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Polyherbal Strategies for Type 2 Diabetes: Clinical Evidence and Mechanistic Rationale for Bitter Melon, Black Cumin, Celery, Curry Leaves and Fenugreek

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ABSTRACT

Type 2 diabetes mellitus is a complex metabolic disorder characterised by hyperglycaemia, insulin resistance, pancreatic β-cell dysfunction, inflammation and oxidative stress. Multitarget botanical interventions may support glycaemic and metabolic management through diverse biological activities. This review evaluated clinical evidence for *Nigella sativa*, *Trigonella foenum-graecum*, *Momordica charantia*, *Apium graveolens* and *Murraya koenigii* in Type 2 diabetes and examined the mechanistic rationale for polyherbal approaches. Twenty clinical trials met the inclusion criteria. *N. sativa* improved fasting glucose and HbA1c, with seed oil showing more consistent effects on lipid and inflammatory parameters than seed powder. *T. foenum-graecum* reduced fasting glucose, HbA1c and atherogenic lipids, particularly at higher whole-seed doses, whereas fibre-free extracts mainly affected fasting and postprandial glycaemia and triglyceride concentrations. *M. charantia* produced modest improvements in glycaemic control with crude extracts and greater reductions in HbA1c and triglycerides with peptide-enriched formulations. *A. graveolens* improved glycaemic, lipid and blood pressure parameters with seed extracts rich in 3-*n*-butylphthalide, whereas low-dose whole-plant powder mainly reduced body fat. *M. koenigii* improved glycaemic indices and measures of central adiposity in short-term interventions. Study heterogeneity, small sample sizes, short intervention periods and variation in herbal preparations limited direct comparison across studies. Available evidence suggests complementary mechanisms among these botanicals, including improved insulin sensitivity, insulin-mimetic activity, reduced carbohydrate absorption, antioxidant effects, anti-inflammatory activity and lipid modulation. A polyherbal approach represents a plausible mechanistic strategy, although direct clinical evidence for synergistic effects remains unavailable. This review describes current clinical evidence for five botanicals with complementary antidiabetic activities and outlines priorities for future combination–based clinical research.

1 | Introduction

Diabetes mellitus is a chronic metabolic disorder characterised by persistent hyperglycaemia arising from impaired insulin secretion, defective insulin action or both [1]. Fasting plasma glucose concentrations below 99 mg/dL are considered normal; values between 100 and 125 mg/dL indicate prediabetes and concentrations of ≥ 126 mg/dL support a diagnosis of diabetes [2]. Global diabetes prevalence has reached alarming levels, with approximately 537 million adults affected in 2021. Projections indicate increases to 643 million by 2030 and 783 million by 2045 [3].

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Diabetes is broadly classified into Type 1 and Type 2 diseases. Type 1 diabetes is an autoimmune disorder in which CD4+ and CD8+ T cells target pancreatic β-cells, resulting in impaired insulin production. Type 2 diabetes mellitus (T2DM) accounts for more than 90% of diabetes cases and is strongly associated with obesity, physical inactivity and genetic susceptibility [4, 5]. A substantial public health and economic burden continues to accompany the increasing prevalence of T2DM worldwide.

Pharmacological interventions remain the foundation of T2DM management. Common therapeutic options include metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors and sodium-glucose co-transporter-2 (SGLT2) inhibitors [6]. Significant improvements in glycaemic control have been achieved with these agents. Treatment limitations nevertheless remain important. Gastrointestinal intolerance, hypoglycaemia, hepatotoxicity, renal complications, contraindications and poor long-term adherence may reduce therapeutic effectiveness in some patients [7, 8]. No pharmacological intervention is currently approved specifically for prevention of T2DM beyond lifestyle-based strategies such as dietary modification and physical activity [9].

