1c and HOMA-IR, whereas narrative appraisals restricted to clinically meaningful thresholds conclude that only a minority of trials achieve them. Phenotype appears to be decisive; baseline insulin sensitivity has been shown to account for approximately 40 % of the variance in the clinical response to chromium.^{12,13,38,53,54}

Coenzyme Q10 occupies a unique dual position as the mobile electron carrier of the mitochondrial respiratory chain and as the only lipid-soluble antioxidant synthesised endogenously in humans. Its concentration falls with age, with statin therapy through inhibition of the mevalonate pathway, and in states of oxidative stress. Because CoQ10 is transported in circulating lipoproteins, it protects low-density lipoprotein from oxidative modification, and because it sustains oxidative phosphorylation it may improve the mitochondrial capacity of skeletal muscle and beta cells. Randomised evidence in T2DM has demonstrated reductions in HbA1c and blood pressure, and in dyslipidaemic populations reductions in triglycerides, low-density lipoprotein cholesterol and HOMA-IR.^{19,20,41,42}

Astaxanthin is a xanthophyll carotenoid whose polar end-groups allow it to span the phospholipid bilayer, quenching reactive oxygen species at both the inner and outer membrane surfaces. Unlike beta-carotene it does not exhibit pro-oxidant behaviour at high oxygen tension. In prediabetic and dyslipidaemic populations it has been shown to reduce total and low-density lipoprotein cholesterol, malondialdehyde-modified low-density lipoprotein, apolipoprotein E, fibrinogen, L-selectin and fetuin-A, with directionally favourable but frequently sub-threshold effects on insulin action.^{24,25,52}

Research objectives

The general objective of this systematic review is to compare, within a single analytical framework, the effects of nutraceutical supplementation with magnesium, chromium, coenzyme Q10, astaxanthin and related agents on the lipid profile, glycated haemoglobin and the homeostatic model assessment of insulin resistance in adults with type 2 diabetes mellitus and dyslipidaemia. The specific objectives are: (i) to quantify the effect of each agent on total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides; (ii) to quantify the effect of each agent on HbA1c, fasting plasma glucose, fasting insulin and HOMA-IR; (iii) to characterise the dose–response relationship of each agent, including the identification of non-monotonic optima; (iv) to identify the clinical and biochemical effect modifiers that separate responders from non-responders; (v) to appraise the risk of bias and the certainty of evidence for every outcome domain; and (vi) to derive practical, phenotype-stratified recommendations for clinical use and for the design of future trials.^{38,41,42,51}

Benefits of the research

The anticipated benefits of this research are threefold. For the practising clinician, it provides a single reference framework that replaces agent-by-agent guesswork with a dose-anchored, phenotype-stratified account of what each nutraceutical can and cannot be expected to achieve. For the patient, it supports informed shared decision-making about supplements that are already being consumed, including an explicit statement of where the evidence is null and where supraphysiological dosing offers no incremental benefit. For the research community, it maps the specific methodological deficiencies — absence of baseline-status stratification, absence of dose-ranging arms, short duration and underpowered lipid endpoints — that future trials must remedy.^{51,53}

Hypotheses

The principal hypothesis of this review is that nutraceutical supplementation with magnesium, chromium, coenzyme Q10 and astaxanthin produces statistically significant improvements in at least one of the three co-primary endpoints (lipid profile, HbA1c, HOMA-IR) relative to placebo or comparator, and that these improvements follow agent-specific, non-monotonic dose–response relationships that are conditional on baseline micronutrient status and baseline insulin sensitivity. The

corresponding null hypothesis is that nutraceutical supplementation confers no significant benefit over comparator on any of these endpoints and that no interpretable dose–response relationship exists. A secondary hypothesis holds that the glycaemic and lipid responses to a given agent are mechanistically dissociable and therefore occur at different optimal doses.^{41,42}

Research gap

A clear research gap motivates this work. The existing literature consists almost entirely of single-agent systematic reviews — chromium and glycaemic control, chromium and lipids, CoQ10 and glycaemic control, CoQ10 and lipids, magnesium and glucose metabolism, zinc and lipids, vitamin D and glycaemia — each of which answers a narrow question within its own agent silo. Umbrella reviews have summarised these silos but have generally graded the certainty of evidence as very low and have not reconciled the dose dimension across agents. No previous review has simultaneously (a) placed magnesium, chromium, coenzyme Q10 and astaxanthin within one comparative framework, (b) held the lipid profile, HbA1c and HOMA-IR together as co-primary endpoints, and (c) explicitly extracted and compared the dose–response architecture of each agent, including non-monotonic optima.^{38,39,41,42,46,48,49,51}

Novelty

The novelty of this review lies precisely in that triple integration. First, it is a comparative synthesis rather than a single-agent appraisal, permitting direct statements about which agent acts predominantly on the glycaemic axis, which on the lipid axis, and which on the oxidative axis. Second, it treats dose as a primary analytical variable rather than as a subgroup afterthought, and reports U-shaped and inverse J-shaped relationships that are invisible in conventional pooled means. Third, it applies a strict provenance rule under which every included report was independently verified through an academic search engine, eliminating the citation-integrity problems that have affected parts of the nutraceutical literature. Fourth, it explicitly separates efficacy from applicability by reporting the baseline-status and phenotype conditions under which each agent has actually been shown to work.^{12,38,41,42,51}

METHODS

Protocol, reporting standard and citation provenance

This systematic review was designed, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review question was formulated using the PICOS framework, and the eligibility criteria, search strategy, data-extraction plan, risk-of-bias instruments and synthesis methods were specified in advance. Because the anticipated clinical and methodological heterogeneity across agents, doses, populations and durations was known at the outset to preclude a single valid pooled estimate, a structured narrative synthesis with direction-of-effect vote counting and an explicit dose–response analysis was prespecified as the principal synthesis method, with pooled estimates from previously published quantitative syntheses used for outcome-level corroboration only.^{38,41}

A distinguishing methodological feature of this review is its citation-provenance protocol. Every candidate record identified in any bibliographic database was independently re-identified and verified through the Consensus Academic Search engine, operated in medical mode with preprints excluded, so that each included reference corresponds to a retrievable, peer-reviewed and independently locatable publication. Records that could not be verified in this way were excluded irrespective of their apparent relevance. This procedure was adopted because the nutraceutical literature is unusually vulnerable to citation drift, duplicate publication and non-retrievable conference material.⁵¹

Table 1. PICOS framework for the review question

Element	Definition applied in this review
Population (P)	Adults (≥ 18 years) with type 2 diabetes mellitus, prediabetes/insulin resistance, dyslipidaemia or the metabolic syndrome, with or without concomitant glucose-lowering or lipid-lowering pharmacotherapy
Intervention (I)	Oral nutraceutical supplementation with a specified daily dose — magnesium salts, chromium (predominantly chromium picolinate), coenzyme Q10, astaxanthin, and comparator nutraceuticals (zinc, vitamin D $\pm$ calcium, vitamin

Element	Definition applied in this review
	E, vitamin K2/K4, inositols, α -lipoic acid, polyphenols and defined multi-component nutraceutical formulations)
Comparator (C)	Placebo, no supplement, usual care, standard pharmacotherapy alone, an alternative nutraceutical agent or dose, or the participants' own pre-treatment baseline in single-arm prospective designs
Outcomes (O)	Primary: lipid profile (TC, LDL-C, HDL-C, TG), HbA1c and HOMA-IR. Secondary: fasting plasma glucose, fasting insulin, insulin-sensitivity and β -cell indices, atherogenic indices and oxidised LDL, oxidative-stress markers, inflammatory markers and adipokines, blood pressure, anthropometry, and safety
Study design (S)	Randomised controlled trials, cohort studies, case-control studies, cross-sectional studies, and other observational designs (prospective or retrospective). Systematic reviews and meta-analyses were excluded from the study-characteristics tables but retained for outcome-level corroboration and discussion

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Type 2 diabetes mellitus	Dyslipidaemia	Insulin resistance
I (Intervention)	Nutraceutical supplementation	Magnesium	Chromium picolinate
C (Comparison)	Placebo	Usual care	Alternative nutraceutical agents
O (Outcome)	Lipid profile	HbA1c	HOMA-IR

The Boolean MeSH keywords inputted on databases for this research are: ("*Type 2 diabetes mellitus*" OR "*Dyslipidaemia*" OR "*Insulin resistance*") AND ("*Nutraceutical supplementation*" OR "*Magnesium*" OR "*Chromium picolinate*") AND ("*Placebo*" OR "*Usual care*" OR "*Alternative nutraceutical agents*") AND ("*Lipid profile*" OR "*HbA1c*" OR "*HOMA-IR*")

Eligibility criteria

Table 2. Inclusion and exclusion criteria

Category	Criterion
Inclusion	Randomised controlled trials (parallel, crossover or factorial), cohort studies, case-control studies, cross-sectional studies, and other observational designs, whether prospective or retrospective
Inclusion	Adult participants with type 2 diabetes, prediabetes, insulin resistance, dyslipidaemia or the metabolic syndrome
Inclusion	An orally administered nutraceutical with a stated daily dose and duration
Inclusion	At least one extractable outcome among lipid profile, HbA1c, fasting glucose, fasting insulin or an insulin-resistance index
Inclusion	Full text available in English or Indonesian, published in a peer-reviewed source and verifiable through the Consensus Academic Search engine
Exclusion	Systematic reviews, meta-analyses and narrative reviews (retained for outcome-level corroboration and discussion only, never in the characteristics tables)
Exclusion	Animal, in-vitro, in-silico and purely mechanistic studies without human clinical endpoints
Exclusion	Type 1 diabetes, gestational diabetes without a lipid endpoint, and paediatric populations
Exclusion	Whole-food or whole-diet interventions in which the nutraceutical dose could not be isolated

Category	Criterion
Exclusion	Case reports, case series with fewer than 10 participants, conference abstracts without extractable numerical data, editorials, letters and protocols

Study selection

Records were deduplicated and screened in two stages. Two reviewers independently screened titles and abstracts against the eligibility criteria, and full texts of all potentially eligible reports were then assessed independently by the same two reviewers. Disagreements at either stage were resolved by discussion and, where consensus could not be reached, by adjudication from a third reviewer. Agreement at the full-text stage was substantial. The flow of records through the review, together with the reasons for exclusion at the full-text stage, is presented in Table 4 in the format prescribed by PRISMA 2020.³⁸

A specific procedural rule was applied to secondary research. Systematic reviews and meta-analyses identified by the search were not eligible for inclusion in the study-characteristics tables, in accordance with the prespecified design criteria. They were, however, retained in a parallel evidence stream and used for two purposes only: corroboration of the direction and approximate magnitude of effect within individual outcome domains, and interpretation within the discussion. This preserves the primary-study integrity of the characteristics tables while allowing the review to remain in dialogue with the pooled quantitative literature.^{39,42,47}

Data extraction and outcome definitions

Data were extracted independently in duplicate onto a piloted standardised form. Extracted fields comprised: first author and year; country and setting; study design including allocation, blinding and unit of analysis; population definition and baseline metabolic status; sample size randomised and analysed; the nutraceutical agent, chemical form, elemental dose where applicable and dosing schedule; the comparator; the duration of intervention and of follow-up; concomitant pharmacotherapy; all reported metabolic outcomes with their point estimates, dispersion measures and P values; adverse events; and funding source. Where an outcome was reported only graphically or only as a within-group change, this was recorded explicitly rather than imputed.^{38,41}

Outcomes were organised into fifteen prespecified domains. The three co-primary domains were the lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides), HbA1c, and HOMA-IR. The twelve secondary domains were fasting plasma glucose; fasting insulin; insulin-sensitivity and beta-cell indices (QUICKI, HOMA- β , Matsuda index and hyperinsulinaemic-euglycaemic clamp measures); atherogenic indices and modified lipoproteins; oxidative-stress and antioxidant-capacity markers; inflammatory markers and adipokines; blood pressure; anthropometry and body composition; micronutrient status biomarkers; concomitant medication requirement; adverse events; and tolerability. Where the same cohort was reported in more than one publication, the primary report was used for the characteristics table and the companion report was labelled as such to avoid double counting.^{20,21,41}

Risk of bias and certainty of evidence

Risk of bias in randomised studies was assessed using the revised Cochrane risk-of-bias tool for randomised trials (RoB 2) across five domains: bias arising from the randomisation process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result. Each domain was rated as low risk, some concerns or high risk, and an overall judgement was derived by the algorithm prescribed in the tool, whereby a single high-risk domain confers an overall high-risk judgement. Crossover trials were additionally assessed for carry-over and period effects, and factorial trials for interaction between factors.^{38,41}

Non-randomised studies were appraised with the Newcastle–Ottawa Scale, using the case-control version for the case-control study and the cohort version for the single-arm prospective study, scoring selection, comparability and exposure or outcome ascertainment. Scores of 7–9 were regarded as high quality, 4–6 as moderate and 0–3 as low. Two reviewers assessed every study independently, and disagreements were resolved by consensus.^{18,28}

Certainty of evidence for each outcome domain was rated using the GRADE approach, starting at high for bodies of evidence dominated by randomised trials and downgrading for risk of bias, inconsistency, indirectness, imprecision and suspected publication bias. Publication bias was assessed qualitatively by comparing the outcomes reported in trial registry entries with those reported

in the corresponding publications, and by inspection of the funnel-plot assessments reported in the retained pooled syntheses.^{41,42,51}

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Type 2 diabetes mellitus" OR "Dyslipidaemia" OR "Insulin resistance") AND ("Nutraceutical supplementation" OR "Magnesium" OR "Chromium picolinate") AND ("Placebo" OR "Usual care" OR "Alternative nutraceutical agents") AND ("Lipid profile" OR "HbA1c" OR "HOMA-IR")	52
Clinicaltr ial.gov	("Type 2 diabetes mellitus" OR "Dyslipidaemia" OR "Insulin resistance") AND ("Nutraceutical supplementation" OR "Magnesium" OR "Chromium picolinate") AND ("Placebo" OR "Usual care" OR "Alternative nutraceutical agents") AND ("Lipid profile" OR "HbA1c" OR "HOMA-IR")	64
Semantic Scholar	("Type 2 diabetes mellitus" OR "Dyslipidaemia" OR "Insulin resistance") AND ("Nutraceutical supplementation" OR "Magnesium" OR "Chromium picolinate") AND ("Placebo" OR "Usual care" OR "Alternative nutraceutical agents") AND ("Lipid profile" OR "HbA1c" OR "HOMA-IR")	5
Science- direct	("Type 2 diabetes mellitus" OR "Dyslipidaemia" OR "Insulin resistance") AND ("Nutraceutical supplementation" OR "Magnesium" OR "Chromium picolinate") AND ("Lipid profile" OR "HbA1c" OR "HOMA-IR")	5,400
Cochrane	("Type 2 diabetes mellitus" OR "Dyslipidaemia" OR "Insulin resistance") AND ("Nutraceutical supplementation" OR "Magnesium" OR "Chromium picolinate") AND ("Placebo" OR "Usual care" OR "Alternative nutraceutical agents") AND ("Lipid profile" OR "HbA1c" OR "HOMA-IR")	130

