

Efficacy and Safety of Homeopathic Medicines in Diabetes, Pre-Diabetes, and Related Complications: Protocol for a Systematic Review and Meta-Analysis

Subhranil Saha

D. N. De Homoeopathic Medical College and Hospital, Kolkata, Govt. of West Bengal

Soumya Bhattacharyya

D. N. De Homoeopathic Medical College and Hospital, Kolkata, Govt. of West Bengal

Shubhamoy Ghosh

D. N. De Homoeopathic Medical College and Hospital, Kolkata, Govt. of West Bengal

Sharmishtha Gupta

Dept. of Science and Technology and Biotechnology, Govt. of West Bengal

Abhijit Dutta

drabhijitdutta1@gmail.com

Ministry of Ayush, Government of India, New Delhi <https://orcid.org/0000-0002-1864-0685>

Systematic Review

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Abstract

Background

Diabetes mellitus and pre-diabetes affect nearly one billion adults globally and carry a substantial complication burden including peripheral neuropathy. A significant proportion of patients with diabetes use homeopathic medicines as adjunctive therapy. Despite this, the controlled-trial evidence for homeopathic interventions across the full diabetes-complications spectrum has not been quantitatively synthesised.

Objectives

This protocol describes the methods for a systematic review and meta-analysis to evaluate the efficacy and safety of homeopathic medicines compared with placebo in adults with pre-diabetes, Type 1 or Type 2 diabetes mellitus, or established diabetic complications, on glycaemic outcomes (fasting blood glucose [FBS], 2-hour oral glucose tolerance test [OGTT], glycosylated haemoglobin [HbA1c]), neuropathic symptom scores (Neuropathy Total Symptom Score-6 [NTSS-6]), disease progression, and adverse events.

Methods

Five electronic databases (PubMed/MEDLINE, Scopus, Cochrane CENTRAL, CAM-Quest) and grey literature sources (CTRI India, ClinicalTrials.gov, WHO ICTRP, ProQuest Dissertations) will be searched from inception without language restriction. Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) with concurrent control groups are eligible. Two independent reviewers will screen, extract, and assess risk of bias using Cochrane RoB 2 (RCTs) and ROBINS-I (CCTs). Where ≥ 2 clinically comparable studies report the same outcome, random-effects meta-analysis (DerSimonian-Laird; Hartung-Knapp-Sidik-Jonkman [HKSJ] correction) will be applied. Certainty of evidence will be assessed using the GRADE framework. The review is reported in accordance with PRISMA-P 2015¹ and PRISMA 2020.²

Dissemination:

Findings will be published in a peer-reviewed journal and the completed systematic review submitted alongside this protocol.

1 | BACKGROUND AND RATIONALE

1.1 Burden of Diabetes and Pre-Diabetes

Diabetes mellitus (DM), encompassing Type 2 diabetes (T2DM), Type 1 diabetes (T1DM), pre-diabetes, and gestational diabetes, is among the most significant public health challenges of the 21st century. The International Diabetes Federation (IDF) estimated that 537 million adults were living with diabetes in 2021, a figure projected to reach 783 million by 2045, with the greatest burden in South and South-East Asia.³ Pre-diabetes, defined by impaired fasting glucose (IFG: 100–125 mg/dL), impaired glucose tolerance (IGT: OGTT 140–199 mg/dL), or HbA1c 5.7–6.4%, affects an additional 541 million individuals globally.³ Annual conversion from pre-diabetes to T2DM is estimated at 5–10% per year in the absence of structured intervention, and at approximately 75–78 per 1,000 person-years in Indian cohorts.⁴

Diabetic peripheral neuropathy (DPN) affects 20–50% of patients with T1DM or T2DM over the disease course and is the leading cause of diabetes-related disability, foot ulceration, and lower-limb amputation.⁵ Pharmacological management of established DPN remains challenging: pregabalin and duloxetine, the most commonly prescribed agents, produce modest effect sizes ($d \approx 0.4$ – 0.7) and carry significant burdens of adverse effects including dizziness, sedation, and weight gain.⁶

1.2 Homeopathy as Adjunctive Therapy in Diabetes

Against this background, use of complementary and alternative medicine (CAM), including homeopathy, among patients with diabetes is substantial. Population surveys in South Asia, Europe, and Latin America report CAM use rates of 20–40% in diabetic populations, with homeopathy among the most commonly utilised modalities.^{7,8} Homeopathy encompasses several distinct prescribing paradigms: (i) classical or Kentian individualised prescribing, in which a single remedy is selected on the totality of the patient's physical, emotional, and constitutional symptoms; (ii) semi-individualised or condition-specific prescribing from a pre-identified set of remedies; (iii) isopathic preparations, including low-potency minerals such as Selenium 7CH used for targeted biochemical effects; and (iv) complex or combination homeopathic products. These paradigms differ fundamentally in their mechanistic assumptions and should be evaluated separately in systematic reviews.