Medicinal plants and nutraceuticals have attracted increasing attention as adjunctive interventions for metabolic disorders [10–12]. Traditional medical systems, including Ayurveda, Traditional Chinese Medicine and Unani medicine, have long utilised botanical preparations for the management of diabetes [13]. Clinical and experimental evidence has increasingly supported the antidiabetic potential of black cumin (*Nigella sativa* [NS]), bitter melon (BM) (*Momordica charantia* [MC]), celery (*Apium graveolens* [AG]), curry leaves (*Murraya koenigii* [MK]) and fenugreek (*Trigonella foenum-graecum* [TFG]) [14–16]. Reported benefits include improvements in glycaemic control, lipid metabolism, oxidative stress and inflammatory processes.

Most clinical studies have evaluated these botanicals individually. Limited evidence is available regarding their combined use in polyherbal interventions. Multiple pathological processes contribute to T2DM, including insulin resistance, β-cell dysfunction, chronic inflammation, oxidative stress and dysregulated lipid metabolism. Botanical combinations that target several of these pathways may represent a plausible therapeutic approach. Direct clinical evidence supporting additive, synergistic or superior effects of such combinations remains limited [17].

Clinical evidence relating to black cumin, BM, celery, curry leaves and fenugreek has expanded considerably during recent years. Differences in formulations, dosages, treatment duration and study design have also become increasingly apparent. A clear evaluation of current clinical findings is needed. This review examines clinical evidence published between 2019 and 2024 for these five botanicals and discusses the mechanistic rationale supporting polyherbal approaches. Current evidence remains insufficient to determine whether botanical combinations provide additive, synergistic or clinically greater benefits than the individual botanicals. This review describes the clinical evidence supporting these botanicals in T2DM and outlines the rationale and future research priorities for combination-based interventions.

2 | Methods

2.1 | Search Strategy and Eligibility Criteria

A comprehensive literature search was conducted up to 30 March 2024 using PubMed, Scopus, Web of Science, Google Scholar and the clinical trial registry ClinicalTrials.gov. Separate searches were performed for each selected medicinal plant using predefined keywords and Boolean operators. Search terms included 'diabetes,' 'type 2 diabetes mellitus,' 'patients,' 'clinical trials,' 'hypoglycaemic,' and 'blood glucose' combined with plant-specific terms, including 'fenugreek' OR *Trigonella foenum-graecum*, 'black cumin' OR *Nigella sativa*, 'bitter melon' OR *Momordica charantia*, 'celery' OR *Apium graveolens* and 'curry leaves' OR *Murraya koenigii*. The filter 'NOT review' was applied to exclude review articles and focus the search on original clinical studies.

Human clinical studies published between 2019 and 2024 were screened according to predefined eligibility criteria. Additional limits were applied where available, including human clinical studies, publication years 2019–2024 and free full-text availability. The free full-text filter was applied to ensure that all included studies could be accessed and evaluated in full. This criterion may have excluded otherwise relevant studies that were not freely accessible. All retrieved references were exported to Microsoft Excel for screening.

2.2 | Inclusion and Exclusion Criteria

Eligible studies were clinical trials conducted in human participants diagnosed with T2DM. Randomised controlled trials (RCTs) were prioritised; however, nonrandomised trials were included when RCT evidence was limited. Studies with at least 35 participants were included to reduce the influence of very small studies [18]. This threshold was used as a pragmatic eligibility criterion and was not derived from a formal sample-size calculation. Outcomes of interest included glycaemic parameters such as fasting blood glucose (FBG), glycated haemoglobin (HbA1c) and random blood glucose (RBG), together with lipid profile and body composition measures. Studies were excluded if they were (i) review articles, (ii) animal or in vitro studies, (iii) cross-sectional or observational studies without an intervention, (iv) non-English publications or (v) trials reporting outcomes unrelated to glycaemic or metabolic parameters.