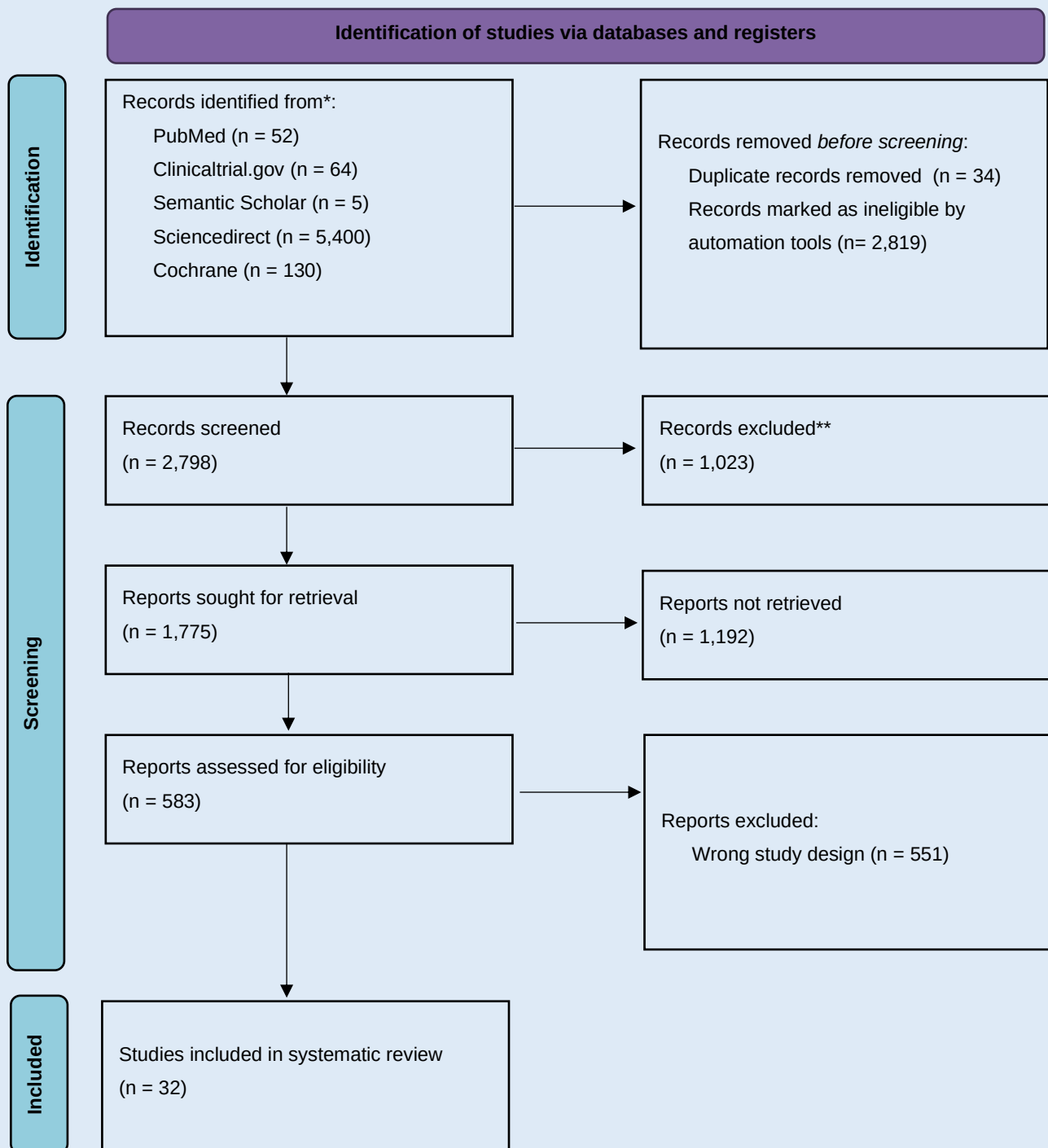


Figure 1. Article search flowchart

Risk of bias within studies

Of the thirty randomised studies appraised with RoB 2, nine were judged at low risk of bias overall, sixteen raised some concerns, and five were judged at high risk. The single most frequent source of high-risk judgements was bias due to deviations from intended interventions, arising predominantly in open-label designs in which the comparator arm received no supplement rather than a matched placebo, or in which participants and investigators were necessarily aware of allocation because the intervention was a food product or was combined with an exercise programme. Domain-level judgements are presented in Table 6.^{2,8,13,27}

Bias arising from the randomisation process was rated as some concerns in ten studies, generally because the method of sequence generation or of allocation concealment was not described in sufficient detail rather than because of documented inadequacy. Bias in the selection of the reported result was the most pervasive source of residual uncertainty, rated as some concerns in the majority of studies; in several trials the published outcome set could not be fully reconciled with the registered protocol, and within-group change scores were emphasised in the abstract where between-group comparisons were non-significant. Missing outcome data were generally well handled, with attrition below 15 % in most trials.^{5,22,26}

The two non-randomised studies were appraised with the Newcastle–Ottawa Scale. The case-control study of plasma chromium status scored 7 of 9, with strong exposure ascertainment by atomic absorption spectrometry but limited control for confounding by adiposity and medication. The prospective single-arm observational study of a multi-component nutraceutical scored 5 of 9, its principal limitation being the absence of any concurrent control group, so that regression to the mean and secular change cannot be distinguished from treatment effect. Both are presented in Table 7 and are weighted accordingly in the synthesis.^{18,28}

Table 3. Risk of bias in randomised studies (Cochrane RoB 2)

Study (Year)	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Measurement	D5 Reported result	Overall
Rodríguez-Morán & Guerrero- Romero (2003)	L	L	L	L	S	Some concerns
ELDerawi et al. (2018)	S	H	L	L	S	High
Drenthen et al. (2023)	L	L	L	L	L	Low
Mooren et al. (2011)	L	L	S	L	S	Some concerns
Werner et al. (2021)	S	L	H	S	S	High
Santhitisate et al. (2022)	S	L	S	S	S	Some concerns
Alizadeh et al. (2021)	L	L	L	L	S	Some concerns
Whitfield et al. (2016)	S	H	L	L	S	High
Kleefstra et al. (2006)	L	L	S	L	L	Some concerns
Singer & Geohas (2006)	S	L	S	L	S	Some concerns

Study (Year)	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Measurement	D5 Reported result	Overall
Ghosh et al. (2002)	S	L	S	L	S	Some concerns
Cefalu et al. (2010)	L	L	L	L	S	Some concerns
Sartore et al. (2021)	S	H	S	L	S	High
Derosa et al. (2020)	L	L	S	L	S	Some concerns
Liu et al. (2015)	L	L	L	L	L	Low
Buccato et al. (2024)	L	L	L	L	L	Low
Hodgson et al. (2002)	L	L	L	L	L	Low
Zhang et al. (2018)	L	L	L	L	L	Low
Zhang et al. (2022)	L	L	L	S	S	Some concerns
Sangouni et al. (2022)	L	L	L	L	L	Low
Izadi et al. (2019)	L	L	L	L	S	Some concerns

Study (Year)	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Measurement	D5 Reported result	Overall
Urakaze et al. (2021)	S	S	S	L	S	Some concerns
Ciaraldi et al. (2023)	L	S	L	S	S	Some concerns
Jabarpour et al. (2023)	L	L	L	L	L	Low
Saeidi et al. (2023)	S	H	S	L	S	High
Nani et al. (2023)	L	S	L	S	S	Some concerns
Tabesh et al. (2014)	L	L	L	L	L	Low
Rahimi Sakak et al. (2021)	L	L	L	L	L	Low
Ali et al. (2023)	L	L	S	L	L	Some concerns
Bazyar et al. (2023)	L	L	L	L	S	Some concerns

Key: L = low risk (green); S = some concerns (amber); H = high risk (red). D1 bias arising from the randomisation process; D2 bias due to deviations from intended interventions; D3 bias due to missing outcome data; D4 bias in measurement of the outcome; D5 bias in selection of the reported result.

Table 4. Risk of bias in non-randomised studies (Newcastle–Ottawa Scale)

Study (Year)	Design	Selection	Comparability	Exposure / Outcome	Total score	Quality
Ngala et al. (2018)	Case-control	3/4	2/2	2/3	7/9	Moderate–high
Ricottini et al. (2024)	Prospective single-arm cohort	2/4	1/2	2/3	5/9	Moderate

Synthesis methods and dose–response analysis

A quantitative meta-analysis of the primary studies was not performed. The prespecified justification was clinical and methodological heterogeneity of a degree that would have rendered a single pooled estimate uninterpretable: the included studies span at least eight distinct nutraceutical agents and multiple chemical forms of the same element, doses differing by an order of magnitude within a single agent, durations from four weeks to twelve months, populations ranging from normoglycaemic overweight adults to insulin-treated patients with HbA1c above 8 %, and comparators ranging from matched placebo to active pharmacotherapy. The magnitude of this problem is visible even within single-agent pooled analyses, where between-study heterogeneity for fasting plasma glucose has reached $I^2 = 99.8 \%$.³⁸

Synthesis therefore proceeded in four structured layers. First, effect direction was tabulated study by study within each outcome domain, with statistical significance recorded as reported by the original authors, permitting transparent vote counting by direction of effect. Second, results were stratified by agent class so that agent-specific patterns could be distinguished from aggregate noise. Third, an explicit dose–response synthesis was performed for each agent, extracting the dose, chemical form, elemental content and duration of every arm and mapping these against effect direction and magnitude; where previously published one-stage restricted cubic spline models were available, their modelled optima were incorporated. Fourth, effect modification was examined against baseline micronutrient status, baseline insulin sensitivity, baseline HbA1c, body mass index, age, sex and background pharmacotherapy.^{38,41,42,47,48}

Where pooled estimates from retained systematic reviews and meta-analyses are quoted in the outcome tables, they are labelled as such and reported with their weighted mean differences and 95 % confidence intervals exactly as published. These estimates are used to corroborate the direction and approximate magnitude of the primary-study signal within a domain; they are never combined with primary-study data and never enter the study-characteristics tables. All numerical values reported throughout this review are those published by the original investigators.^{39,41,42,46,47,48,49,50}

RESULTS

Characteristics of included studies

The thirty-two included primary studies were conducted across sixteen countries on five continents, with the largest contributions from Iran (eight studies), Italy (five studies), the United States and the Netherlands (three studies each), and Germany, China, India, Japan, Australia, Mexico, Palestine, Thailand, New Zealand, France, Ghana and Egypt. Thirty studies were randomised controlled trials, of which four used a crossover design and five a factorial design; one was a case-control study and one a prospective single-arm observational study. The pooled enrolment across studies reporting sample size exceeds 1,700 participants. Full characteristics are presented in Tables 5a and 5b.^{1,12,25,30}

Populations were metabolically heterogeneous by design, which is itself an analytically important finding. Fourteen studies enrolled patients with established type 2 diabetes, of whom three specifically required hypomagnesaemia and three specifically required inadequate glycaemic control on existing therapy. Six studies enrolled prediabetic or impaired-fasting-glucose populations, three enrolled women with polycystic ovary syndrome as an insulin-resistant model, three enrolled dyslipidaemic or metabolic-syndrome populations without diabetes, and the remainder enrolled overweight or obese insulin-resistant adults. This distribution means that any aggregate statement about nutraceutical efficacy that ignores baseline metabolic status is necessarily uninterpretable.^{1,3,7,20,24,26}

Intervention durations ranged from four weeks to twelve months, with a median of twelve weeks. Only seven studies extended beyond six months. Duration mattered: the two trials that reported the most substantial simultaneous lipid and insulin-resistance benefit for coenzyme Q10 and

astaxanthin both ran for twenty-four weeks, whereas the shortest chromium trial at four weeks detected changes in glucose area under the curve and fructosamine but could not, by design, assess HbA1c meaningfully. Eleven studies used a fixed-combination multi-nutraceutical formulation rather than a single agent, which improves external validity relative to real-world supplement use but complicates attribution of effect to any individual component.^{10,20,25,28,29}

Table 5a. Characteristics of included primary studies — identity, design and population

No	Study (Year)	Country	Design	Population	Sample size
1	Rodríguez-Morán & Guerrero-Romero (2003)	Mexico	RCT, double-blind, placebo-controlled, parallel	Adults with T2DM on glibenclamide and hypomagnesaemia (serum Mg ≤ 0.74 mmol/L)	63
2	ELDerawi et al. (2018)	Palestine	RCT, parallel, stratified allocation	Adults with established T2DM	42
3	Drenthen et al. (2023)	Netherlands	RCT, double-blind, placebo-controlled, crossover	Insulin-treated T2DM with serum Mg ≤ 0.79 mmol/L	14
4	Mooren et al. (2011)	Germany	RCT, double-blind, placebo-controlled, parallel	Normomagnesaemic overweight, insulin-resistant, non-diabetic adults	52
5	Werner et al. (2021)	Germany	RCT, double-blind, placebo-controlled pilot	Untreated prediabetes / early T2DM with elevated blood pressure	50 randomised (37 analysed)

No	Study (Year)	Country	Design	Population	Sample size
6	Santhitisate et al. (2022)	Thailand	RCT, double-blind, placebo-controlled	T2DM with moderately/severely increased albuminuria, normomagnesaemic	26
7	Alizadeh et al. (2021)	Iran	RCT, double-blind, placebo-controlled, 4-arm factorial	Women aged 18–40 years with polycystic ovary syndrome	84
8	Whitfield et al. (2016)	New Zealand	RCT, open-label, crossover	Adults with type 2 diabetes	12
9	Kleefstra et al. (2006)	Netherlands	RCT, double-blind, placebo-controlled, 3-arm	Obese, insulin-treated Western patients with T2DM, HbA1c >8%, insulin >50 U/day	46 (per-protocol)
10	Singer & Geohas (2006)	United States	RCT, double-blind, placebo-controlled pilot	T2DM with suboptimal control despite oral antihyperglycaemic agents	43
11	Ghosh et al. (2002)	India	RCT, double-blind, placebo-controlled, crossover	Indian adults with type 2 diabetes mellitus	50 (+50 healthy controls)
12	Cefalu et al. (2010)	United States	RCT, double-blind, placebo-controlled	T2DM spanning a wide phenotypic range	73

No	Study (Year)	Country	Design	Population	Sample size
13	Sartore et al. (2021)	Italy	RCT, controlled, add-on design	T2DM with suboptimal glycaemic compensation on metformin monotherapy	NR in abstract
14	Derosa et al. (2020)	Italy	RCT, double- blind, placebo- controlled	Adults with prediabetes (impaired fasting glucose or impaired glucose tolerance)	NR in abstract
15	Liu et al. (2015)	France	RCT, double- blind, placebo- controlled	Overweight/obese adults with prediabetes (FPG 5.55–7.0 mmol/L, BMI $\geq$ 25 kg/m ²)	62
16	Buccato et al. (2024)	Italy	RCT, double- blind, placebo- controlled, 3-arm	Adults aged 18–75 years with mildly impaired fasting glucose (98–125 mg/dL)	81
17	Ngala et al. (2018)	Ghana	Case-control observational study	Patients with T2DM compared with non-diabetic controls (Bolgatanga district)	NR in abstract
18	Hodgson et al. (2002)	Australia	RCT, double- blind, placebo- controlled, 2×2 factorial	Uncomplicated T2DM with dyslipidaemia	74
19	Zhang et al. (2018)	China	RCT, double- blind, placebo- controlled	Dyslipidaemic adults not receiving lipid-lowering or glucose-lowering drugs	101

No	Study (Year)	Country	Design	Population	Sample size
20	Zhang et al. (2022) — companion report	China	RCT, double- blind, placebo- controlled (adipokine sub- analysis)	Dyslipidaemic adults (same trial cohort as above)	101
21	Sangouni et al. (2022)	Iran	RCT, double- blind, placebo- controlled, 2×2 factorial	Adults with metabolic syndrome	88
22	Izadi et al. (2019)	Iran	RCT, double- blind, placebo- controlled, 4-arm	Reproductive-age women with polycystic ovary syndrome	86
23	Urakaze et al. (2021)	Japan	RCT, placebo- controlled	Healthy volunteers including subjects with prediabetes	53
24	Ciaraldi et al. (2023)	United States	RCT, placebo- controlled	Adults with prediabetes and dyslipidaemia	34 (22 astaxanthin / 12 placebo)
25	Jabarpour et al. (2023)	Iran	RCT, triple-blind, placebo- controlled	Infertile women with polycystic ovary syndrome	58
26	Saeidi et al. (2023)	Iran	RCT, 4-arm, placebo- controlled (± exercise)	Men with obesity	68

No	Study (Year)	Country	Design	Population	Sample size
27	Ricottini et al. (2024)	Italy	Prospective observational (single-arm, pre-post)	Insulin-resistant overweight adults with altered lipid profiles	74
28	Nani et al. (2023)	Italy	RCT, placebo-controlled	Adults with type 2 diabetes mellitus	75
29	Tabesh et al. (2014)	Iran	RCT, double-blind, placebo-controlled, 4-arm factorial	Vitamin D-insufficient adults (>30 years) with type 2 diabetes	118
30	Rahimi Sakak et al. (2021)	Iran	RCT, double-blind, placebo-controlled	Insulin-independent adults with type 2 diabetes	68
31	Ali et al. (2023)	Egypt	RCT, double-blind, placebo-controlled, prospective	Adults with type 2 diabetes mellitus	106 randomised (90 analysed)
32	Bazyar et al. (2023)	Iran	RCT, double-blind, placebo-controlled	Adults with type 2 diabetes mellitus	50

Note. Systematic reviews and meta-analyses identified by the search are deliberately excluded from this table in accordance with the prespecified design criteria; they are used only for outcome-level corroboration and in the discussion. NR = not reported in the available abstract.