Despite widespread patient utilisation, the controlled-trial evidence for homeopathic interventions across the full diabetes-complications spectrum has not been comprehensively synthesised, which is also required for practice recommendation⁹. The Mathie et al. (2014) meta-analysis of individualised homeopathy found a small but statistically significant overall effect across a broad range of conditions, but did not include a diabetes-specific subgroup.¹⁰ The Australian National Health and Medical

Research Council (NHMRC) 2015 assessment concluded there was no good-quality evidence for homeopathy in any health condition, but that review predates all four RCTs now available in the diabetes/neuropathy domain.¹¹

Since 2015, four new RCTs have been published or completed in this field: Guha et al. (2023) in pre-diabetes;¹² Banerjee et al. (2024) in pre-diabetes;¹³ Mehra et al. (2021) in diabetic distal symmetric polyneuropathy (DDSP);¹⁴ and Chandra (2024) in peripheral diabetic neuropathy (PDN).¹⁵ Additionally, Van der Veen (2001) conducted a controlled trial of Selenium 7CH in T1DM, the first homeopathic trial targeting the selenium-glutathione peroxidase oxidative stress pathway in T1DM, which has not been included in any prior systematic review.¹⁶ A comprehensive meta-analysis incorporating all available evidence is therefore both timely and feasible.

1.3 Rationale for This Review

The present systematic review and meta-analysis is warranted because, no prior review has systematically examined homeopathic interventions across the full spectrum of diabetes complications.

2 | OBJECTIVES

Primary objective

To determine whether homeopathic medicines, compared with placebo or active control, significantly reduce fasting blood glucose (FBS), 2-hour oral glucose tolerance test (OGTT), glycosylated haemoglobin (HbA1c), or neuropathy total symptom scores (NTSS-6) in adults with pre-diabetes, T1DM, T2DM, or diabetic peripheral neuropathy.

Secondary objectives

(i) To assess the effect of homeopathic medicines on pain instruments (DN4, DNE, SF-MPQ), quality of life (WHOQOL-BREF, DSC-R, MYMOP-2), and oxidative stress markers (TAS, GSH-Px); (ii) to determine rates of progression from pre-diabetes to T2DM; (iii) to evaluate the safety of homeopathic preparations as adjunctive therapy by documenting adverse events and serious adverse events (SAEs); (iv) to assess the certainty of the available evidence using GRADE; and (v) to identify evidence gaps to inform future research priorities.

3 | METHODS

This protocol is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P 2015) statement.¹ The corresponding

systematic review is reported in accordance with PRISMA 2020.² The protocol was registered in PROSPERO [CRD420261353082]. All deviations from this pre-specified protocol will be documented and justified in the final review manuscript.

3.1 Eligibility Criteria

Eligibility will be assessed using the PICOS (Population, Intervention, Comparator, Outcomes, Study design) framework.¹⁷ Full inclusion and exclusion criteria are detailed in Table 1.