2.3 | Study Selection Process

A total of 188 records were identified through database searching. Removal of duplicate records ($n = 31$) left 157 articles for screening. Abstract screening excluded studies that did not meet the eligibility criteria, including animal studies, non-English publications and studies reporting outcomes unrelated to glycaemic or metabolic parameters. Full texts of 86 articles were assessed for eligibility. Twenty studies met the inclusion criteria and were included in the review, whereas 66 studies were excluded at the full-text stage because they did not satisfy the predefined eligibility criteria. Two reviewers independently assessed study eligibility at the full-text stage. Any disagreements were resolved through discussion and consensus. Study selection followed the PRISMA 2020 guidelines [19]. Figure 1 illustrates the study selection process.

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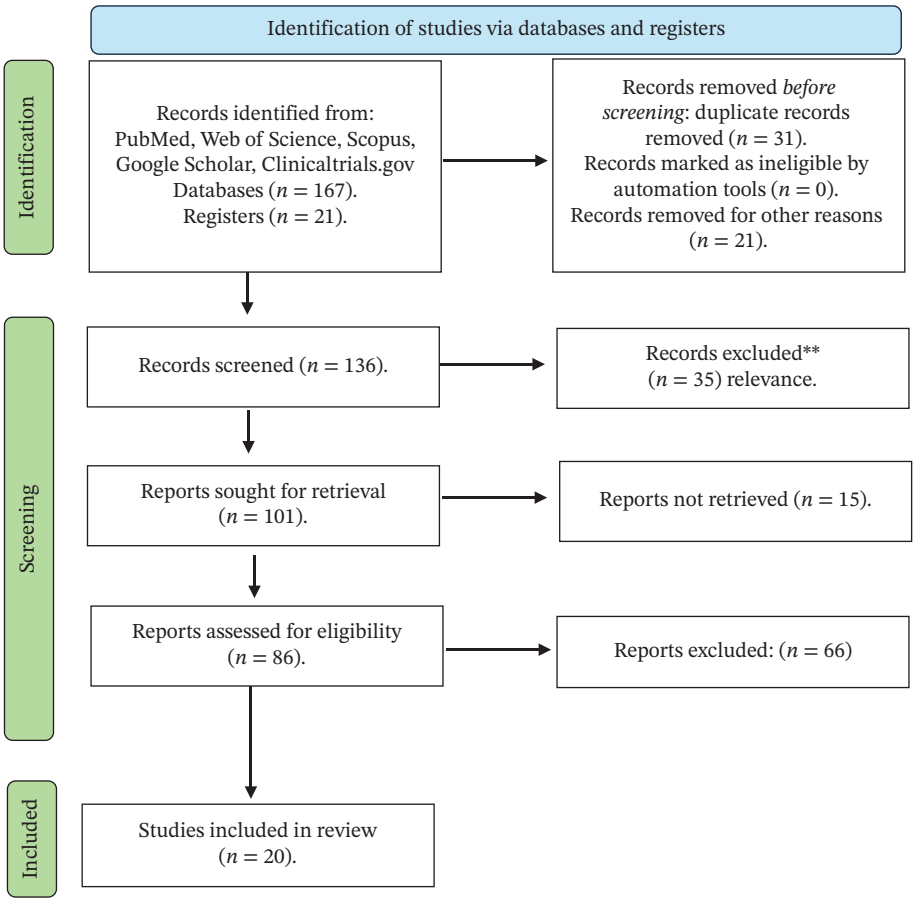


FIGURE 1 | PRISMA 2020 flowchart showing the study selection process.

2.4 | Data Extraction

Two reviewers independently extracted data from all eligible full-text articles. Extracted information included study reference, participant characteristics, intervention and dose, comparator or control, treatment duration and outcomes of interest.

2.5 | Risk of Bias (RoB) Assessment

RoB in the RCTs was assessed using the Cochrane RoB 2 tool. Assessment covered five domains: the randomisation process, deviations from intended interventions, missing outcome data, outcome measurement and selection of the reported result. Two reviewers independently performed the assessment. Each domain was classified as 'low risk,' 'some concerns,' or 'high risk.' Results were visualised using the automated RoB 2 graphical output (Figures 2 and 3).