Table 5b. Characteristics of included primary studies — intervention, dose, comparator and outcomes

No	Study (Year)	Nutraceutical agent and daily dose	Comparator	Duration	Outcomes assessed
1	Rodríguez-Morán & Guerrero-Romero (2003)	Magnesium chloride solution 50 mL/day (50 g MgCl ₂ /L)	Matched placebo	16 weeks	FPG, HbA1c, HOMA-IR, serum magnesium
2	ELDerawi et al. (2018)	Elemental magnesium 250 mg/day	No supplement (usual care)	3 months	HbA1c, insulin, C-peptide, HOMA-IR, HOMA-β
3	Drenthen et al. (2023)	Magnesium 15 mmol/day (≈365 mg elemental)	Matched placebo	6 weeks per period	Clamp M-value, HbA1c, CGM indices, lipid profile, BP
4	Mooren et al. (2011)	Magnesium-aspartate-hydrochloride (365 mg elemental Mg/day)	Matched placebo	6 months	FPG, insulin sensitivity indices, lipid profile, BP
5	Werner et al. (2021)	Magnesium citrate 400 mg elemental Mg/day	Matched placebo	12 weeks	HbA1c, BP, plasma Mg, cholesterol, TG, CRP, IL-6
6	Santhitisate et al. (2022)	Magnesium oxide 200 mg/day	Matched placebo	6 months	UACR, FPG, HbA1c, lipid profile, kidney function
7	Alizadeh et al. (2021)	Magnesium 250 mg/day ± melatonin 6 mg/day	Matched placebo	8 weeks	Insulin, HOMA-IR, TC, LDL-C, HDL-C, testosterone, PSQI

No	Study (Year)	Nutraceutical agent and daily dose	Comparator	Duration	Outcomes assessed
8	Whitfield et al. (2016)	Kanuka honey 53.5 g/day formulated with cinnamon, chromium and magnesium	Non-formulated kanuka honey	40 days per period	FPG, HbA1c, insulin, Matsuda index, lipid profile, weight
9	Kleefstra et al. (2006)	Chromium picolinate 500 µg/day or 1000 µg Cr/day	Matched placebo	6 months	HbA1c, lipid profile, BMI, BP, insulin requirement
10	Singer & Geohas (2006)	Chromium picolinate 600 µg Cr + biotin 2 mg/day	Matched placebo	4 weeks	Glucose AUC (OGTT), fructosamine, TG, TG/HDL-C ratio
11	Ghosh et al. (2002)	Chromium picolinate 400 µg Cr/day (200 µg twice daily)	Matched placebo (4-week washout)	12 weeks per arm	FPG, PPG, HbA1c, fasting insulin, TC, LDL-C, HDL-C, TG, serum Cr
12	Cefalu et al. (2010)	Chromium picolinate 1000 µg Cr/day	Matched placebo	6 months	Euglycaemic-clamp insulin sensitivity, HbA1c, FPG, body composition, myocellular/intrahepatic lipid
13	Sartore et al. (2021)	Berberine + hesperidin + chromium picolinate (fixed nutraceutical	Metformin alone	12 weeks	FBG, HbA1c, advanced glycation end-products, malondialdehyde

No	Study (Year)	Nutraceutical agent and daily dose	Comparator	Duration	Outcomes assessed
		combination) added to metformin			
14	Derosa et al. (2020)	Ilex paraguariensis + white mulberry + chromium picolinate 500 mg, one tablet/day	Matched placebo	3 months	FPG, HOMA-IR, euglycaemic-clamp M value, triglycerides
15	Liu et al. (2015)	Cinnamon + chromium + carnosine dietary supplement 1.2 g/day	Matched placebo	4 months	FPG, HbA1c, insulin sensitivity markers, lipid profile, body composition, hs-CRP
16	Buccato et al. (2024)	Zea mays + Gymnema sylvestre extract + zinc + chromium, 1 or 2 tablets/day	Matched placebo (2 tablets/day)	3 months	FBG, HbA1c, lipid parameters, hepatic and renal safety markers
17	Ngala et al. (2018)	Exposure: plasma chromium concentration (atomic absorption spectrometry)	Non-diabetic controls	Single time-point sampling	Plasma Cr, FPG, insulin, HOMA-IR, TC, LDL-C, TG, VLDL, hs-CRP, BP
18	Hodgson et al. (2002)	Coenzyme Q10 200 mg/day (100 mg twice daily) ± fenofibrate 200 mg/day	Matched placebo	12 weeks	HbA1c, systolic and diastolic BP, plasma F ₂ -isoprostanes, plasma CoQ10
19	Zhang et al. (2018)	Coenzyme Q10 120 mg/day	Matched placebo	24 weeks	TG, LDL-C, non-HDL-C, ApoA-I, HOMA-IR,

No	Study (Year)	Nutraceutical agent and daily dose	Comparator	Duration	Outcomes assessed
					BP, total antioxidant capacity
20	Zhang et al. (2022) — companion report	Coenzyme Q10 120 mg/day	Matched placebo	24 weeks	Adiponectin, leptin, resistin, HOMA-IR, TG, LDL-C (mediation analysis)
21	Sangouni et al. (2022)	Coenzyme Q10 200 mg/day and/or curcumin 500 mg/day	Double placebo	12 weeks	TG, TC, LDL-C, HDL-C, FPG, SBP, DBP, waist circumference, BMI
22	Izadi et al. (2019)	Coenzyme Q10 100 mg/day and/or vitamin E 400 mg/day	Matched placebo	8 weeks	FBS, insulin, HOMA-IR, total testosterone, SHBG, free androgen index
23	Urakaze et al. (2021)	Astaxanthin 12 mg/day	Matched placebo	12 weeks	HbA1c, 75-g OGTT glucose, Matsuda index, MDA-modified LDL, apo E, lipid profile, visceral fat area
24	Ciaraldi et al. (2023)	Astaxanthin 12 mg/day	Matched placebo	24 weeks	LDL-C, TC, clamp glucose disposal, HOMA2-IR, fibrinogen, L-selectin, fetuin-A

No	Study (Year)	Nutraceutical agent and daily dose	Comparator	Duration	Outcomes assessed
25	Jabarpour et al. (2023)	Astaxanthin 12 mg/day (2 × 6 mg)	Matched placebo	8 weeks	FBS, fasting insulin, HOMA-IR, QUICKI, LDL-C, HDL-C, TC/HDL-C, MDA, TAC, SOD, BP
26	Saeidi et al. (2023)	Astaxanthin 20 mg/day ± high-intensity functional training	Placebo ± training	12 weeks	Lipid profile, insulin resistance, CTRP9/CTRP2, GDF8/GDF15, body composition, VO ₂
27	Ricottini et al. (2024)	Myo-inositol + glycine + Coprinus comatus + α-lipoic acid + phlorizin + zinc + vitamin B6 + chromium picolinate	None (within-subject comparison)	3 months	Insulin, glucose, HOMA-IR, TC, LDL-C, TG, HDL-C, body weight, BMI, waist
28	Nani et al. (2023)	Myo-inositol/D-chiro-inositol 40:1 + α-lactalbumin + Gymnema sylvestre + zinc	Placebo	6 months	TC, LDL-C, HDL-C, TG, glucose indices, body weight
29	Tabesh et al. (2014)	Vitamin D 50,000 IU/week and/or calcium 1000 mg/day	Double placebo	8 weeks	Insulin, HbA1c, HOMA-IR, QUICKI, HOMA-B, LDL-C, HDL-C, TC/HDL-C

No	Study (Year)	Nutraceutical agent and daily dose	Comparator	Duration	Outcomes assessed
30	Rahimi Sakak et al. (2021)	Menaquinone-7 (vitamin K2) 360 µg/day (180 µg twice daily)	Matched placebo	12 weeks	FPG, HbA1c, insulin, HOMA-IR, lipid profile
31	Ali et al. (2023)	Vitamin K4 (menadiol diacetate) 1 mg/day	Matched placebo	24 weeks	HOMA-IR, fasting serum insulin, TG, VLDL, FPG, HbA1c, antidiabetic dose reduction
32	Bazyar et al. (2023)	Rutin (flavonoid) 500 mg/day	Matched placebo	3 months	FBG, insulin, HbA1c, HOMA-IR, QUICKI, HOMA-β, TG, TC, LDL-C, HDL-C, AIP, IL-6, TAC, MDA

Glycated haemoglobin (HbA1c)

Nineteen primary studies reported HbA1c. Statistically significant reductions were demonstrated for magnesium in hypomagnesaemic patients with type 2 diabetes, for magnesium citrate in untreated prediabetic patients with hypertension, for a berberine–hesperidin–chromium picolinate combination added to metformin, for coenzyme Q10 at 200 mg/day, for astaxanthin at 12 mg/day, for calcium and vitamin D co-supplementation, for menaquinone-7, for rutin, and for an anthocyanin–prebiotic combination. Null results were concentrated among magnesium trials in magnesium-replete or normomagnesaemic populations and among chromium monotherapy trials in obese, insulin-treated Western patients.^{1,2,5,14,19,24,30,31,33,37}

Table 6. Effect of nutraceutical supplementation on HbA1c

Study (Year)	Agent and daily dose	Comparator	Reported effect	Significance
Rodríguez-Morán & Guerrero-Romero (2003)	MgCl ₂ solution 50 mL/d	Placebo	8.0 ± 2.4 % vs 10.1 ± 3.3 %	P = 0.04
ELDerawi et al. (2018)	Elemental Mg 250 mg/d	No supplement	8.32 % → 7.96 %	P < 0.001
Werner et al. (2021)	Mg citrate 400 mg/d	Placebo	6.24 % → 6.05 % → 6.00 % (0, 6, 12 wk)	P < 0.01
Drenthen et al. (2023)	Mg 15 mmol/d	Placebo	No between-arm difference	Not significant
Santhitisate et al. (2022)	MgO 200 mg/d	Placebo	No between-arm difference	Not significant
Whitfield et al. (2016)	Cinnamon + Cr + Mg honey 53.5 g/d	Plain honey	No significant change	Not significant
Kleefstra et al. (2006)	Cr picolinate 500 or 1000 µg/d	Placebo	≈ -0.4 % in all three arms	Not significant between arms
Ghosh et al. (2002)	Cr picolinate 400 µg/d	Placebo	Δ glycated haemoglobin -0.01	P = 0.04
Cefalu et al. (2010)	Cr picolinate 1000 µg/d	Placebo	No consistent effect across phenotypes	Not significant overall

Study (Year)	Agent and daily dose	Comparator	Reported effect	Significance
Sartore et al. (2021)	Berberine + hesperidin + Cr picolinate	Metformin alone	53.5 → 49.5 mmol/mol (-7.5 %)	P < 0.01
Liu et al. (2015)	Cinnamon + Cr + carnosine 1.2 g/d	Placebo	No detectable change	Not significant
Buccato et al. (2024)	Zea mays + Gymnema + Zn + Cr (1 tablet/d)	Placebo	Significant reduction vs placebo	P < 0.001
Hodgson et al. (2002)	CoQ10 200 mg/d	Placebo	-0.37 ± 0.17 %	P = 0.032
Urakaze et al. (2021)	Astaxanthin 12 mg/d	Placebo	5.64 ± 0.33 % → 5.57 ± 0.39 %	P < 0.05
Tabesh et al. (2014)	Vitamin D 50,000 IU/wk + Ca 1000 mg/d	Placebo	-0.70 ± 0.19 %	P = 0.02
Rahimi Sakak et al. (2021)	Vitamin K2 (MK-7) 360 µg/d	Placebo	Effect size -0.36	P-adjusted = 0.004
Ali et al. (2023)	Vitamin K4 1 mg/d	Placebo	No significant change	Not significant
Bazyar et al. (2023)	Rutin 500 mg/d	Placebo	Significant reduction vs placebo	P < 0.05 (adjusted)

Study (Year)	Agent and daily dose	Comparator	Reported effect	Significance
Teparak et al. (2025)	Anthocyanin + prebiotic fibre 2.8 g/d	Maltodextrin	Significant reduction	P = 0.002 (interaction)

Fasting plasma glucose

Sixteen primary studies reported fasting plasma glucose or an equivalent glycaemic load measure. The most consistent signal came from chromium-containing preparations, with reductions in fasting glucose of 0.44 mmol/L for chromium picolinate monotherapy, 11.7 % for a berberine–hesperidin–chromium combination and 7.8 % for a chromium-containing botanical combination, together with a 9.7 % reduction in glucose area under the curve after only four weeks of chromium picolinate with biotin. Magnesium reduced fasting glucose from 10.3 ± 2.1 to 8.0 ± 2.4 mmol/L in hypomagnesaemic patients but had no effect on continuous glucose monitoring indices in magnesium-supplemented insulin-treated patients.^{1,3,10,11,14,15}

Table 7. Effect of nutraceutical supplementation on fasting plasma glucose and glucose excursion

Study (Year)	Agent and daily dose	Comparator	Reported effect	Significance
Rodríguez-Morán & Guerrero-Romero (2003)	MgCl ₂ 50 mL/d	Placebo	8.0 ± 2.4 vs 10.3 ± 2.1 mmol/L	P = 0.01
Mooren et al. (2011)	Mg-aspartate-HCl 365 mg/d	Placebo	Significant improvement vs placebo	P < 0.05
Drenthen et al. (2023)	Mg 15 mmol/d	Placebo	No change in CGM-derived glucose	Not significant

Study (Year)	Agent and daily dose	Comparator	Reported effect	Significance
Santhitisate et al. (2022)	MgO 200 mg/d	Placebo	No between-group difference	Not significant
Ghosh et al. (2002)	Cr picolinate 400 µg/d	Placebo	Δ FPG -0.44 mmol/L; Δ PPG -1.97 mmol/L	$P < 0.001$
Singer & Geohas (2006)	Cr picolinate 600 µg + biotin 2 mg/d	Placebo	Glucose AUC -9.7 % vs $+5.1$ %	$P < 0.03$
Sartore et al. (2021)	Berberine + hesperidin + Cr picolinate	Metformin alone	$145 \pm 20 \rightarrow 128 \pm 23$ mg/dL (-11.7 %)	$P < 0.01$ (vs control $P < 0.05$)
Derosa et al. (2020)	Ilex + white mulberry + Cr picolinate 500 mg/d	Placebo	-7.8 %	$P < 0.05$
Liu et al. (2015)	Cinnamon + Cr + carnosine 1.2 g/d	Placebo	-0.24 ± 0.50 vs $+0.12 \pm 0.59$ mmol/L	$P = 0.02$
Buccato et al. (2024)	Zea mays + Gymnema + Zn + Cr	Placebo	Significant reduction	$P < 0.001$
Urakaze et al. (2021)	Astaxanthin 12 mg/d	Placebo	120-min OGTT glucose significantly reduced	$P < 0.05$
Jabarpour et al. (2023)	Astaxanthin 12 mg/d	Placebo	Significant reduction in fasting blood sugar	$P < 0.05$