Table 1
PICOS eligibility criteria

Domain	Specification
Population	Adults (≥ 18 years) with: (a) pre-diabetes [impaired fasting glucose (IFG) 100–125 mg/dL; impaired glucose tolerance (IGT): OGTT 2-hr 140–199 mg/dL; or HbA1c 5.7–6.4%]; (b) Type 1 diabetes mellitus (T1DM); (c) Type 2 diabetes mellitus (T2DM); (d) gestational diabetes mellitus; (e) metabolic syndrome; or (f) any established diabetic complication including peripheral neuropathy, nephropathy, retinopathy, or cardiovascular disease
Intervention	Any homeopathic preparation, including: (a) individualised/classical (Kentian) prescribing; (b) fixed-combination or complex homeopathic preparations; (c) isopathic or low-potency mineral preparations (e.g., Selenium 7CH); (d) mother tinctures or potentised herbal preparations; at any potency, dose, frequency, or treatment duration; delivered as monotherapy or adjunct to conventional care
Comparator	Identical-looking placebo; conventional pharmacotherapy; lifestyle intervention (diet, exercise, yoga); no active treatment; or an alternative homeopathic preparation. Active standard care co-administered equally to both arms was permitted
Outcomes (Primary)	Fasting blood glucose/sugar (FBS/FBG, mg/dL or mmol/L); 2-hour post-challenge glucose on oral glucose tolerance test (OGTT 2-hr PG, mg/dL); glycosylated haemoglobin (HbA1c, %); Neuropathy Total Symptom Score-6 (NTSS-6); progression from pre-diabetes to T2DM (dichotomous)
Outcomes (Secondary)	Douleur Neuropathique 4 questionnaire (DN4); Diabetic Neuropathy Examination (DNE) score; Short-Form McGill Pain Questionnaire (SF-MPQ, all sub-scores); quality of life instruments (WHOQOL-BREF, DSC-R, MYMOP-2); oxidative stress markers (TAS, GSH-Px, Ferritin, Albumin, Uric Acid); nerve conduction studies (NCS); adverse events and serious adverse events (SAEs); homeopathic aggravations
Study Design	Randomised controlled trials (RCTs; parallel-arm; any blinding status) and non-randomised controlled clinical trials (CCTs) with concurrent control groups. Excluded: cross-over designs, observational studies, case series, single-arm trials, systematic reviews
Context	Any clinical setting; any country; any healthcare system; homeopathy delivered as primary or adjunctive therapy

RCT = randomised controlled trial; CCT = controlled clinical trial; OGTT = oral glucose tolerance test; HbA1c = glycosylated haemoglobin; FBS = fasting blood sugar; NTSS-6 = Neuropathy Total Symptom Score-6; T1DM/T2DM = Type 1/2 diabetes mellitus; DPN = diabetic peripheral neuropathy; DDSP = diabetic distal symmetric polyneuropathy; TAS = Total Antioxidant Status; GSH-Px = Glutathione Peroxidase; DSC-R = Diabetes Symptom Checklist-Revised; MYMOP-2 = Measure Yourself Medical Outcome Profile-2; SAEs = serious adverse events.

Studies reporting outcomes in subgroups will be included provided the subgroup of interest can be extracted independently. Studies in which homeopathy is delivered as a named commercial product will be eligible provided the comparator is placebo or a non-homeopathic control. Studies without a concurrent control group, single-arm observational studies, case series, and case reports, will be excluded. Studies in animal models or in vitro settings will be excluded.

3.2 Information Sources and Search Strategy

The following electronic databases will be searched from inception to the search date (15 March 2026) without language restriction: (1) PubMed/MEDLINE via PubMed.gov; (2) Scopus (Elsevier); (3) Cochrane Central Register of Controlled Trials (Cochrane CENTRAL); and (4) CAM-Quest (specialist complementary medicine database). Grey literature sources will include the Clinical Trial Registry India (CTRI; ctri.nic.in), ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (WHO ICTRP; trialsearch.who.int), ProQuest Dissertations and Theses Global, and OpenGrey.

Reference lists of all included studies and the three most directly relevant prior systematic reviews will be hand-searched. Key journals will be hand-searched for the preceding five years: Homeopathy (Elsevier); Explore: The Journal of Science and Healing (Elsevier); Complementary Therapies in Medicine; Indian Journal of Research in Homoeopathy. No language restriction will be applied; non-English articles will be translated using Google Translate with verification by a bilingual team member.

Search strategies were developed iteratively using Medical Subject Headings (MeSH terms for PubMed), Emtree (Scopus), and free-text terms, and were tested for sensitivity against five known eligible studies before final execution. A summary of databases, key terms, and record counts is provided in Table 2.