3 | Results

3.1 | Study Characteristics

A total of 20 clinical trials met the inclusion criteria and were included in this review. The included trials evaluated NS in 247 participants, TFG in 455 participants, MC in 279 participants, AG in 95 participants and MK in 245 participants. Two additional studies included interventions such as resistance training and cinnamon supplementation; however, only data related to the selected medicinal plants were extracted for analysis [20, 21]. All included trials enrolled both male and female participants. Intervention duration ranged from 30 days to 12 weeks.

All included studies employed a randomised design, although seven trials did not include a placebo control group. One study used dietary modification as the comparator intervention [22]. Study designs varied across the included trials. Information on product standardisation was inconsistently reported. Most trials reported the plant part, formulation and dose, whereas information on active-marker content and phytochemical standardisation was often unavailable. Available information is presented in the corresponding study descriptions. Figure 1 outlines the identification, screening, eligibility assessment and inclusion of studies. Methodological quality was evaluated using the Cochrane RoB 2 tool. Figure 2 presents the overall RoB assessment across the included studies. Most studies were classified as low risk, although some were assigned 'some concerns' in one or more domains. Figure 3 depicts the study-level distribution of RoB judgements.

3.2 | NS (Black Cumin)

Five clinical trials examined NS supplementation in patients with T2DM (Table 1). Most studies reported improvements in FBG and HbA1c, together with favourable changes in lipid parameters. Seed oil preparations were associated with improvements in total cholesterol (TC) and triglycerides (TGs) in several studies, whereas seed powder also demonstrated favourable metabolic effects. Differences in formulation may contribute to variability

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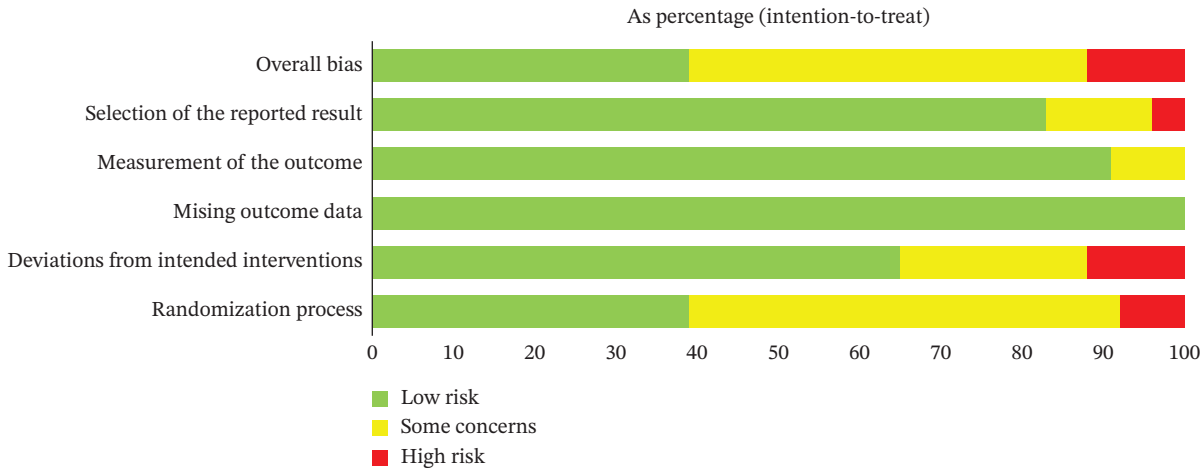


FIGURE 2 | Risk-of-bias assessment of included studies based on the Cochrane Risk of Bias 2 (RoB 2) tool.

in reported outcomes. Two trials reported reduced insulin resistance, while several studies observed reductions in oxidative stress markers such as malondialdehyde (MDA). The clinical findings indicate potential benefits of NS for glycaemic and metabolic outcomes in individuals with T2DM.