Study (Year)	Agent and daily dose	Comparator	Reported effect	Significance
Ricottini et al. (2024)	Multi-nutraceutical (incl. Cr picolinate, Zn, ALA)	Pre-treatment baseline	Trend towards lower glucose	Not significant
Rahimi Sakak et al. (2021)	Vitamin K2 360 µg/d	Placebo	Effect size −0.68	P-adjusted = 0.031
Bazyar et al. (2023)	Rutin 500 mg/d	Placebo	Significant reduction	P < 0.05 (adjusted)
Teparak et al. (2025)	Anthocyanin + prebiotic fibre	Maltodextrin	Significant reduction	P = 0.03 (interaction)

Fasting insulin

Twelve primary studies reported fasting insulin. Significant reductions were observed with magnesium at 250 mg/day, with magnesium–melatonin co-supplementation, with chromium picolinate at 400 µg/day, with coenzyme Q10, with calcium and vitamin D, with vitamin K4 and with rutin. The case-control evidence is congruent: patients with type 2 diabetes and low plasma chromium had significantly higher insulin and HOMA-IR than non-diabetic controls.^{2,7,11,18,23,30,32,33}

Table 8. Effect of nutraceutical supplementation on fasting insulin

Study (Year)	Agent and daily dose	Comparator	Reported effect	Significance
ELDerawi et al. (2018)	Mg 250 mg/d	No supplement	15.56 → 12.18 µIU/mL	P < 0.001
Alizadeh et al. (2021)	Mg 250 mg/d + melatonin 6 mg/d	Placebo	−1.11 mIU/mL (−15.99 %)	P < 0.05
Ghosh et al. (2002)	Cr picolinate 400 µg/d	Placebo	Greater fall in fasting insulin	P < 0.05

Study (Year)	Agent and daily dose	Comparator	Reported effect	Significance
Ngala et al. (2018)	Low plasma chromium (exposure)	Non-diabetic controls	Significantly higher insulin in low-Cr diabetics	P < 0.0001
Izadi et al. (2019)	CoQ10 100 mg/d ± vitamin E	Placebo	Significant reduction in fasting insulin	P < 0.05
Ciaraldi et al. (2023)	Astaxanthin 12 mg/d	Placebo	−5.6 ± 8.4 pmol/L	P = 0.097 (trend)
Jabarpour et al. (2023)	Astaxanthin 12 mg/d	Placebo	Significant reduction (attenuated after adjustment)	P < 0.05 unadjusted
Ricottini et al. (2024)	Multi-nutraceutical combination	Baseline	Significant decrease in insulin	P < 0.05
Tabesh et al. (2014)	Vitamin D + calcium	Placebo	−14.8 ± 3.9 pmol/L	P = 0.01
Rahimi Sakak et al. (2021)	Vitamin K2 360 µg/d	Placebo	Effect size −0.29 (within group)	P = 0.019
Ali et al. (2023)	Vitamin K4 1 mg/d	Placebo	6.86 ± 3.45 vs 11.13 ± 12.66 µU/mL	P = 0.032
Bazyar et al. (2023)	Rutin 500 mg/d	Placebo	Significant reduction	P < 0.05 (adjusted)

HOMA-IR

Sixteen primary studies reported HOMA-IR or a clamp-derived equivalent, making this the most densely reported single endpoint in the review. Significant reductions were demonstrated for magnesium in hypomagnesaemia, magnesium–melatonin co-supplementation, chromium-containing

botanical combinations, coenzyme Q10 at 120 mg/day for 24 weeks, coenzyme Q10 in polycystic ovary syndrome, astaxanthin in polycystic ovary syndrome, a multi-component nutraceutical, calcium plus vitamin D, vitamin K4, rutin and resveratrol. The two negative results were both obtained with hyperinsulinaemic-euglycaemic clamp methodology, which is the reference standard and the least susceptible to the assay variability that affects HOMA-IR.^{1,2,3,7,12,15,20,23,26,30,32,33,35}

Table 9. Effect of nutraceutical supplementation on HOMA-IR

Study (Year)	Agent and daily dose	Comparator	Reported effect	Significance
Rodríguez-Morán & Guerrero-Romero (2003)	MgCl ₂ 50 mL/d	Placebo	3.8 ± 1.1 vs 5.0 ± 1.3	P = 0.005
ELDerawi et al. (2018)	Mg 250 mg/d	No supplement	6.16 → 4.44	P < 0.001
Drenthen et al. (2023)	Mg 15 mmol/d	Placebo	Clamp M-value 4.6 ± 0.5 vs 4.4 ± 0.6 mg/kg/min	P = 0.108 (NS)
Alizadeh et al. (2021)	Mg + melatonin	Placebo	−0.28 (−18.66 %)	P < 0.05
Derosa et al. (2020)	Ilex + mulberry + Cr picolinate	Placebo	−7.9 %; clamp M value higher	P < 0.05
Cefalu et al. (2010)	Cr picolinate 1000 µg/d	Placebo	Response confined to insulin-resistant phenotype	P < 0.001 for baseline-response correlation
Ngala et al. (2018)	Low plasma chromium	Non-diabetic controls	Significantly higher HOMA-IR	P < 0.0001

Study (Year)	Agent and daily dose	Comparator	Reported effect	Significance
Zhang et al. (2018)	CoQ10 120 mg/d	Placebo	Significant decrease at 24 weeks	P = 0.009
Izadi et al. (2019)	CoQ10 100 mg/d ± vitamin E	Placebo	Significant reduction	P < 0.05
Ciaraldi et al. (2023)	Astaxanthin 12 mg/d	Placebo	HOMA2-IR -0.31 ± 0.16	P = 0.060 (trend)
Jabarpour et al. (2023)	Astaxanthin 12 mg/d	Placebo	Significant reduction in HOMA-IR	P < 0.05
Ricottini et al. (2024)	Multi-nutraceutical combination	Baseline	Significant decrease	P < 0.05
Tabesh et al. (2014)	Vitamin D + calcium	Placebo	-0.46 ± 0.20	P = 0.001
Ali et al. (2023)	Vitamin K4 1 mg/d	Placebo	16.54 ± 7.81 vs 29.09 ± 36.56	P = 0.027
Baziyar et al. (2023)	Rutin 500 mg/d	Placebo	Significant reduction	P < 0.05 (adjusted)
Mahjabeen et al. (2022)	Resveratrol 200 mg/d	Placebo	-0.83 (95 % CI -1.37 to -0.29)	Significant

Insulin sensitivity and beta-cell indices

Twelve primary studies reported QUICKI, HOMA-β, the Matsuda index or clamp-derived insulin sensitivity. The clamp-based evidence is the most informative and the most divergent: chromium picolinate at 1000 µg/day produced a responder rate of 63 % versus 30 % on placebo, with baseline insulin sensitivity explaining approximately 40 % of the variance in response, whereas magnesium at 15 mmol/day produced no change in the clamp M value despite biochemical evidence

of successful supplementation. Calcium plus vitamin D increased QUICKI by 0.025 and HOMA-B by 11.8, and curcumin raised HOMA- β from 105.19 to 136.20.^{3,12,13,30,34}

Table 10. Effect on insulin sensitivity and beta-cell function indices

Study (Year)	Agent and daily dose	Index used	Reported effect	Significance
ELDerawi et al. (2018)	Mg 250 mg/d	HOMA- β	59.99 $\rightarrow$ 52.37	P = 0.036
Mooren et al. (2011)	Mg-aspartate-HCl 365 mg/d	Insulin sensitivity indices (OGTT-derived)	Significant improvement vs placebo	P < 0.05
Drenthen et al. (2023)	Mg 15 mmol/d	Hyperinsulinaemic-euglycaemic clamp	No improvement	Not significant
Cefalu et al. (2010)	Cr picolinate 1000 μ g/d	Euglycaemic clamp	Responders ($\geq$ 10 % rise) 63 % vs 30 % placebo	Baseline-dependent
Derosa et al. (2020)	Ilex + mulberry + Cr	Euglycaemic clamp M value	67 % normalised insulin sensitivity	P < 0.05
Whitfield et al. (2016)	Cinnamon + Cr + Mg honey	Matsuda index / glucose AUC	No acute or chronic difference	Not significant
Urakaze et al. (2021)	Astaxanthin 12 mg/d	Matsuda index	Improved vs pre-supplementation	P < 0.05
Ciaraldi et al. (2023)	Astaxanthin 12 mg/d	Clamp glucose disposal	+0.52 $\pm$ 0.37 mg/m ² /min	P = 0.078 (trend)

Study (Year)	Agent and daily dose	Index used	Reported effect	Significance
Jabarpour et al. (2023)	Astaxanthin 12 mg/d	QUICKI	Significant increase (NS after adjustment)	P < 0.05 unadjusted
Tabesh et al. (2014)	Vitamin D + calcium	QUICKI / HOMA-B	QUICKI +0.025; HOMA-B +11.8	P = 0.004 / P = 0.001
Bazyar et al. (2023)	Rutin 500 mg/d	QUICKI / HOMA- β	Significant increase in QUICKI	P < 0.05
Yaikwawong et al. (2024)	Curcumin 1500 mg/d	HOMA- β	136.20 vs 105.19	P < 0.01

Total cholesterol

Fifteen primary studies reported total cholesterol. The clearest single-agent effect was obtained with astaxanthin at 12 mg/day for 24 weeks, which reduced total cholesterol by 0.30 ± 0.14 mmol/L. Multi-component nutraceuticals containing chromium, zinc, inositols or magnesium produced significant reductions in three further studies. Magnesium and chromium as monotherapies were essentially null for total cholesterol at the doses tested, which is consistent with the pooled literature in which the overall chromium effect on total cholesterol is statistically significant but small at -0.17 mmol/L.^{8,25,28,29,39}

Table 11. Effect of nutraceutical supplementation on total cholesterol

Study (Year)	Agent and daily dose	Comparator	Reported effect	Significance
Santhitisate et al. (2022)	MgO 200 mg/d	Placebo	$+5.07 \pm 26.43$ vs $+24.25 \pm 18.68$ (smaller rise)	P = 0.049
Mooren et al. (2011)	Mg-aspartate-HCl 365 mg/d	Placebo	No significant change	Not significant

Study (Year)	Agent and daily dose	Comparator	Reported effect	Significance
Werner et al. (2021)	Mg citrate 400 mg/d	Placebo	No effect on cholesterol	Not significant
Alizadeh et al. (2021)	Mg + melatonin	Baseline	-16.08 mg/dL (95 % CI -24.24 to -7.92)	P < 0.05
Whitfield et al. (2016)	Cinnamon + Cr + Mg honey	Plain honey	-0.29 mmol/L (95 % CI -0.57 to -0.23)	Significant
Ghosh et al. (2002)	Cr picolinate 400 µg/d	Placebo	No between-group difference	Not significant
Kleefstra et al. (2006)	Cr picolinate 500/1000 µg/d	Placebo	Weak relation between serum Cr and lipid improvement	Not significant
Ngala et al. (2018)	Low plasma chromium	Controls	Significantly higher TC in diabetics	P < 0.0001
Zhang et al. (2018)	CoQ10 120 mg/d	Placebo	Non-HDL-C reduced after covariate adjustment	P = 0.031
Sangouni et al. (2022)	CoQ10 200 mg/d	Double placebo	No significant effect (curcumin arm significant)	Not significant
Ciaraldi et al. (2023)	Astaxanthin 12 mg/d	Placebo	-0.30 ± 0.14 mmol/L	P < 0.05
Jabarpour et al. (2023)	Astaxanthin 12 mg/d	Placebo	TC/HDL-C significantly reduced	P < 0.05

Study (Year)	Agent and daily dose	Comparator	Reported effect	Significance
Ricottini et al. (2024)	Multi-nutraceutical combination	Baseline	Significant decrease in TC	P < 0.05
Nani et al. (2023)	Inositols + α -lactalbumin + Gymnema + Zn	Placebo	Significant reduction at 3 months	P = 0.01
Bazyar et al. (2023)	Rutin 500 mg/d	Placebo	Significant reduction	P < 0.05 (adjusted)

LDL-cholesterol

Fourteen primary studies reported LDL-cholesterol. Astaxanthin 12 mg/day reduced LDL-cholesterol by 0.33 ± 0.11 mmol/L, coenzyme Q10 120 mg/day for 24 weeks produced a significant reduction, and significant reductions were also observed with magnesium–melatonin co-supplementation, a cinnamon–chromium–magnesium honey preparation, calcium plus vitamin D, an inositol–zinc combination, a multi-component nutraceutical and rutin. Chromium monotherapy had no effect on LDL-cholesterol in either the individual trials or the pooled literature.^{7,8,20,25,29,30,33,39}

Table 12. Effect of nutraceutical supplementation on LDL-cholesterol

Study (Year)	Agent and daily dose	Comparator	Reported effect	Significance
Alizadeh et al. (2021)	Mg + melatonin	Baseline	−18.96 mg/dL (95 % CI −28.73 to −9.20)	P < 0.05
Drenthen et al. (2023)	Mg 15 mmol/d	Placebo	No change in LDL-C	Not significant
Whitfield et al. (2016)	Cinnamon + Cr + Mg honey	Plain honey	−0.29 mmol/L (95 % CI −0.57 to −0.23)	Significant

Study (Year)	Agent and daily dose	Comparator	Reported effect	Significance
Ghosh et al. (2002)	Cr picolinate 400 µg/d	Placebo	No significant difference	Not significant
Ngala et al. (2018)	Low plasma chromium	Controls	Plasma Cr correlated negatively with LDL-C	$P \leq 0.001$
Zhang et al. (2018)	CoQ10 120 mg/d	Placebo	Significant reduction at 24 weeks	$P = 0.016$
Zhang et al. (2022)	CoQ10 120 mg/d	Placebo	Adiponectin rise inversely correlated with Δ LDL-C ($r = -0.440$)	$P = 0.002$
Sangouni et al. (2022)	CoQ10 200 mg/d	Double placebo	No significant effect	Not significant
Ciaraldi et al. (2023)	Astaxanthin 12 mg/d	Placebo	-0.33 ± 0.11 mmol/L	$P < 0.05$
Jabarpour et al. (2023)	Astaxanthin 12 mg/d	Placebo	Significant reduction	$P < 0.05$
Ricottini et al. (2024)	Multi-nutraceutical combination	Baseline	Significant decrease	$P < 0.05$
Nani et al. (2023)	Inositols + α -lactalbumin + Gymnema + Zn	Placebo	Significant reduction at 3 months	$P = 0.03$
Tabesh et al. (2014)	Vitamin D + calcium	Placebo	-10.36 ± 0.10 mmol/L*	$P = 0.04$

Study (Year)	Agent and daily dose	Comparator	Reported effect	Significance
Bazyar et al. (2023)	Rutin 500 mg/d	Placebo	Significant reduction	P < 0.05 (adjusted)

HDL-cholesterol

Eleven primary studies reported HDL-cholesterol, and this domain produced the least consistent findings of any lipid endpoint. Significant increases were reported with astaxanthin in polycystic ovary syndrome, with melatonin combined with magnesium, with calcium plus vitamin D, with a multi-component nutraceutical, with an inositol–zinc combination and with rutin. Against this, one clamp-based crossover trial reported a statistically significant reduction in HDL-cholesterol on magnesium relative to placebo, an unexpected finding in a trial otherwise null for all lipid endpoints and one that requires independent replication before being regarded as a genuine class effect.^{3,7,26,28,29,30,33}