Table 2
Information sources and search strategy summary

Database/Source	Date	Key Terms (abbreviated)	Filters
PubMed/MEDLINE (NLM; via pubmed.gov)	15 Mar 2026	MeSH: "Homeopathy"; "Diabetes Mellitus"; "Diabetic Neuropathies"; "Prediabetic State" Free text: homeopath*, homoeopath*, individualised homeopath*, selenium 7CH, diabetes, NTSS-6, HbA1c, fasting blood glucose, OGTT, oxidative stress Filter: RCT[PT]; CCT[PT]	Inception- 15 March 2026; no language restriction
Scopus (Elsevier)	15 Mar 2026	TITLE-ABS-KEY: (homeopath* OR homoeopath*) AND (diabetes OR diabetic neuropath* OR NTSS-6 OR HbA1c OR oral glucose tolerance OR oxidative stress) AND (randomized controlled trial OR double-blind OR placebo-controlled)	Inception- 15 March 2026; no language restriction
Cochrane CENTRAL (Cochrane Library)	15 Mar 2026	MeSH: [Homeopathy] explode; [Diabetes Mellitus] explode; [Diabetic Neuropathies] explode; [Prediabetic State] explode Free text: homeopath*; diabetes; NTSS-6; HbA1c; fasting blood glucose	Inception- 15 March 2026; no language restriction
CAM-Quest (specialist CAM database)	15 Mar 2026	Keywords: homeopathy AND diabetes; homoeopathy AND diabetes; homeopathy AND neuropathy; homeopathy AND pre-diabetes; selenium AND homeopathy AND diabetes	Inception- 15 March 2026
CTRI India (ctri.nic.in) [Grey literature]	15 Mar 2026	Intervention = homeopathy/homoeopathy; Condition = diabetes/neuropathy	All statuses
ClinicalTrials.gov [Grey literature]	15 Mar 2026	homeopathy AND diabetes; homeopathic AND neuropathy	All statuses; all phases
WHO ICTRP [Grey literature]	15 Mar 2026	homeopath* AND diabetes	All statuses
ProQuest Dissertations & Theses Global [Grey literature]	15 Mar 2026	(homeopathy OR homoeopathy) AND (diabetes OR neuropathy); selenium AND homeopathy AND diabetes	Inception- 15 March 2026

Database/Source	Date	Key Terms (abbreviated)	Filters
Hand-searching (journals + reference lists)	15 Mar 2026	Reference lists of 5 included studies + 3 prior SRs (Saha 2013; Mathie 2014; NHMRC 2015); journals: Homeopathy; Explore; Complementary Therapies in Medicine; Indian J Res Homoeopathy (last 5 years)	Last 5 years (journals); all years (ref lists)

CTRI = Clinical Trial Registry India; WHO ICTRP = WHO International Clinical Trials Registry Platform; SR = systematic review; NHMRC = National Health and Medical Research Council (Australia); Rayyan QCRI = web-based systematic review screening tool., = not quantified separately; grey literature records were combined and deduplicated together. Searches will be conducted on 15 March 2026.

3.3 Study Selection

All records will be imported into Rayyan QCRI for deduplication and screening management.¹⁸ Screening will proceed in two stages:

- Stage 1, Title and abstract screening:** Two independent reviewers (AD and PB) will independently screen all titles and abstracts against the PICOS eligibility criteria. Each record will be classified as 'include', 'exclude', or 'uncertain'. Discrepancies will be resolved by discussion; if consensus cannot be reached, a third reviewer (SS) will adjudicate.
- Stage 2, Full-text assessment:** Full texts of all 'include' and 'uncertain' records from Stage 1 will be retrieved and assessed independently by the same two reviewers against the complete eligibility criteria. Reasons for exclusion at full-text stage will be documented and reported in the PRISMA 2020 flow diagram.² Inter-rater agreement (Cohen's κ) will be calculated at this stage as well.

Eligibility decisions will be made independently of knowledge of results. Reviewers will not be masked to author names, journal names, or publication years.

3.4 Data Extraction

A standardised data extraction form was developed a priori in Microsoft Excel, based on the Cochrane data extraction template.¹⁷ Data will be extracted independently and in duplicate by two reviewers. Discrepancies will be resolved by re-checking the original paper and discussion; unresolved discrepancies will be adjudicated by the senior author. Primary study authors will be contacted to clarify missing or ambiguous data only if two independent reviewers agree the missing information is critical for the primary analysis and cannot be estimated from available data.

Variables extracted from each included study are detailed in Table 3.