3.3 | TFG (Fenugreek)

Seven clinical trials investigated fenugreek supplementation in patients with T2DM (Table 2). Six studies reported reductions in FBG and/or HbA1c. Several studies also reported favourable changes in lipid parameters, including reductions in TC, low-density lipoprotein (LDL) cholesterol and TGs, together with increases in high-density lipoprotein (HDL) cholesterol. One study did not observe significant improvements in glycaemic outcomes. Differences in dose, formulation, treatment duration and study design may have contributed to variability in the reported findings. Overall, the available clinical evidence suggests potential benefits of fenugreek supplementation for glycaemic control and lipid-related outcomes in individuals with T2DM.

Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
NS1	NA	*N. sativa oil*	Sunflower oil	NA	43	+	!	+	+	+	+
TFG1	NA	*T. foenum–graecum*	Metformin	NA	114	!	!	+	!	+	!
TFG2	NA	Fenugreek seed solution	Antidiabetic drugs	NA	50	+	!	+	+	+	+
TFG3	NA	Fenugreek powder	Wheat powder	NA	64	+	+	+	+	+	+
MC1	NA	*M. Charantia*	Placebo	NA	90	+	+	+	+	+	+
MC2	NA	mcIRBP–19–BGE*	Placebo starch	NA	41	+	!	+	+	+	+
AG1	NA	Celery powder	Starch placebo	NA	36	+	+	+	+	+	+
NS4	NA	*N. sativa oil*	Medium chain triglyceride	NA	50	+	+	+	+	+	+
NS3	NA	*N. sativa seeds*	Maltodextrin	NA	20	+	+	+	+	+	+
NS5	NA	*N. sativa*	Baseline	NA	45	!	−	+	+	+	−
MC3	NA	mcIRBP–19*	Hypoglycemic drugs	NA	142	!	+	+	+	+	!
AG2	NA	Celery seed extract	Placebo	NA	59	+	+	+	+	+	+
MK1	NA	*M. koenigii powder*	Control	NA	140	!	+	+	+	+	!
MK2	NA	*M. koenigii powder*	Control	NA	45	−	−	+	+	−	−
TFG4	NA	Fenugreek seed powder	Dietary modification	NA	60	!	+	+	+	!	!
TFG5	NA	TFG seed extract	Maltodextrin	NA	48	+	+	+	+	+	+
TFG6	NA	Fenugreek solution	No supplement	NA	60	!	!	+	+	+	!
TFG7	NA	Fenugreek powder	Baseline	NA	52	!	−	+	+	!	−
MK3	NA	*M. koenigi powder*	Control	NA	60	−	+	+	+	+	!
NS2	NA	*N. sativa oil*	Metformin	NA	62	!	+	+	+	!	!

*Bitter melon peptide

+ Low risk
! Some concerns
− High risk

D1 Randomisation process
D2 Deviations from the intended intervention
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

FIGURE 3 | Study-level distribution of risk-of-bias judgements based on the Cochrane Risk of Bias 2 (RoB 2) assessment.

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TABLE 1 | Study characteristics of articles retrieved from *N. sativa* search.

Investigation	Participants (number of patients)	Treatment group/dose/duration	Comparator/background treatment	Outcomes of interest	References
Glucose and lipid profile of diabetic patients	45 (3 subgroups based on BG levels)	G1 ($n = 15$): NS 1 g/day, 30 d. G2 ($n = 15$): NS 2 g/day, 30 d. G3 ($n = 15$): NS 3 g/day, 30 d.	None (single-arm trial)	Reduction in BG in all treatment groups; no significant change in LDL or HDL	[23]
Cardiometabolic profile of diabetic patients	50	($n = 25$): NS oil 2 × 500 mg/day, 8 w	($n = 25$): 2 sunflower oil placebo capsules/daily	Reduction in FBG, HbA1c, TC, TG, LDL, WC; no significant change in HDL or HOMA-IR	[24]
Inflammation, oxidative stress, FBG and lipid profile	50	(n = 34): NS oil 2 × 500 mg/daily (8 w)	($n = 16$): 2 medium-chain triglyceride oil placebo capsules/daily	Reduction in FBG, TC, LDL, MDA; increase in HDL	[25]
Metabolic profile of diabetic patients	62	(n = 33): NS oil 3 × 450 mg/daily (12 w)	($n = 29$): metformin 2 g/daily	Reduction in weight, WC, BMI	[26]
Biochemical profile of diabetic patients	40	(n = 10): NS seed powder 4 × 500 mg/daily (8 w)	($n = 10$): maltodextrin placebo capsules 4 × 500 mg/day	Reduction in insulin, glucose, HOMA-IR, TC, TG, LDL, AST, ALT, ALP; increase in HDL	[21]