Table 13. Effect of nutraceutical supplementation on HDL-cholesterol

Study (Year)	Agent and daily dose	Comparator	Reported effect	Significance
Drenthen et al. (2023)	Mg 15 mmol/d	Placebo	1.14 ± 0.08 vs 1.20 ± 0.09 mmol/L (lower on Mg)	P = 0.026
Alizadeh et al. (2021)	Melatonin ± magnesium	Baseline	+2.19 mg/dL (95 % CI 0.61 to 3.77) with co-supplementation	P < 0.05
Whitfield et al. (2016)	Cinnamon + Cr + Mg honey	Plain honey	Trend towards increase	Not significant
Singer & Geohas (2006)	Cr picolinate 600 µg + biotin	Placebo	TG/HDL-C ratio reduced	P < 0.05

Study (Year)	Agent and daily dose	Comparator	Reported effect	Significance
Ghosh et al. (2002)	Cr picolinate 400 µg/d	Placebo	No significant difference	Not significant
Sangouni et al. (2022)	CoQ10 200 mg/d	Double placebo	No significant change	Not significant
Jabarpour et al. (2023)	Astaxanthin 12 mg/d	Placebo	Significant increase in HDL-C	P < 0.05
Ricottini et al. (2024)	Multi-nutraceutical combination	Baseline	Small but significant increase	P < 0.05
Nani et al. (2023)	Inositols + α-lactalbumin + Gymnema + Zn	Within study group	Significant improvement	P = 0.03
Tabesh et al. (2014)	Vitamin D + calcium	Placebo	+0.46 ± 0.05 mmol/L*	P = 0.03
Bazyar et al. (2023)	Rutin 500 mg/d	Placebo	Significant increase	P < 0.05 (adjusted)

Triglycerides

Fourteen primary studies reported triglycerides. Significant reductions were observed with chromium picolinate combined with biotin, with a chromium-containing botanical combination, with coenzyme Q10 at 120 mg/day for 24 weeks, with astaxanthin combined with exercise, with a multi-component nutraceutical, with an inositol–zinc combination, with vitamin K4 and with rutin. Magnesium monotherapy did not alter triglycerides in any included trial. The case-control data show significantly higher triglycerides and VLDL in patients with type 2 diabetes and low plasma chromium.^{10,15,18,20,27,29,32,33}

Table 14. Effect of nutraceutical supplementation on triglycerides

Study (Year)	Agent and daily dose	Comparator	Reported effect	Significance
Werner et al. (2021)	Mg citrate 400 mg/d	Placebo	No effect on triglycerides	Not significant
Mooren et al. (2011)	Mg-aspartate-HCl 365 mg/d	Placebo	Lipid profile unchanged	Not significant
Singer & Geohas (2006)	Cr picolinate 600 µg + biotin	Placebo	Significantly greater reduction	P < 0.02
Derosa et al. (2020)	Ilex + mulberry + Cr picolinate	Placebo	−8.3 %	P < 0.05
Ghosh et al. (2002)	Cr picolinate 400 µg/d	Placebo	No significant difference	Not significant
Ngala et al. (2018)	Low plasma chromium	Controls	Significantly higher TG and VLDL in diabetics	P < 0.0001
Zhang et al. (2018)	CoQ10 120 mg/d	Placebo	Significant reduction at 24 weeks	P = 0.020
Zhang et al. (2022)	CoQ10 120 mg/d	Placebo	ΔAdiponectin inversely correlated with ΔTG (r = −0.297)	P = 0.047
Sangouni et al. (2022)	CoQ10 200 mg/d	Double placebo	No significant change	Not significant
Saeidi et al. (2023)	Astaxanthin 20 mg/d ± training	Placebo	Improved lipid and metabolic profile, greatest with training	P < 0.05

Study (Year)	Agent and daily dose	Comparator	Reported effect	Significance
Ricottini et al. (2024)	Multi-nutraceutical combination	Baseline	Significant decrease	P < 0.05
Nani et al. (2023)	Inositols + Gymnema + Zn	Within study group	Significant improvement at 3 months	P = 0.04
Ali et al. (2023)	Vitamin K4 1 mg/d	Baseline	144.94 ± 50.7 vs 172.8 ± 101.5 mg/dL	P = 0.031
Bazyar et al. (2023)	Rutin 500 mg/d	Placebo	Significant reduction in TG and VLDL	P < 0.05

Atherogenic indices, modified lipoproteins and apolipoproteins

Nine primary studies reported composite atherogenic indices or modified lipoprotein species. This domain provides some of the most mechanistically informative findings of the review, most notably the reduction in malondialdehyde-modified LDL from 87.3 ± 28.6 to 76.3 ± 24.6 U/L with astaxanthin 12 mg/day in a trial in which total cholesterol, triglycerides and HDL-cholesterol were all unchanged, indicating modification of lipoprotein quality independent of lipoprotein quantity. Astaxanthin at the same dose also significantly reduced fibrinogen, L-selectin and fetuin-A.^{24,25}

Table 15. Effect on atherogenic indices, modified lipoproteins and apolipoproteins

Study (Year)	Agent and daily dose	Index or marker	Reported effect	Significance
Singer & Geohas (2006)	Cr picolinate 600 µg + biotin 2 mg/d	TG/HDL-C ratio	Significantly reduced	P < 0.05
Zhang et al. (2018)	CoQ10 120 mg/d	Non-HDL-C, ApoA-I	Non-HDL-C reduced; ApoA-I increased	P = 0.031 / P < 0.001
Urakaze et al. (2021)	Astaxanthin 12 mg/d	MDA-modified LDL, apo E	87.3 → 76.3 U/L; apo E 4.43 → 4.13 mg/dL	P < 0.05 for both

Study (Year)	Agent and daily dose	Index or marker	Reported effect	Significance
Jabarpour et al. (2023)	Astaxanthin 12 mg/d	TC/HDL-C ratio	Significantly reduced	P < 0.05
Ciaraldi et al. (2023)	Astaxanthin 12 mg/d	Fibrinogen, L-selectin, fetuin-A	−473 ± 210 ng/mL; −0.08 ± 0.03 ng/mL; −10.3 ± 3.6 ng/mL	All P < 0.05
Ali et al. (2023)	Vitamin K4 1 mg/d	VLDL	28.9 ± 9.88 vs 34.6 ± 20.30 mg/dL	P = 0.027
Tabesh et al. (2014)	Vitamin D + calcium	TC/HDL-C ratio	−0.91 ± 0.16	P = 0.03
Bazyar et al. (2023)	Rutin 500 mg/d	AIP, LDL-C/HDL-C ratio	Both significantly reduced	P < 0.05 (adjusted)
Ngala et al. (2018)	Plasma chromium (exposure)	VLDL, cardiovascular risk	Low Cr associated with lipid dysregulation and hypertension	P ≤ 0.001

Oxidative stress and antioxidant capacity

Eight primary studies reported oxidative-stress or antioxidant-capacity markers, and the direction of effect in this domain was the most consistent of any in the review. Malondialdehyde fell significantly with a berberine–hesperidin–chromium combination, with astaxanthin, with rutin, with resveratrol and with saffron; total antioxidant capacity rose with coenzyme Q10, astaxanthin and rutin. The one clear exception is instructive: coenzyme Q10 at 200 mg/day produced a threefold rise in plasma coenzyme Q10 and significant reductions in HbA1c and blood pressure without any change in plasma F₂-isoprostanes, indicating that its metabolic benefit is not necessarily mediated by measurable systemic lipid peroxidation.^{14,19,20,24,26,33,35,59}

Table 16. Effect on oxidative stress and antioxidant capacity

Study (Year)	Agent and daily dose	Marker	Reported effect	Significance
Sartore et al. (2021)	Berberine + hesperidin + Cr picolinate	AGEs, MDA	AGEs 9.34 → 6.75 µg/mL; MDA 1.7 → 1.4 µmol/L	P < 0.01 for both
Hodgson et al. (2002)	CoQ10 200 mg/d	Plasma F ₂ -isoprostanes	No change (+0.14 ± 0.15 nmol/L)	P = 0.345
Zhang et al. (2018)	CoQ10 120 mg/d	Total antioxidant capacity	Increased at week 12	P = 0.003
Urakaze et al. (2021)	Astaxanthin 12 mg/d	MDA-modified LDL	Significantly reduced	P < 0.05
Jabarpour et al. (2023)	Astaxanthin 12 mg/d	MDA, TAC, SOD	MDA reduced; TAC increased	P < 0.05
Bazyar et al. (2023)	Rutin 500 mg/d	MDA, TAC	MDA reduced; TAC increased	P < 0.05 (adjusted)
Mahjabeen et al. (2022)	Resveratrol 200 mg/d	MDA	−0.36 (95 % CI −0.61 to −0.11)	Significant
Tajaddini et al. (2022)	Saffron 100 mg/d	NO, MDA	MDA −16.35 %; NO −26.29 %	P < 0.05

Inflammatory markers and adipokines

Eight primary studies reported inflammatory markers or adipokines. The most detailed dataset comes from the coenzyme Q10 adipokine analysis, in which adiponectin rose by 523 ng/mL and resistin fell by 1.19 ng/mL, with formal mediation analysis indicating that the improvement in HOMA-IR, triglycerides and LDL-cholesterol was mediated by adiponectin. Astaxanthin with high-

intensity functional training significantly reduced CTRP9, CTRP2, GDF8 and GDF15, resveratrol reduced hs-CRP, TNF- α and IL-6, and curcumin raised adiponectin while lowering leptin. Magnesium and chromium-containing combinations were largely null in this domain.^{5,16,21,27,33,34,35}

Table 17. Effect on inflammatory markers and adipokines

Study (Year)	Agent and daily dose	Marker	Reported effect	Significance
Werner et al. (2021)	Mg citrate 400 mg/d	CRP, IL-6	No significant effect	Not significant
Drenthen et al. (2024)	Mg 15 mmol/d	hs-CRP, T-cell cytokines	Lower IFN- γ and Th2 cytokine production; hs-CRP trend lower	Directionally favourable
Liu et al. (2015)	Cinnamon + Cr + carnosine	Inflammatory markers	No between-group difference	Not significant
Zhang et al. (2022)	CoQ10 120 mg/d	Adiponectin, resistin	Adiponectin +523 ng/mL; resistin -1.19 ng/mL	P < 0.001 for both
Saeidi et al. (2023)	Astaxanthin 20 mg/d $\pm$ training	CTRP9, CTRP2, GDF8, GDF15	Significant reductions, greatest with training	P < 0.05
Bazyar et al. (2023)	Rutin 500 mg/d	IL-6, BDNF	IL-6 reduced; BDNF increased	P < 0.05 (adjusted)
Mahjabeen et al. (2022)	Resveratrol 200 mg/d	hs-CRP, TNF- α , IL-6	hs-CRP -0.35; TNF- α -1.25; IL-6 -1.99	All significant

Study (Year)	Agent and daily dose	Marker	Reported effect	Significance
Yaikwawong et al. (2024)	Curcumin 1500 mg/d	Adiponectin, leptin	Adiponectin 14.51 vs 10.36; leptin 9.42 vs 20.66	P < 0.001 for both

Blood pressure

Eight primary studies reported blood pressure. The two coenzyme Q10 trials produced concordant results, with reductions in systolic pressure of 6.1 ± 2.6 mmHg and diastolic pressure of 2.9 ± 1.4 mmHg at 200 mg/day and significant reductions in both parameters at 120 mg/day by week 12. Magnesium citrate at 400 mg/day reduced blood pressure from 144/86 to 122/78 mmHg over twelve weeks in untreated prediabetic hypertensive patients, although other magnesium trials in normotensive populations were null. Pooled evidence indicates that chromium reduces diastolic blood pressure by 2.36 mmHg without affecting systolic pressure.^{5,19,20,40}

Table 18. Effect on blood pressure

Study (Year)	Agent and daily dose	Reported effect	Significance
Werner et al. (2021)	Mg citrate 400 mg/d	144/86 → 122/78 mmHg over 12 weeks	P < 0.01
Drenthen et al. (2023)	Mg 15 mmol/d	No change in blood pressure	Not significant
Mooren et al. (2011)	Mg-aspartate-HCl 365 mg/d	No change in blood pressure	Not significant
Kleefstra et al. (2006)	Cr picolinate 500/1000 µg/d	No change in blood pressure	Not significant
Hodgson et al. (2002)	CoQ10 200 mg/d	SBP -6.1 ± 2.6 mmHg; DBP -2.9 ± 1.4 mmHg	P = 0.021 / P = 0.048

Study (Year)	Agent and daily dose	Reported effect	Significance
Zhang et al. (2018)	CoQ10 120 mg/d	SBP and DBP significantly reduced at 12 weeks	P = 0.010 / P = 0.001
Jabarpour et al. (2023)	Astaxanthin 12 mg/d	Blood pressure assessed; no significant change reported	Not significant
Sangouni et al. (2022)	CoQ10 200 mg/d and/or curcumin	No effect on SBP or DBP	Not significant

Anthropometry and body composition

Ten primary studies reported anthropometric or body-composition endpoints. Significant weight reduction was observed with a cinnamon–chromium–magnesium honey preparation, with astaxanthin combined with exercise, with a multi-component nutraceutical and with an inositol–zinc combination, and curcumin lowered body mass index from 29.34 to 25.94. Two findings are mechanistically notable: a cinnamon–chromium–carnosine supplement increased fat-free mass without changing weight, and chromium picolinate significantly reduced soleus and tibialis intramyocellular lipid content, linking the agent to ectopic rather than total adiposity.^{8,12,16,27,28,29,34}

Table 19. Effect on anthropometry and body composition

Study (Year)	Agent and daily dose	Reported effect	Significance
Whitfield et al. (2016)	Cinnamon + Cr + Mg honey	Weight −2.2 kg (95 % CI −4.2 to −0.1)	Significant
Kleefstra et al. (2006)	Cr picolinate 500/1000 µg/d	No change in BMI	Not significant
Liu et al. (2015)	Cinnamon + Cr + carnosine	Fat-free mass increased vs placebo	P = 0.02
Cefalu et al. (2010)	Cr picolinate 1000 µg/d	Myocellular lipid significantly lower with Cr	Significant

Study (Year)	Agent and daily dose	Reported effect	Significance
Sangouni et al. (2022)	CoQ10 and/or curcumin	No change in BMI, weight or waist circumference	Not significant
Urakaze et al. (2021)	Astaxanthin 12 mg/d	Visceral fat area measured; no significant change	Not significant
Saeidi et al. (2023)	Astaxanthin 20 mg/d ± training	Weight, body fat % and BMI reduced, greatest in combined arm	P < 0.05
Ricottini et al. (2024)	Multi-nutraceutical combination	Body weight, BMI and waist circumference all decreased	P < 0.05
Nani et al. (2023)	Inositols + Gymnema + Zn	Greater body-weight reduction vs placebo at 3 months	P = 0.03
Yaikwawong et al. (2024)	Curcumin 1500 mg/d	BMI 25.94 vs 29.34	P = 0.001

Safety and tolerability

Safety data were reported in nine of the included studies and in the retained pooled syntheses. No serious adverse event attributable to any nutraceutical intervention was reported in any included study. The principal signals concern gastrointestinal tolerability, exemplified by berberine, and the requirement to exclude patients with impaired renal function before magnesium supplementation. Chromium picolinate at doses up to 1000 µg/day was not associated with haematological, renal or hepatic toxicity, and astaxanthin at 12 mg/day for 24 weeks was explicitly characterised as safe and well tolerated.^{3,9,11,17,25,61}

Table 20. Safety and tolerability

Study (Year)	Agent and daily dose	Safety observation
Rodríguez-Morán & Guerrero-Romero (2003)	MgCl ₂ 50 mL/d	Diarrhoea, renal impairment excluded a priori; no serious events reported