Table 3
Data extraction items

Category	Variables extracted
Study identification	First author; year; journal/source; title; country; trial registration number; ethics approval; funding source
Study design	RCT/CCT; randomisation method; allocation concealment; blinding level; number of parallel arms; phase designation
Participants	N enrolled; N analysed; N per arm; age (mean $\pm$ SD); sex; BMI (kg/m ²); diagnostic criteria; duration of illness; key co-morbidities; baseline medications; baseline outcome values (mean $\pm$ SD) per arm
Intervention	Preparation name; prescribing approach (individualised/classical, semi-individualised, fixed-combination, isopathic, mother tincture); potency (centesimal, decimal, LM); dose; frequency; treatment duration; total number of remedies prescribed; most frequently prescribed remedies; vehicle; manufacturer (where stated)
Comparator	Type (identical-looking placebo, active control); blinding method; active co-interventions present in both arms
Outcomes (primary)	Instrument name; timing; means, SDs, 95% CIs, t-statistics, F-statistics, partial η^2 , Cohen's d; p-values; analysis method (ANOVA, ANCOVA, repeated-measures ANOVA, ITT vs per-protocol); Bonferroni thresholds where specified
Outcomes (secondary)	Same statistical data for all pre-specified secondary outcomes; quality-of-life scores; adverse events (type, severity, CTCAE grade); SAEs; homeopathic aggravations; withdrawals and reasons
Missing data	Method (ITT, complete case, LOCF, multiple imputation); proportion missing; reasons; whether dropout reasons were balanced across arms
Risk of bias	All signalling questions for RoB 2 (5 domains; 4 RCTs) and ROBINS-I (7 domains; 1 CCT) completed independently per study
Additional	Funding source; conflicts of interest; CONSORT/RedHot adherence; protocol deviations noted

SDs = standard deviations; CIs = confidence intervals; ANOVA = analysis of variance; ANCOVA = analysis of covariance; ITT = intention-to-treat; LOCF = last observation carried forward; CTCAE = Common Terminology Criteria for Adverse Events; CONSORT = Consolidated Standards of Reporting Trials; RedHot = Reporting Data on Homeopathic Treatments (CONSORT extension for homeopathy¹⁷).

Handling of missing data: Where endpoint standard deviations (SDs) are reported but change-score SDs are not, change-score SDs will be estimated as: $SD_{change} = \sqrt{(SD_{pre}^2 + SD_{post}^2 - 2r \cdot SD_{pre} \cdot SD_{post})}$, where r is the within-person correlation coefficient, assumed to be r = 0.5 (conservative default per Cochrane guidelines).¹⁷ Where only standard errors (SEM) or 95% CIs are reported, SDs will be back-calculated. Where mean differences and

95% CIs are reported without SDs, the standard error will be calculated as: $SE = (\text{upper CI} - \text{lower CI}) / (2 \times z_{0.0005})$, where $z_{0.0005} = 1.96$.

3.5 Risk of Bias Assessment

Risk of bias in RCTs will be assessed using the Cochrane Risk of Bias 2 (RoB 2) tool,¹⁹ which evaluates five domains: (D1) randomisation process; (D2) deviations from intended interventions; (D3) missing outcome data; (D4) measurement of outcomes; and (D5) selection of reported results. Each domain will be assigned a judgement of 'Low risk', 'Some concerns', or 'High risk'. The overall RoB 2 rating will follow the worst-domain rule.

Risk of bias in the non-randomised CCT will be assessed using the Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool,²⁰ which evaluates seven domains: (D1) confounding; (D2) selection of participants; (D3) classification of interventions; (D4) deviations from intended interventions; (D5) missing data; (D6) measurement of outcomes; and (D7) selection of reported results. Domain ratings are: 'Low', 'Moderate', 'Serious', or 'Critical' risk of bias.

Conservative rating for grey literature sources

For unpublished theses, Domain 5 (reporting bias; RoB 2) and Domain 7 (reporting bias; ROBINS-I) will be rated conservatively at a minimum of 'Some concerns'/'Serious', because selective outcome reporting cannot be excluded in the absence of independent peer review. Similarly, single-investigator studies conducting both prescribing and outcome assessment with subjective instruments will be rated 'Some concerns' in Domain 2 (deviations) due to the potential for unblinding.

Risk of bias will be assessed independently by two reviewers. Discrepancies will be resolved by discussion and adjudication by the senior author. Risk of bias will not be used as grounds for exclusion from the systematic review; instead, it will be incorporated into GRADE certainty-of-evidence ratings and into pre-specified sensitivity analyses.