Note: Product standardisation and active-marker content are reported only where specified in the original studies.
Abbreviations: 30 d, 30 days; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BG, blood glucose; BMI, body mass index; FBG, fasting blood glucose; G, group; HDL, high-density lipoprotein; HOMA-IR, homoeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; MDA, malondialdehyde; N, number; *NS*, *N. sativa*; RBG, random blood glucose; TC, total cholesterol; TG, triglyceride; w, weeks; WC, waist circumference.

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TABLE 2 | Study characteristics from articles retrieved from *T. foenum-graecum* search.

Investigation	Participants (number of patients)	Treatment group/dose/duration	Comparator/background treatment	Outcomes of interest	References
Fenugreek in diabetic patients	52	(n = 26): TFG powder 4 × 10 g/daily (12 w)	None	Reductions in WC, FBG, HbA1c, serum creatinine, LDL; increase in HDL	[20]
Hyperglycaemia profile of diabetic patients	60	(n = 30): TFG 10 g/daily soaked in 100 mL water (3 w)	30: no intervention	Reduction in blood glucose	[27]
Lipid profile of diabetic patients	114	(n = 57): TFG seed powder 2 × 25 g/daily (4 w)	(*n* = 57): metformin	Reductions in TC, G, LDL; increase in HDL	[28]
Biochemical profile of diabetic patients	50	(n = 25): TFG powder 3 × 5 g/daily mixed with water as well as antidiabetic drugs (8 w)	(*n* = 25): antidiabetic drugs in both groups	Reductions in FBG, ALT, ALP	[29]
Glucose and lipid profiles of diabetic patients	62	(n = 31): TFG seed powder 2 × 5 g/daily (8 w)	(*n* = 31): Wheat flour placebo 2 × 5 g/daily	Reductions in FBG, HbA1c, BMI, WC; improvement in quality of life	[30]
Efficacy of Fenugreek extract	57	(n = 30): TFG seed dried extract 2 × 250 mg/daily (12 w)	(*n* = 27): maltodextrin placebo 2 × daily	Reduction in FBG and TG; no significant changes in HbA1c, TC, HDL, LDL	[31]
Blood glucose of diabetic patients	60	(n = 30): TFG seed powder 2 × 10 g/daily (8 w)	(*n* = 30): no intervention	Reductions in FBG, RBG, HbA1c	[22]

Note: Product standardisation and active-marker content are reported only where specified in the original study.
Abbreviations: 30 d, 30 days; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BG, blood glucose; BMI, body mass index; d, days; FBG, fasting blood glucose; G, group; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HOMA-IR, homoeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; MDA, malondialdehyde; N, number; NS, *N. sativa*; RBG, random blood glucose; TC, total cholesterol; TFG, *T. foenum-graecum*; TG, triglyceride; w, weeks; WC, waist circumference.

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3.4 | MC (BM)

Three RCTs assessed BM interventions (Table 3). All reported improvements in glycaemic parameters, with reductions in FBG observed across studies and reductions in HbA1c reported in studies evaluating mcIRBP-19-enriched preparations. Effects on lipid parameters were less consistent, with some studies reporting favourable changes and others showing no significant effect. Extracts enriched with mcIRBP-19, an insulin-mimetic peptide, produced the most consistent improvements in glycaemic outcomes. BM shows potential as a glucose-lowering intervention, although additional well-designed clinical trials are required to clarify its effects on lipid metabolism.