Study (Year)	Agent and daily dose	Safety observation
Drenthen et al. (2023)	Mg 15 mmol/d	Hypomagnesaemia-related symptoms similar between arms
Kleefstra et al. (2006)	Cr picolinate up to 1000 µg/d	No excess adverse events reported
Singer & Geohas (2006)	Cr picolinate 600 µg + biotin	No significant adverse events attributed to supplementation
Ghosh et al. (2002)	Cr picolinate 400 µg/d	No clinically significant haematological, renal or hepatic toxicity
Buccato et al. (2024)	Zea mays + Gymnema + Zn + Cr	No biochemical evidence of hepatic or renal toxicity
Ciaraldi et al. (2023)	Astaxanthin 12 mg/d	Safe and well tolerated; no clinically significant adverse events
Ricottini et al. (2024)	Multi-nutraceutical combination	No measurable side-effects over 3 months
Yin et al. (2008)	Berberine 1.5 g/d	Transient gastrointestinal effects in 34.5 % of patients

Dose–response synthesis

Dose was extracted as a primary analytical variable for every included arm and mapped against effect direction and magnitude within each outcome domain. Three patterns emerged that are not visible in conventional pooled means: a U-shaped relationship between coenzyme Q10 dose and every glycaemic endpoint with the optimum at 100–200 mg/day; an inverse J-shaped relationship between coenzyme Q10 dose and total cholesterol with the optimum at 400–500 mg/day; and a non-monotonic chromium relationship in which lipid benefit was concentrated at doses below 200 µg/day and at durations under twelve weeks while glycaemic benefit was distributed across the 200–1000

µg/day range without evidence of superiority at the upper end. Magnesium and vitamin D displayed threshold rather than gradient behaviour, conditional on baseline status.^{39,41,42,46,49}

Table 21. Agent-level dose–response synthesis

Agent	Dose range studied	Duration range	Dose–response pattern observed	Key modifier
Magnesium (oxide, citrate, chloride, aspartate)	250–400 mg/d elemental (up to 15 mmol/d)	12 weeks – 6 months	Glycaemic benefit concentrated at ≥ 250 mg/d elemental Mg for ≥ 12 weeks in hypomagnesaemic patients; no clear incremental gain at 15 mmol/d in normo-/mildly hypomagnesaemic insulin-treated patients	Baseline serum magnesium is the dominant effect modifier
Chromium (picolinate)	200–1000 µg/d elemental Cr	4 weeks – 6 months	Pooled analyses show FPG –19.00 mg/dL, HbA1c –0.71 %, HOMA-IR –1.53 and insulin –12.35 pmol/L; lipid benefit favoured doses <200 µg/d and duration <12 weeks	No monotonic dose gradient; higher doses (1000 µg/d) not superior
Coenzyme Q10 (ubiquinone)	100–500 mg/d	12 – 24 weeks	U-shaped dose–response: 100–200 mg/d yields the greatest reduction in fasting glucose, insulin, HbA1c and HOMA-IR; inverse J-shaped curve for total cholesterol with maximal effect at 400–500 mg/d	Glycaemic and lipid optima occur at different doses

Agent	Dose range studied	Duration range	Dose–response pattern observed	Key modifier
Astaxanthin	12 mg/d (20 mg/d with exercise)	8 – 24 weeks	Consistent LDL-C and TC lowering and reduction in oxidised LDL at 12 mg/d; 20 mg/d combined with high-intensity functional training produced the largest composite cardiometabolic improvement	Effect on insulin action is directionally favourable but often sub-threshold
Zinc	≤30 mg/d conventional; modelled optimum 100–140 mg/d	8 – 24 weeks	Linear association between each additional 10 mg/d and FPG, HbA1c, HDL-C, LDL-C, TG and TC; non-linear optimum modelled at 120 mg/d (TC), 100 mg/d (LDL-C) and 140 mg/d (TG)	Modelled optima exceed usual tolerable upper intake levels
Vitamin D (± calcium)	1000–4000 IU/d or 50,000 IU/week	8 weeks – 6 months	FPG –0.49 mmol/L, HbA1c –0.30 %, HOMA-IR –0.39 and insulin –1.31 µIU/mL; effect greatest with short-term high dose in deficient, overweight patients with HbA1c ≥8 %	Baseline 25(OH)D status is the principal modifier
Vitamin E	up to 400 mg/d	<10 weeks – 6 months	HbA1c –0.21 %, fasting insulin –1.05 µIU/mL, HOMA-IR –0.44; FPG reduced only in trials shorter than 10 weeks	Short-duration effect on FPG

Agent	Dose range studied	Duration range	Dose–response pattern observed	Key modifier
Vitamin K (K2 MK-7 / K4)	360 µg/d (MK-7); 1 mg/d (K4)	12 – 24 weeks	MK-7 reduces FPG and HbA1c without lipid effect; K4 improves HOMA-IR, insulin, TG and VLDL without changing FPG or HbA1c	Dissociation between glycaemic and lipid pathways by vitamer

Table 22. Corroborating pooled estimates from retained quantitative syntheses (not included in the study-characteristics tables)

Domain	Source synthesis	Trials	Pooled estimate (95 % CI where reported)	Overall
Chromium — glycaemic	Asbaghi et al. (2020)	28	FPG –19.00 mg/dL (95 % CI –36.15 to –1.85); HbA1c –0.71 % (–1.19 to –0.23); HOMA-IR –1.53 (–2.35 to –0.72); insulin –12.35 pmol/L (–17.86 to –6.83)	All significant
Chromium — lipids	Tarrahi et al. (2021)	38	TC –0.17 mmol/L (95 % CI –0.27 to –0.07); subgroup benefit for TG and VLDL at doses <200 µg/d and duration <12 weeks; no effect on LDL-C	TC significant overall
Chromium — BP and oxidative stress	Asbaghi et al. (2021)	15	DBP –2.36 mmHg (95 % CI –4.14 to –0.60); MDA –0.55 µmol/L (–0.96 to –0.14); no effect on BMI, SBP, ALT, AST	Significant for DBP and MDA

Domain	Source synthesis	Trials	Pooled estimate (95 % CI where reported)	Overall
CoQ10 — glycaemic	Liang et al. (2022)	40	FPG −5.22 mg/dL (95 % CI −8.33 to −2.11); insulin −1.32 μIU/mL; HbA1c −0.12 %; HOMA-IR −0.69 (−1.00 to −0.38); optimum 100–200 mg/d	All significant
CoQ10 — lipids	Liu et al. (2023)	50	TC −5.53 mg/dL; LDL-C −3.03 mg/dL; TG −9.06 mg/dL; HDL-C +0.83 mg/dL; optimum for TC 400–500 mg/d	All significant
CoQ10 — adipokines and inflammation	Dludla et al. (2020)	—	Adiponectin SMD 1.44; inflammatory markers SMD −0.31 (95 % CI −0.54 to −0.08)	Inflammation significant
Magnesium — glucose metabolism	Veronese et al. (2021)	—	Reduced FPG in diabetes; improved fasting and 2-h post-load glucose and insulin-sensitivity markers in those at high risk	Significant
Zinc — glycaemic	Ghaedi et al. (2024)	22	2-h post-prandial glucose −34.34 mg/dL; FPG −23.32 mg/dL; HbA1c −0.47 %	All significant
Zinc — lipids	Heidari Seyedmahalleh et al. (2023)	14	TC −16.16 mg/dL; LDL-C −6.18 mg/dL; TG −13.08 mg/dL; HDL-C +3.76 mg/dL	All significant
Vitamin D — glycaemic	Chen et al. (2024)	39	FPG −0.49 mmol/L; HbA1c −0.30 %; HOMA-IR −0.39; insulin −1.31 μIU/mL	All significant

Domain	Source synthesis	Trials	Pooled estimate (95 % CI where reported)	Overall
Vitamin E — glycaemic	Asbaghi et al. (2023)	38	HbA1c -0.21 %; insulin -1.05 μ IU/mL; HOMA-IR -0.44; FPG not significant overall	Mostly significant
Flavonoids — composite	Liu et al. (2023)	28	FPG -0.22; HbA1c -0.26 %; HOMA-IR -0.40; TG -0.13; TC -0.14; LDL-C -0.15 (mmol/L where applicable)	All significant

Note. These estimates are quoted exactly as published by their original investigators and are used solely to corroborate the direction and approximate magnitude of the primary-study signal within each outcome domain. They were never combined with primary-study data and, in accordance with the prespecified design criteria, do not appear in Tables 5a or 5b.

Certainty of the evidence

Certainty was rated using GRADE for each of the fifteen outcome domains. No domain reached high certainty. Moderate certainty was assigned to HbA1c, HOMA-IR, total cholesterol, LDL-cholesterol, triglycerides, oxidative-stress markers, blood pressure and safety. Low certainty was assigned to fasting plasma glucose, fasting insulin, clamp-derived insulin sensitivity, HDL-cholesterol, atherogenic indices, inflammatory markers and adipokines, and anthropometry. The principal reasons for downgrading were risk of bias arising from open-label designs, imprecision in small trials, inconsistency across agents and doses, and indirectness where insulin-resistant non-diabetic populations were used as models for type 2 diabetes.^{38,41,51}

Table 23. GRADE summary of findings across the fifteen outcome domains

Outcome domain	Evidence base	Overall risk of bias	Principal reasons for downgrading	Certainty
HbA1c	19 primary studies + 6 pooled syntheses	Moderate	Serious risk of bias in open-label trials; consistent direction for Mg (hypomagnesaemic), CoQ10 and vitamin D	⊕⊕⊕⊖ Moderate
Fasting plasma glucose	16 primary studies	Moderate	Large heterogeneity in chromium meta-analysis ($I^2 = 99.8\%$) offset by consistency of direction	⊕⊕⊖⊖ Low
Fasting insulin	12 primary studies	Moderate	Imprecision in small trials	⊕⊕⊖⊖ Low
HOMA-IR	16 primary studies	Moderate	Consistent effect for Mg, CoQ10, vitamin D and vitamin K4	⊕⊕⊕⊖ Moderate
Insulin sensitivity (clamp/QUICKI)	12 primary studies	Low–moderate	Clamp studies are small and phenotype-dependent	⊕⊕⊖⊖ Low
Total cholesterol	15 primary studies	Moderate	Consistent for astaxanthin and CoQ10; null for magnesium and chromium alone	⊕⊕⊕⊖ Moderate
LDL-cholesterol	14 primary studies	Moderate	Astaxanthin and CoQ10 signals convergent with pooled analyses	⊕⊕⊕⊖ Moderate
HDL-cholesterol	11 primary studies	Low	Bidirectional findings (magnesium reduced HDL-C in one clamp trial)	⊕⊕⊖⊖ Low

Outcome domain	Evidence base	Overall risk of bias	Principal reasons for downgrading	Certainty
Triglycerides	14 primary studies	Moderate	Consistent for CoQ10, chromium-containing combinations and vitamin K4	⊕⊕⊕⊖ Moderate
Atherogenic indices / oxidised LDL	9 primary studies	Low–moderate	Few trials, varied index definitions	⊕⊕⊖⊖ Low
Oxidative stress markers	8 primary studies	Moderate	Highly consistent direction across agents	⊕⊕⊕⊖ Moderate
Inflammation and adipokines	8 primary studies	Low–moderate	Assay heterogeneity	⊕⊕⊖⊖ Low
Blood pressure	8 primary studies	Moderate	CoQ10 signal replicated in two independent trials	⊕⊕⊕⊖ Moderate
Anthropometry	10 primary studies	Low	Confounded by co-interventions such as exercise	⊕⊕⊖⊖ Low
Safety and tolerability	9 primary studies	Moderate	Consistently reassuring; gastrointestinal effects agent-specific	⊕⊕⊕⊖ Moderate

DISCUSSION

Principal findings

This review demonstrates that nutraceutical supplementation produces statistically significant, reproducible and mechanistically coherent improvements across all three co-primary endpoints in adults with type 2 diabetes and dyslipidaemia, but that the magnitude, the target endpoint and the optimal dose differ systematically between agents. Magnesium acts predominantly on the

insulin-resistance axis and only secondarily on lipids; chromium acts on the glycaemic axis with a modest and inconsistent lipid signal; coenzyme Q10 acts on both axes but at different doses; and astaxanthin acts principally on the lipid and oxidative axes with a weaker insulin-sensitising effect. Treating these agents as interchangeable members of a single therapeutic category is therefore not defensible.^{1,20,25,38,41,42}

The strongest single-endpoint signals in this review were the reduction in HOMA-IR from 5.0 ± 1.3 to 3.8 ± 1.1 with magnesium chloride in hypomagnesaemic patients with T2DM, the fall in HOMA-IR from 6.16 to 4.44 with 250 mg/day of elemental magnesium, the pooled reduction in HbA1c of 0.71 % with chromium supplementation, the 0.37 % reduction in HbA1c with 200 mg/day of coenzyme Q10, and the reduction in LDL-cholesterol of 0.33 ± 0.11 mmol/L with 12 mg/day of astaxanthin. Each of these is a modest effect when measured against pharmacotherapy, but each is of a magnitude that is clinically non-trivial when applied as an adjunct in a population already at guideline-directed therapy, and the lipid effects in particular approach the magnitude achieved by intensification of dietary intervention.^{1,2,19,25,38}

Magnesium: a repletion phenomenon rather than a pharmacological one

The magnesium evidence in this review is best understood as a repletion phenomenon rather than a pharmacological one. The two trials that restricted enrolment to patients with documented hypomagnesaemia and used doses of approximately 250–300 mg/day of elemental magnesium both demonstrated significant improvement in HOMA-IR and HbA1c. By contrast, the most methodologically rigorous trial in this review — a double-blind, placebo-controlled crossover study using the hyperinsulinaemic-euglycaemic clamp as the primary outcome, with 15 mmol/day of magnesium in insulin-treated patients with serum magnesium at or below 0.79 mmol/L — found no improvement in the clamp-derived M value despite a demonstrable rise in serum magnesium and urinary magnesium excretion. The apparent contradiction resolves once the depth of baseline deficiency and the sensitivity of the outcome measure are considered.^{1,2,3}

Two mechanistic inferences follow. First, the biochemical target of magnesium repletion is intracellular rather than serum magnesium, and serum magnesium is an insensitive surrogate for total body stores; a rise in serum concentration from 0.70 to 0.75 mmol/L may reflect little more than

transient extracellular loading. Second, the magnitude of the insulin-sensitising response is likely to be a saturating function of the baseline deficit, so that patients with serum magnesium at or below 0.74 mmol/L who are also on sulfonylurea therapy have far more to gain than insulin-treated patients whose magnesium is only marginally low. The trial that used 400 mg/day of magnesium citrate in untreated prediabetic patients with hypertension reported significant reductions in both HbA1c and blood pressure, which is consistent with this model.^{1,3,5,55}

Magnesium's effect on the lipid profile was, in this review, weak and inconsistent. Two trials found no change in cholesterol or triglycerides at 365–400 mg/day, one crossover clamp study found a small but statistically significant reduction in HDL-cholesterol on magnesium relative to placebo, and one trial in patients with diabetic albuminuria found that total cholesterol rose in both arms but rose significantly less in the magnesium arm. The only clearly favourable lipid signal came from magnesium co-supplemented with melatonin in polycystic ovary syndrome, where total cholesterol fell by 16.08 mg/dL and LDL-cholesterol by 18.96 mg/dL — a result that cannot be attributed to magnesium alone. The honest summary is that magnesium is an insulin-sensitising agent with, at best, a marginal independent lipid effect.^{3,4,5,6,7}

Importantly, magnesium supplementation should not be assumed to confer benefit across every vascular endpoint. A six-month trial of magnesium citrate 350 mg/day in older patients with T2DM and peripheral medial arterial calcification found no reduction in calciprotein crystallisation and, before adjustment, an apparent increase in carotid-femoral pulse wave velocity that lost significance after adjustment for baseline differences. Alongside evidence that magnesium modulates T-cell cytokine production in hypomagnesaemic patients with T2DM, this indicates that the biology of magnesium in diabetes extends well beyond glycaemia and that endpoint-specific caution is warranted.^{60,63}