3.6 Outcomes and Prioritisation

Primary and secondary outcomes are listed in the PICOS table (Table 1). The outcome hierarchy, instrument details, timing, and minimum clinically important differences (MCIDs) are summarised in Table 4. MCIDs were sourced from published validation studies and clinical guidelines: HbA1c MCID = 0.5% absolute reduction (American Diabetes Association 2022 consensus); NTSS-6 MCID = 1.5–2.0 point reduction.²¹

Table 4
Outcome hierarchy, instruments, timing, and minimum clinically important differences (MCIDs)

Outcome Category	Instrument / Measure	Population(s)	Timing	MCID / Response Threshold
Primary, Glycaemic	FBS/FBG (mg/dL)	Pre-diabetes; T2DM; T1DM	Baseline; every 1–2 months; final	Pre-diabetes: FBS < 100 mg/dL = normalisation T2DM: ≥10% reduction from baseline
Primary, Glycaemic	OGTT 2-hr PG (mg/dL)	Pre-diabetes	Baseline; 3- or 6-month final	Response: OGTT < 140 mg/dL Change: ≥15 mg/dL clinically meaningful
Primary, Glycaemic	HbA1c (%)	All diabetic populations	Baseline; 3- and/or 6-month final	MCID: ≥0.5% absolute reduction (ADA 2022 consensus)
Primary, Neuropathy	NTSS-6 (range 0–28.44)	T2DM+DDSP; PDN	Baseline; monthly; final	MCID: 1.5–2.0 point reduction (Bastyr et al., Clin Ther 2005) ¹¹
Primary, Progression	Progression to T2DM (dichotomous)	Pre-diabetes	3-month and 6-month assessments	HbA1c ≥ 6.5% or FBS ≥ 126 mg/dL at follow-up
Secondary, Neuropathy	DN4 (range 0–10)	PDN; DDSP	Baseline; monthly; final	Score ≥ 4: probable neuropathic pain MCID: ≥1.5 points
Secondary, Neuropathy	DNE (range 0–16)	PDN; DDSP	Baseline; monthly; final	Score > 3: confirmed neuropathy MCID: ≥2 points
Secondary, Pain	SF-MPQ (PRI, Sensory, Affective, VAS)	PDN	Baseline; monthly; final	VAS: ≥1.3 cm reduction PRI: ≥5 point reduction

Outcome Category	Instrument / Measure	Population(s)	Timing	MCID / Response Threshold
Secondary, Quality of life	WHOQOL-BREF; DSC-R; MYMOP-2	T2DM; PDN; Pre-diabetes	Baseline; final	WHOQOL-BREF: ≥ 8 points per domain DSC-R: $\geq 10\%$ subscale reduction
Secondary, Oxidative stress	TAS (ABTS++, mmol/L); GSH-Px (U/g Hb); Albumin; Uric acid; Ferritin	T1DM	Baseline; 6-week	No established MCID; directional change assessed
Safety	Adverse events; SAEs; Homeopathic aggravations	All populations	Continuous throughout trial	Any SAE attributable to intervention; homeopathic aggravation = transient exacerbation of existing symptoms

NTSS-6 = Neuropathy Total Symptom Score-6; DN4 = Douleur Neuropathique 4 questionnaire; DNE = Diabetic Neuropathy Examination; SF-MPQ = Short-Form McGill Pain Questionnaire; VAS = Visual Analogue Scale; PRI = Pain Rating Index; WHOQOL-BREF = World Health Organization Quality of Life abbreviated instrument; DSC-R = Diabetes Symptom Checklist-Revised; MYMOP-2 = Measure Yourself Medical Outcome Profile-2; TAS = Total Antioxidant Status; GSH-Px = Glutathione Peroxidase; DDSP = diabetic distal symmetric polyneuropathy; PDN = peripheral diabetic neuropathy; FBG = fasting blood glucose; MCID = minimum clinically important difference; ADA = American Diabetes Association. Bastyr EJ et al. Clin Ther. 2005;27:1278-1294.

3.7 Statistical Analysis Plan

Statistical analyses will be performed using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) with the meta (v7.0-0) and metafor (v4.4-0) packages.

3.7.1 Meta-Analysis Methods

Where ≥ 2 studies report the same outcome in clinically comparable populations, random-effects meta-analysis will be performed using the DerSimonian-Laird (DL) method for estimating τ^2 (between-study variance).²² Confidence intervals for the pooled estimate will be calculated using the Hartung-Knapp-Sidik-Jonkman (HKSJ) correction, which provides more accurate interval coverage when the number of studies is small.¹⁷ Mean differences (MD; 95%CI) will be used for continuous outcomes; risk ratios (RR; 95%CI) using the Mantel-Haenszel method for dichotomous outcomes.

Statistical heterogeneity will be quantified using three complementary measures: (i) Cochran's Q statistic (χ^2 test; significant at $p < 0.10$ given inherent low power); (ii) I^2 statistic (proportion of total variability due to between-study variance; thresholds: $<25\%$ low, $25-50\%$ moderate, $50-75\%$ substantial, $> 75\%$ considerable); and (iii) τ^2 (absolute between-study variance). The I^2 statistic alone will not determine pooling appropriateness, clinical and methodological heterogeneity will also be considered, consistent with Cochrane guidance.¹⁷

3.7.2 Pre-Specified Decision Rules for Non-Pooling

The following rules were specified a priori to determine when outcomes will not be pooled regardless of statistical heterogeneity:

1. **Rule 1 (Statistical threshold):** Pooling will not be performed when $I^2 > 75\%$, regardless of statistical significance of individual studies.
2. **Rule 2 (Clinical heterogeneity, prescribing paradigm):** Studies represent fundamentally different homeopathic prescribing paradigms: These studies will be reported individually, and a hypothetical pooled estimate will be presented in supplementary materials to demonstrate the degree of heterogeneity.
3. **Rule 3 (Clinical heterogeneity, population):** Outcomes will not be pooled across pre-diabetes studies and T2DM + PDN studies because these represent clinically distinct conditions with different baselines, treatment targets, and mechanisms of expected HbA1c change. A hypothetical pooled estimate will be presented in supplementary materials.
4. **Rule 4 (Data quality):** Any individual study data element assessed as biologically implausible (e.g., a standard deviation incompatible with the known physiological range of the measurement in the study population) will be excluded from the relevant pool and documented as a sensitivity analysis. The scenario analysis including the excluded data point will be presented in supplementary materials.

3.7.3 Sensitivity Analyses

The following sensitivity analyses are pre-specified:

- **Leave-one-out (LOO) analysis:** For each pooled outcome, each study will be omitted in turn and the pool re-estimated to assess whether the result is driven by any single study.
- **FBS scenario analysis:** A scenario analysis pooling both pre-diabetes FBS studies (Guha 2023 and Banerjee 2024) will be presented in supplementary materials, despite Banerjee 2024 FBS being excluded from the primary pool under Rule 4. The resulting pool weight distribution will be reported to demonstrate why the scenario pool is not analytically equivalent to a true $k = 2$ meta-analysis.
- **Risk of bias sensitivity:** Pooled estimates will be re-computed including only studies rated 'Low' risk of bias overall by RoB 2.

3.7.4 Small-Study Effects and Publication Bias

Formal statistical tests for funnel plot asymmetry (Egger's test, Begg's test) will not be performed because the number of studies contributing to any single pool is fewer than 10, as recommended by the Cochrane Handbook¹⁷ and the methodological guidance of Sterne et al. (2011).²³ A narrative assessment of publication bias will be conducted for each outcome, considering: grey literature inclusion; trial registration verification; symmetry of positive and negative results; and any known institutional or geographic clustering of studies.

3.8 Certainty of Evidence

Certainty of the evidence for each pre-specified outcome will be rated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.²⁴ Starting points are High certainty for RCTs and Low certainty for CCTs/non-randomised designs. Certainty will be downgraded or upgraded based on five domains.

GRADE assessments will be presented in a Summary of Findings (SoF) table following the GRADEpro GDT template.²⁵ All GRADE ratings will be agreed by two reviewers independently and any discrepancies resolved by a third reviewer.

4 | REVIEW TEAM, GOVERNANCE, AND ETHICS

4.1 Deviations from Protocol

Any deviations from this pre-specified protocol will be documented in a structured log. Each entry will include: the original protocol specification; the actual approach taken; the reason for the deviation; and the date. Deviations will be disclosed and justified in the final review publication. Post-hoc sensitivity analyses arising from deviations will be explicitly labelled as unplanned.