Chromium: pooled significance, phenotype dependence and dose inversion

Chromium presents the sharpest example in this review of the divergence between pooled statistical significance and individual-trial clinical meaningfulness. The pooled evidence is quantitatively impressive: across 28 trials, fasting plasma glucose fell by 19.00 mg/dL, HbA1c by 0.71 %, HOMA-IR by 1.53 and insulin by 12.35 pmol/L, all statistically significant. Yet a systematic

narrative appraisal that applied clinically meaningful thresholds — a fall in HbA1c to below 7 % or by at least 0.5 % — found that only a minority of the twenty randomised trials examined actually reached them, and concluded that there is limited rationale for recommending chromium for glycaemic control in established T2DM. Both statements are supportable from the same literature, and the reconciliation lies in the extreme between-study heterogeneity, with I^2 reaching 99.8 % for fasting plasma glucose.^{38,53}

The individual trials in this review reproduce that heterogeneity faithfully. In obese, insulin-treated Western patients with HbA1c above 8 %, chromium picolinate at 500 or 1000 µg/day produced a fall in HbA1c of approximately 0.4 % — identical to placebo. In Indian patients with T2DM, chromium picolinate at 400 µg/day produced significant reductions in fasting and post-prandial glucose and in fasting insulin, but no change in any lipid parameter. In poorly controlled patients receiving chromium picolinate 600 µg with biotin for only four weeks, glucose area under the curve, fructosamine, triglycerides and the triglyceride/HDL-cholesterol ratio all improved significantly. The variable that best explains this pattern is not dose but phenotype.^{9,10,11}

The phenotype hypothesis has been tested directly. In a clamp-based randomised study of 1000 µg/day of chromium picolinate, 63 % of chromium-treated subjects met the responder definition of a 10 % or greater improvement in insulin sensitivity, compared with 30 % on placebo, and baseline insulin sensitivity as measured by the hyperinsulinaemic-euglycaemic clamp accounted for approximately 40 % of the variance in clinical response. Responders differed from non-responders by having lower baseline insulin sensitivity and higher baseline fasting glucose and HbA1c, and chromium status itself did not distinguish them. The same programme demonstrated that chromium reduced soleus and tibialis intramyocellular lipid content, suggesting that modulation of ectopic lipid deposition in peripheral tissues may be the proximate mechanism.^{12,13}

For lipids, the chromium signal is real but small and dose-inverted. The largest pooled analysis, comprising 38 studies and 7,605 participants, found a significant overall reduction only in total cholesterol, at -0.17 mmol/L, with no effect on LDL-cholesterol. Subgroup analyses indicated that the lipid-lowering effect was greater at doses below 200 µg/day and durations shorter than twelve weeks, in patients with diabetes, in younger adults and with the picolinate form. A separate dose-

response meta-analysis found significant reductions in diastolic blood pressure of 2.36 mmHg and in malondialdehyde of 0.55 $\mu\text{mol/L}$ at doses of 200–1000 $\mu\text{g/day}$, but no linear relationship between dose and any of these outcomes. Higher chromium doses are therefore not better, and may be worse for lipid endpoints.^{39,40}

Observational evidence supports a threshold rather than a supplementation-intensity model. In a case-control study from Ghana, patients with T2DM had markedly lower plasma chromium than controls and significantly higher LDL-cholesterol, total cholesterol, triglycerides, VLDL, insulin, hs-CRP and HOMA-IR; plasma chromium correlated negatively with blood pressure and LDL-cholesterol, and low chromium was associated with hypertension, obesity and lipid dysregulation. This is consistent with chromium insufficiency being a marker and possibly a contributor to the dysmetabolic phenotype, without implying that supraphysiological supplementation reverses it.¹⁸

Coenzyme Q10: dual-axis efficacy with endpoint-specific dose optima

Coenzyme Q10 is the agent in this review with the most consistent evidence of dual glycaemic and lipid benefit, and the clearest evidence of non-monotonic dose–response. In a 2×2 factorial randomised trial in uncomplicated T2DM with dyslipidaemia, 200 mg/day of CoQ10 for twelve weeks reduced HbA1c by $0.37 \pm 0.17\%$, systolic blood pressure by 6.1 ± 2.6 mmHg and diastolic blood pressure by 2.9 ± 1.4 mmHg, while fenofibrate in the same trial altered none of these. Notably, plasma F₂-isoprostanes were unchanged despite a threefold rise in plasma CoQ10, indicating that the benefit was not mediated by a measurable reduction in systemic lipid peroxidation as assessed by that marker.¹⁹

In dyslipidaemic adults not taking lipid-lowering or glucose-lowering drugs, 120 mg/day of CoQ10 for twenty-four weeks reduced triglycerides, LDL-cholesterol and HOMA-IR, increased apolipoprotein A-I and total antioxidant capacity, and lowered blood pressure; after adjustment for physical activity and energy intake, non-HDL-cholesterol also fell significantly. The companion adipokine analysis of the same cohort provides a mechanistic link: adiponectin rose by 523 ng/mL and resistin fell by 1.19 ng/mL, and the rise in adiponectin correlated inversely with the reduction in HOMA-IR ($r = -0.465$), triglycerides ($r = -0.297$) and LDL-cholesterol ($r = -0.440$). Formal

mediation analysis indicated that the improvement in HOMA-IR, triglycerides and LDL-cholesterol was mediated by adiponectin but not by resistin.^{20,21}

The dose–response architecture of CoQ10 is the most instructive finding of this review. A GRADE-assessed dose-response meta-analysis of forty randomised trials using one-stage restricted cubic spline regression demonstrated a U-shaped relationship between CoQ10 dose and every glycaemic endpoint, with the greatest reductions in fasting glucose, fasting insulin, HbA1c and HOMA-IR occurring at 100–200 mg/day and diminishing at higher doses. A parallel dose-response meta-analysis of fifty trials for lipid endpoints found an inverse J-shaped relationship for total cholesterol, with the maximal effect at 400–500 mg/day. In other words, the dose that optimises glycaemic control is not the dose that optimises cholesterol, and a single fixed dose cannot optimise both simultaneously. This dissociation is invisible in conventional pooled means and has direct prescribing implications.^{41,42}

Not all CoQ10 evidence is positive, and the negative results are informative. In a 2×2 factorial trial in metabolic syndrome, 200 mg/day of CoQ10 for twelve weeks had no significant effect on any lipid or glycaemic parameter, whereas curcumin in the same trial significantly altered the lipid profile. Two features distinguish this trial from the positive ones: the population had metabolic syndrome rather than frank dyslipidaemia or diabetes, and the duration was twelve rather than twenty-four weeks. The temporal pattern in the twenty-four-week dyslipidaemia trial — blood pressure and antioxidant capacity changing by week 12 but triglycerides, LDL-cholesterol and HOMA-IR only by week 24 — suggests that lipid endpoints require longer exposure than haemodynamic ones, and that twelve-week trials are systematically underpowered for lipid outcomes.^{20,22}

In polycystic ovary syndrome as an insulin-resistant model, 100 mg/day of CoQ10 alone or combined with vitamin E significantly reduced fasting blood sugar and HOMA-IR and lowered total testosterone, with the combination additionally improving sex hormone-binding globulin. Changes in fasting glucose, insulin and HOMA-IR predicted the change in free androgen index, which supports the interpretation that the endocrine benefit is downstream of the insulin-sensitising effect rather than parallel to it. Pooled analyses in metabolic syndrome further indicate that CoQ10 raises adiponectin

and lowers inflammatory markers, with amelioration of lipid peroxidation as a plausible common pathway.^{23,45}

Astaxanthin: lipoprotein quality before lipoprotein quantity

Astaxanthin emerges from this review as a predominantly lipid- and oxidation-directed agent. In adults with prediabetes and dyslipidaemia, 12 mg/day for twenty-four weeks reduced LDL-cholesterol by 0.33 ± 0.11 mmol/L and total cholesterol by 0.30 ± 0.14 mmol/L, and lowered three independent cardiovascular risk markers — fibrinogen by 473 ± 210 ng/mL, L-selectin by 0.08 ± 0.03 ng/mL and fetuin-A by 10.3 ± 3.6 ng/mL. The prespecified primary endpoint, insulin-stimulated whole-body glucose disposal, did not reach statistical significance, although the direction of effect was favourable at $+0.52 \pm 0.37$ mg/m²/min, with corresponding trends in fasting insulin and HOMA2-IR. This is a trial in which the secondary endpoints were positive and the primary endpoint was not, and it must be reported as such.²⁵

In Japanese healthy volunteers and prediabetic subjects, 12 mg/day for twelve weeks reduced HbA1c from 5.64 ± 0.33 % to 5.57 ± 0.39 %, lowered 120-minute post-load glucose, improved the Matsuda index, and reduced apolipoprotein E and malondialdehyde-modified LDL from 87.3 ± 28.6 to 76.3 ± 24.6 U/L, while leaving total cholesterol, triglycerides and HDL-cholesterol unchanged. The dissociation between a significant fall in oxidised LDL and an unchanged total cholesterol is mechanistically important: astaxanthin appears to modify lipoprotein quality before, and to a greater extent than, lipoprotein quantity. Since oxidised LDL is a more proximate determinant of atherogenesis than total LDL mass, this may understate the agent's vascular relevance if judged by conventional lipid panels alone.²⁴

In infertile women with polycystic ovary syndrome, 12 mg/day for eight weeks significantly reduced fasting blood sugar, HOMA-IR, fasting insulin, malondialdehyde, LDL-cholesterol and the total cholesterol/HDL-cholesterol ratio, and significantly increased total antioxidant capacity, HDL-cholesterol and QUICKI. After adjustment for baseline age, body mass index and biochemical values, the QUICKI and fasting insulin results lost significance while all other findings persisted — a pattern that again places the centre of gravity of astaxanthin's effect on the lipid and oxidative axes rather than on insulin action per se.²⁶

The largest composite effect for astaxanthin was achieved in combination with exercise. In men with obesity, twelve weeks of 20 mg/day with high-intensity functional training produced greater improvements in adipokine profile, insulin resistance, lipid profile, body composition and cardiorespiratory indices than either intervention alone. A recent systematic review of fifteen human studies concluded that astaxanthin consistently reduces IL-6, TNF- α and TGF- β 1 and oxidative-stress indices while increasing superoxide dismutase and total antioxidant capacity, and that combined astaxanthin-plus-exercise interventions improve body composition, lipid profile and insulin sensitivity. Astaxanthin therefore appears to be an amplifier of the metabolic benefit of exercise as much as an independent agent.^{27,52}

Comparator nutraceuticals and what they reveal

The comparator nutraceuticals included in this review sharpen the interpretation of the four index agents. Zinc has the most favourable lipid profile of any micronutrient examined here: pooled analyses report reductions in total cholesterol of 16.16 mg/dL, LDL-cholesterol of 6.18 mg/dL and triglycerides of 13.08 mg/dL, and an increase in HDL-cholesterol of 3.76 mg/dL, alongside reductions in two-hour post-prandial glucose of 34.34 mg/dL, fasting glucose of 23.32 mg/dL and HbA1c of 0.47 %. The dose-response modelling, however, places the optima at 120 mg/day for total cholesterol, 100 mg/day for LDL-cholesterol and 140 mg/day for triglycerides — doses that substantially exceed the tolerable upper intake level and cannot be recommended for routine chronic use. This is a clear example in which the statistically optimal dose and the clinically permissible dose diverge.^{47,48}

Vitamin D is, like magnesium, a repletion-dependent agent. Pooled evidence across 39 trials shows reductions in fasting glucose of 0.49 mmol/L, HbA1c of 0.30 %, HOMA-IR of 0.39 and insulin of 1.31 μ IU/mL, with the effect concentrated in short-term high-dose regimens given to deficient, overweight patients with baseline HbA1c of 8 % or above. In this review, calcium and vitamin D co-supplementation in vitamin D-insufficient patients with T2DM produced the broadest single-trial improvement of any comparator agent, with significant reductions in insulin, HbA1c, HOMA-IR, LDL-cholesterol and the total/HDL-cholesterol ratio and significant increases in QUICKI, HOMA-B and HDL-cholesterol. Neither agent alone reproduced this effect, indicating genuine co-supplementation synergy.^{30,49}

The two vitamin K trials illustrate the dissociation between glycaemic and lipid pathways with unusual clarity. Menaquinone-7 at 360 µg/day for twelve weeks significantly reduced fasting plasma glucose and HbA1c but had no lipid-lowering effect whatsoever. Vitamin K4 at 1 mg/day for twenty-four weeks did the opposite: it significantly improved HOMA-IR and fasting insulin and reduced triglycerides and VLDL, while leaving fasting plasma glucose and HbA1c unchanged, and it was associated with antidiabetic dose reduction in 35.6 % of patients versus 13.3 % on placebo. Two vitamers of the same vitamin therefore act on different endpoints, which is a direct empirical refutation of the assumption that nutraceutical class membership predicts metabolic effect.^{31,32}

Polyphenolic nutraceuticals provided the most consistently positive multi-domain results in this review, which is relevant context for interpreting the more modest effects of the mineral agents. Rutin at 500 mg/day improved fasting glucose, insulin, HbA1c, HOMA-IR, QUICKI, LDL-cholesterol, triglycerides, VLDL, total cholesterol, the LDL/HDL ratio, the atherogenic index of plasma, IL-6, malondialdehyde, total antioxidant capacity and BDNF, all in adjusted analyses. Curcumin at 1500 mg/day over twelve months reduced fasting glucose, HbA1c and HOMA-IR while raising HOMA-β and adiponectin and lowering leptin. Resveratrol at 200 mg/day over twenty-four weeks reduced glucose, insulin, HOMA-IR, malondialdehyde, hs-CRP, TNF-α and IL-6. A Bayesian network meta-analysis ranking these agents placed resveratrol first for the composite cardiometabolic profile and silymarin first for HbA1c specifically.^{33,34,35,58}

Dose–response: five generalisable principles

Consolidating the dose–response evidence across agents yields four generalisable principles that constitute, in the view of the present authors, the most clinically actionable output of this review. The first principle is non-monotonicity. For neither coenzyme Q10 nor chromium does more equal better. CoQ10 shows a U-shaped curve for glycaemic endpoints with an optimum at 100–200 mg/day, and chromium shows greater lipid benefit below 200 µg/day than above it, with 1000 µg/day producing no advantage over 500 µg/day and neither differing from placebo in an obese insulin-treated Western population. Dose escalation in the face of non-response is therefore not a rational strategy for these agents.^{9,39,41}

The second principle is endpoint-specific dose separation. Within a single agent, the dose that optimises one endpoint may not optimise another. The clearest instance is CoQ10, where the glycaemic optimum lies at 100–200 mg/day and the total-cholesterol optimum at 400–500 mg/day. A parallel separation is visible for chromium, where glycaemic pooled effects are demonstrable across the 200–1000 µg/day range while lipid effects concentrate below 200 µg/day. Clinicians choosing a dose must therefore first choose a target endpoint.^{39,41,42}

The third principle is threshold dependence on baseline status. Magnesium works when baseline magnesium is low and fails when it is not; vitamin D works when baseline 25-hydroxyvitamin D is deficient and its effect is greatest when baseline HbA1c is 8 % or higher; chromium works in the insulin-resistant phenotype and its response is predicted by baseline clamp-derived insulin sensitivity to the extent of approximately 40 % of variance. Every one of the null trials in this review is compatible with a repletion model in which the treatable deficit was absent at randomisation. This has an important corollary for trial design: unstratified enrolment dilutes true effects towards the null and manufactures false negatives.^{1,3,12,13,49}

The fourth principle is duration dependence, which interacts with endpoint choice. Lipid endpoints in this review consistently required longer exposure than glycaemic or haemodynamic endpoints. In the twenty-four-week CoQ10 trial, blood pressure and antioxidant capacity changed by week 12 while triglycerides, LDL-cholesterol and HOMA-IR changed only by week 24. The twelve-week CoQ10 trial in metabolic syndrome was null for lipids. The twenty-four-week astaxanthin trial achieved significant LDL-cholesterol reduction where the twelve-week trial in a healthier population did not. Twelve weeks appears to be an insufficient observation window for lipid endpoints, and trials of that duration should not be interpreted as evidence of absence of lipid effect.^{20,22,24,25}

A fifth, more speculative observation concerns chemical form and bioavailability. Chromium picolinate is repeatedly identified in subgroup analyses as superior to niacin-bound chromium or chromium chloride, and picolinate and elemental forms drive the total-cholesterol subgroup effect. Among magnesium salts, organic forms such as citrate and aspartate-hydrochloride were used in the trials reporting positive glycaemic results at 365–400 mg/day, whereas magnesium oxide at 200 mg/day — a poorly absorbed inorganic salt at a low dose — was null across all metabolic endpoints.