4.2 Ethics and Dissemination

Ethics committee approval is not required for this systematic review, which synthesises data from previously published studies and does not involve primary data collection from human participants. The review protocol has been registered in PROSPERO [registration number to be inserted before journal submission]. Findings will be disseminated via: (i) publication of this protocol paper in a peer-reviewed journal; (ii) publication of the systematic review and meta-analysis manuscript in a peer-reviewed journal; and (iii) presentation at relevant scientific conferences in homeopathy research, diabetes, and evidence synthesis. No restriction on publication of findings is anticipated.

5 | DISCUSSION

5.1 Rationale for Methodological Decisions

Several methodological decisions in this protocol warrant specific justification. The decision to include both RCTs and CCTs reflects the relatively small evidence base in homeopathy research for diabetic conditions, restricting to RCTs alone would exclude the CCTs. such CCTs will be assessed rigorously with ROBINS-I and its findings kept separate from the quantitative synthesis of RCTs in all primary analyses.

The decision to include unpublished grey literature (theses) reflects the recognised problem of publication bias in complementary medicine research.²⁶ Methodological rigour will not be relaxed for grey literature sources; a conservative approach to RoB 2 Domain 5 (reporting) and Domain 2 (deviations) will be applied given the absence of peer review. This approach mirrors the Cochrane Handbook recommendation that grey literature should be sought and assessed with equal methodological scrutiny.¹⁷

5.2 Anticipated Challenges and Mitigation

Several challenges are anticipated in conducting this review:

- **Clinical heterogeneity across diabetes-spectrum conditions:** Studies will span pre-diabetes, T1DM, T2DM, and various complications. Subgroup analyses will be conducted by condition type for all outcomes where more than one study is available.
- **Methodological heterogeneity in outcome measurement:** Different studies use OGTT at different timepoints (2-hour, 3-hour), FBS at different fasting durations (8–10h vs 12h), and HbA1c using different assay methods. Where unit differences exist, data will be converted to a common unit.
- **Co-interventions:** This limitation will be addressed by: (a) including the study in the analysis given that co-intervention is balanced across arms; (b) explicitly labelling results from such studies; and (c) conducting a sensitivity analysis excluding co-intervention studies.

- **Grey literature data completeness:** Theses may present data in non-standard formats or may omit descriptive statistics for some groups. Primary authors will be contacted for missing data only when critical information is unavailable and the study is eligible for quantitative synthesis.

5.3 Potential Limitations of the Review

We anticipate the following limitations of the completed review: (i) the evidence base is primarily restricted to some particular geo-location, limiting generalisability to other healthcare contexts; (ii) $k < 10$ for all outcome pools will preclude funnel plot asymmetry testing; (iii) unpublished theses introduce grey literature uncertainty; (iv) primary author contact for missing data was not systematic; and (v) the $r = 0.5$ assumption for SD estimation of change scores, while a conventional default, is unverified for all included populations.

6 | CONCLUSIONS

This protocol establishes the pre-specified methodology for a systematic review and meta-analysis of homeopathic medicines in diabetes, pre-diabetes, and related complications. Key methodological features include: application of Cochrane RoB 2 and ROBINS-I for risk of bias assessment; GRADE for certainty of evidence; DerSimonian-Laird random-effects meta-analysis with HKSJ correction; pre-specified rules for non-pooling under conditions of clinical heterogeneity or data quality concerns; inclusion of grey literature (theses) with equal methodological scrutiny; and transparent reporting of all deviations from protocol. The completed review will provide the first diabetes-specific meta-analytic synthesis of homeopathic controlled trials using current methodological standards.

Declarations

Competing interests:

The authors declare no competing interests. This study was conducted on the authors' own initiative and does not necessarily reflect the official position or the Government.

Ethics

Ethics committee approval is not required for this systematic review. No primary data were collected from human participants.

PROSPERO registration

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Author contributions:

SS: conceptualisation, protocol design, database searching, study selection, risk of bias assessment, writing, original draft. SBh: independent study selection, clinical input, data extraction, writing, review and editing. SG: adjudication, GRADE assessment, supervision, writing, review and editing. SGu: protocol development, grey literature searching, writing, review and editing. PB: independent study selection, clinical input, data extraction, RoB assessment, writing, review and editing. AD: methodological oversight, search, study selection, data extraction, RoB assessment, GRADE assessment, data analysis, policy implications, writing, review and editing. All authors read and approved the final manuscript.

Data availability:

The data are available from the corresponding author upon request.

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