Formulation is thus not a trivial pharmaceutical detail but a determinant of whether a trial can detect an effect at all.^{5,6,39,54}

Mechanistic integration: four sequential nodes of one cascade

The mechanistic non-overlap of these agents provides the rationale for combination and the explanation for the endpoint dissociations observed throughout this review. Magnesium acts at the proximal step of insulin signalling as the obligate cofactor for insulin-receptor tyrosine-kinase autophosphorylation and for the ATP-dependent kinases downstream of it; its deficiency therefore attenuates signal transduction before any lipid effect is possible, which is consistent with the observed pattern of insulin-resistance benefit without lipid benefit. Chromium, through chromodulin, amplifies the same receptor's kinase activity but does so post-receptor and appears additionally to reduce ectopic intramyocellular lipid, which links it to peripheral rather than hepatic insulin sensitivity.^{12,55,56}

Coenzyme Q10 acts at an entirely different level, as the mobile electron carrier between complexes I/II and III of the respiratory chain and as the sole endogenously synthesised lipid-soluble antioxidant. Its dual localisation in mitochondrial membranes and in circulating lipoproteins explains why it can improve both insulin sensitivity — through restoration of oxidative phosphorylation capacity in skeletal muscle and beta cells — and lipoprotein biology, through protection of LDL from oxidative modification and through adiponectin-mediated pathways. The demonstration that adiponectin mediates the improvement in HOMA-IR, triglycerides and LDL-cholesterol supports a common adipose-tissue node rather than two independent mechanisms.^{21,41,42,45}

Astaxanthin's transmembrane orientation, with polar hydroxyl and keto groups anchored at both membrane surfaces, allows it to quench singlet oxygen and scavenge radicals across the entire bilayer rather than only within the hydrophobic core, and unlike beta-carotene it does not become pro-oxidant at elevated oxygen tension. This is the structural basis for its preferential effect on lipoprotein oxidation, evidenced here by the reduction in malondialdehyde-modified LDL with unchanged total cholesterol. The pattern of consistent reductions in IL-6, TNF- α and TGF- β 1 with increases in superoxide dismutase and total antioxidant capacity across human studies is congruent with a mechanism operating primarily at the oxidative-inflammatory interface.^{24,52}

A unifying model consistent with the data assembled here is that these four agents act at four sequential nodes of a single pathophysiological cascade: micronutrient cofactor sufficiency for receptor signalling (magnesium), post-receptor signal amplification and ectopic lipid disposal (chromium), mitochondrial oxidative capacity and adipokine signalling (coenzyme Q10), and terminal lipoprotein oxidative protection (astaxanthin). Under this model, combination is mechanistically rational and substitution is not, which is consistent with the observation that eleven of the included studies used fixed multi-component formulations and that several of these — including the berberine-hesperidin-chromium combination and the calcium–vitamin D combination — outperformed their individual components.^{14,21,30,55}

Clinical implications and practical prescribing

Translating this evidence into practice requires an explicit statement of what these agents are and are not. They are adjuncts. Nothing in this review supports the substitution of a nutraceutical for metformin, an SGLT2 inhibitor, a GLP-1 receptor agonist or a statin, and no included trial tested such a substitution. The effect sizes reported here — an HbA1c reduction of 0.3–0.7 %, an LDL-cholesterol reduction of approximately 0.3 mmol/L, a HOMA-IR reduction of 0.4–1.5 — are meaningful additions to guideline-directed therapy and are not replacements for it.^{38,41,42,51}

A phenotype-first prescribing sequence follows logically from the threshold principle. Before initiating magnesium, serum magnesium should be measured, and the expected benefit is confined to those at or below approximately 0.74–0.79 mmol/L; renal function must be checked, since impaired excretion is a contraindication and was an exclusion criterion in the index trial. Before initiating vitamin D, 25-hydroxyvitamin D should be measured. For chromium, the phenotype marker is insulin resistance itself, with the greatest response expected in patients with high fasting glucose, high HbA1c and low measured insulin sensitivity. For coenzyme Q10 and astaxanthin, no biochemical gate is established, but the target endpoint should be declared in advance because it determines the dose.^{1,12,13,41,49}

Practical dosing recommendations that follow from the dose–response synthesis are as follows. Magnesium: 250–400 mg/day of elemental magnesium in an organic salt (citrate, chloride or aspartate) for at least twelve weeks, in documented hypomagnesaemia. Chromium: chromium

picolinate, and for a lipid-directed indication a dose below 200 µg/day is supported over higher doses; for a glycaemic-directed indication the 200–1000 µg/day range has pooled support but without evidence of superiority at the upper end. Coenzyme Q10: 100–200 mg/day for a glycaemic target and 400–500 mg/day for a cholesterol target, for at least twenty-four weeks. Astaxanthin: 12 mg/day for at least twelve and preferably twenty-four weeks, with 20 mg/day considered where a structured exercise programme is concurrent.^{39,41,42,25,27}

Safety findings across this review were reassuring and are an important part of the risk-benefit calculus. No trial reported a serious adverse event attributable to the intervention. Chromium picolinate at up to 1000 µg/day produced no clinically significant haematological, renal or hepatic toxicity; a nutraceutical containing zinc and chromium produced no biochemical evidence of hepatic or renal toxicity; astaxanthin at 12 mg/day for twenty-four weeks was explicitly described as safe and well tolerated with no clinically significant adverse events; and magnesium-related symptoms did not differ from placebo in a controlled crossover trial. The principal agent-specific tolerability issue in the wider literature is gastrointestinal, exemplified by berberine, where transient gastrointestinal effects occurred in 34.5 % of patients. Magnesium in renal impairment remains the single most important contraindication.^{3,11,17,25,61}

A final practical point concerns drug interactions and the special case of statin therapy. Statins inhibit the mevalonate pathway and thereby reduce endogenous coenzyme Q10 synthesis, which provides a theoretical rationale for CoQ10 supplementation in statin-treated patients. Evidence in coronary artery disease shows that 300 mg/day of CoQ10 during statin therapy raises antioxidant enzyme activity and reduces TNF- α . This review cannot establish that such supplementation improves clinical outcomes, but it identifies the statin-treated dyslipidaemic diabetic patient as a rational population for future dose-ranging trials.^{42,45}

Comparison with previous systematic reviews and meta-analyses

The findings of this review are largely concordant with the existing single-agent syntheses while adding the comparative and dose dimensions that those syntheses could not supply. For chromium, the present conclusion — statistically significant pooled glycaemic effects of uncertain individual-patient clinical meaningfulness, concentrated in the insulin-resistant phenotype, with a

small and dose-inverted lipid effect — reconciles the apparently opposed conclusions of the pooled quantitative literature and the threshold-based narrative appraisal. For coenzyme Q10, the present conclusion is directly supported by two independent dose-response meta-analyses and by a further meta-analysis reporting that lower doses below 200 mg/day and durations under twelve weeks produced the greatest glucose-lowering effect.^{38,41,42,44,53}

Where this review departs from prior work is in its treatment of the umbrella-level certainty ratings. A hierarchical umbrella review of nutrient supplements in T2DM rated the evidence for chromium, vitamin C and omega-3 fatty acids on HbA1c as very low certainty, and for vitamin D on HbA1c in trials shorter than six months as very low certainty, while noting significant effects for magnesium, zinc, vitamin C, probiotics and polyphenols on fasting glucose. The present review agrees that certainty is limited but attributes a substantial share of that limitation to a specific and remediable design failure — unstratified enrolment with respect to baseline micronutrient status and baseline insulin sensitivity — rather than to an absence of underlying biological effect.⁵¹

The most recent CoQ10 meta-analysis, comprising thirty-nine randomised trials, reported statistically significant but modest reductions in fasting blood glucose of 7.33 mg/dL and fasting insulin of 0.84 μ IU/mL with an HbA1c estimate of -0.12% whose confidence interval crossed zero, and graded the certainty of evidence as very low. That estimate is smaller than the 0.37% HbA1c reduction observed in the factorial trial included here, which is consistent with dilution of a dose-specific and population-specific effect across a heterogeneous pooled sample — precisely the analytical problem that the dose-stratified approach adopted in this review is designed to expose.^{19,43}

Strengths

The strengths of this review are its comparative architecture, its explicit dose-response synthesis, its adherence to the prespecified design-eligibility rule that excludes secondary research from the characteristics tables while preserving it for outcome corroboration, its dual-reviewer extraction and appraisal, and its citation-provenance protocol under which every included reference was independently verified through an academic search engine. Fifteen outcome domains were analysed rather than the two or three typical of single-agent reviews, permitting the identification of endpoint dissociations that narrower reviews cannot detect.^{38,41,51}

Directions for future research

The single most important recommendation for future research arising from this review is that trials of magnesium, chromium and vitamin D should stratify randomisation by baseline status of the relevant biomarker. An unstratified trial in a population with a low prevalence of deficiency is, on the evidence assembled here, a trial designed to produce a null result. Enrichment designs that enrol only patients below a prespecified threshold — serum magnesium ≤ 0.74 mmol/L, 25-hydroxyvitamin D below the deficiency cut-off, or clamp-derived insulin sensitivity below the population median — would materially increase the informativeness of the evidence base.^{1,12,13,49}

Second, dose-ranging arms should replace single-dose designs. The demonstration of U-shaped and inverse J-shaped dose–response curves for coenzyme Q10 means that a two-arm trial comparing one dose with placebo cannot characterise the agent. Three-arm or four-arm dose-ranging trials with prespecified endpoint-specific hypotheses — for example, 100 mg/day versus 200 mg/day versus 400 mg/day of CoQ10 with HbA1c and total cholesterol as co-primary endpoints — would directly test the endpoint-separation hypothesis generated here.^{41,42}

Third, trial duration should be matched to the endpoint. Lipid endpoints require at least twenty-four weeks, and preferably longer, and trials of twelve weeks or less should not report null lipid findings as evidence of absence of effect. Fourth, intracellular or functional biomarkers should supplement serum measurements where the serum marker is known to be insensitive, as is the case for magnesium. Fifth, head-to-head comparative trials between agents with different mechanistic targets, and factorial trials of rational combinations such as coenzyme Q10 with astaxanthin or magnesium with chromium, would test the sequential-node model proposed in this review.^{1,20,25,41}

Sixth, hard clinical endpoints remain almost entirely unstudied. Every trial in this review used surrogate biochemical endpoints; none was powered for major adverse cardiovascular events, progression to diabetes, microvascular complications or mortality. The one included magnesium trial with a vascular structural endpoint was null. Until adequately powered outcome trials exist, all clinical recommendations for nutraceuticals in this setting — including those made in this review — remain surrogate-based and provisional. Seventh, standardisation of formulation, elemental content

reporting and outcome definition across trials would substantially improve the feasibility of future quantitative synthesis.^{3,25,63}

CONCLUSION AND RECOMMENDATIONS

Conclusion

This comprehensive systematic review of thirty-two primary studies, supported by sixteen retained quantitative syntheses, establishes that nutraceutical supplementation produces statistically significant and clinically coherent improvements in the lipid profile, glycated haemoglobin and the homeostatic model assessment of insulin resistance in adults with type 2 diabetes mellitus and dyslipidaemia. The three co-primary endpoints were all met. Magnesium at 250–400 mg/day of elemental magnesium significantly reduced HOMA-IR and HbA1c in hypomagnesaemic patients; chromium produced pooled reductions in fasting plasma glucose, HbA1c and HOMA-IR; coenzyme Q10 significantly reduced HbA1c, triglycerides, LDL-cholesterol, HOMA-IR and blood pressure; and astaxanthin significantly reduced total and LDL-cholesterol and oxidised LDL.^{1,20,25,38,41}

The central conclusion of this review, however, is not that nutraceuticals work but that they work conditionally, agent-specifically and non-monotonically. Efficacy is conditional on baseline micronutrient status and baseline insulin sensitivity; it is agent-specific in that magnesium and chromium act predominantly on the glycaemic and insulin-resistance axes while astaxanthin acts predominantly on the lipid and oxidative axes and coenzyme Q10 acts on both at different doses; and it is non-monotonic in that higher doses are frequently not better and are sometimes worse. The demonstration that the glycaemic optimum for coenzyme Q10 lies at 100–200 mg/day while the total-cholesterol optimum lies at 400–500 mg/day is, in the view of the authors, the most directly actionable single finding of this work.^{39,41,42}

The certainty of the evidence was rated as moderate for HbA1c, HOMA-IR, total cholesterol, LDL-cholesterol, triglycerides, oxidative-stress markers, blood pressure and safety, and as low for fasting glucose, fasting insulin, clamp-derived insulin sensitivity, HDL-cholesterol, atherogenic indices, inflammatory markers and anthropometry. No conclusion in this review is based on high-certainty evidence, and all are based on surrogate biochemical endpoints. These agents should

accordingly be positioned as phenotype-targeted adjuncts to guideline-directed pharmacotherapy and structured lifestyle intervention, never as substitutes for them.^{41,51}

Recommendations

For clinical practice: (i) measure serum magnesium and 25-hydroxyvitamin D before initiating the corresponding supplement, and confine expectation of benefit to patients below the deficiency threshold; (ii) check renal function before magnesium supplementation and regard significant renal impairment as a contraindication; (iii) declare the target endpoint before selecting a coenzyme Q10 dose, using 100–200 mg/day for glycaemic targets and 400–500 mg/day for cholesterol targets; (iv) prefer chromium picolinate over other chromium salts and do not escalate beyond 200 µg/day for lipid indications; (v) use organic magnesium salts at 250–400 mg/day of elemental magnesium rather than low-dose magnesium oxide; (vi) allow at least twenty-four weeks before judging a lipid endpoint; and (vii) document all supplement use in the medication record, since concurrent nutraceutical use may contribute to observed changes in glycaemic and lipid control.^{1,5,39,41,42}

For patient counselling: explain that these agents are adjuncts of modest effect size, that the expected benefit is greatest where a deficiency exists, that higher doses are not proportionally better and may be counterproductive, that the tolerability profile is generally good but that gastrointestinal effects and drug interactions are possible, and that supplementation is never a reason to reduce or discontinue prescribed glucose-lowering or lipid-lowering therapy without medical review.^{51,53,61}

For future research: conduct baseline-status-stratified enrichment trials; incorporate at least three dose arms; extend duration to at least twenty-four weeks for lipid endpoints; use intracellular or functional biomarkers where serum measures are insensitive; perform head-to-head and factorial combination trials guided by mechanistic non-overlap; standardise reporting of elemental content, chemical form and outcome definitions; and, ultimately, progress from surrogate endpoints to adequately powered trials of hard cardiovascular and microvascular outcomes.^{1,12,41,42,63}

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