3.5 | AG (Celery)

Two clinical trials investigated AG supplementation in patients with T2DM (Table 4). One study reported reductions in body fat and waist circumference (WC). In contrast, the second study reported reductions in FBG, TC, TGs and LDL cholesterol, together with increased HDL cholesterol. Differences in study outcomes were observed across the two trials.

3.6 | MK (Curry Leaves)

Three clinical trials evaluated MK supplementation in patients with T2DM (Table 5). Reductions in blood glucose and HbA1c were reported in studies that assessed glycaemic outcomes. Favourable changes in anthropometric parameters, including body weight, body mass index (BMI) and WC, were also observed. Improvements in lipid parameters were reported in studies that assessed lipid outcomes. The available clinical evidence indicates beneficial effects of MK on glycaemic, anthropometric and lipid-related outcomes in individuals with T2DM.

4 | Discussion

4.1 | Interpretation

Twenty clinical trials evaluated five medicinal plants for Type 2 diabetes. The clinical evidence base was larger for fenugreek and black cumin than for celery and curry leaves. Several studies reported reductions in FBG and HbA1c; however, substantial between-study heterogeneity precludes conclusions regarding the relative efficacy of the five botanicals. BM also showed favourable effects on glycaemic endpoints, particularly in studies using mcIRBP-19-enriched preparations, although lipid outcomes were less consistent. Evidence for celery and curry leaves was more limited, although favourable effects on glycaemic control, lipid parameters and body composition were reported.

Clinical outcomes were interpreted with greater emphasis on glycaemic measures, particularly HbA1c and fasting glucose, followed by insulin resistance, lipid parameters, anthropometric outcomes and reported safety. Because the studies differed considerably in intervention type, formulation, dose, duration and outcome reporting, the findings were synthesised descriptively rather than used to rank the relative efficacy of the five botanicals. These findings are consistent with previous reports describing glucose-lowering and metabolic benefits of fenugreek, NS and MC. Published evidence has also suggested potential roles for celery flavones and MK carbazole alkaloids in metabolic regulation.

TABLE 3 | Study characteristics from articles retrieved from *M. charantia* search.

Investigation	Participants (number of patients)	Treatment group/dose/duration	Comparator/background treatment	Outcomes of interest	References
Influence of mcIRBP-19* on blood glucose profiles of diabetic patients	142	(n = 64): BMP 2 × 300 mg/day, 12 w	($n = 78$): (physician-prescribed hypoglycaemic drugs)	Reduction in HbA1c	[32]
Glucose profile of diabetic patients	96	(n = 64): MC extract 2 × 1190 mg/day, 12 w	($n = 32$): placebo capsule	Reduction in FBG; no significant change in HbA1c, HDL, LDL, TC or TG	[33]
Influence of *mcIRBP-19 on blood glucose profiles of diabetic patients	41	(n = 21): *mcIRBP-19 capsule 600 mg/day, 12 w	($n = 20$): starch placebo, capsule 600 mg/day	Reductions in FBG and HbA1c	[34]

Note: Product standardisation and active-marker content are reported only where specified in the original study.
Abbreviations: BMP, bitter melon peptide; d, days; FBG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MC, *M. charantia*; N, number; RBG, random blood glucose; TC, total cholesterol; TG, triglyceride; w, weeks; WC, waist circumference.
*mcIRBP-19 is a bitter melon peptide (BMP) comprising 19 amino acids.

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TABLE 4 | Study characteristics from articles retrieved from *A. graveolens* search.

Investigation	Participants (number of patients)	Treatment group/dose/duration	Comparator/background treatment	Outcomes of interest	References
Biochemical profile of diabetic patients	36	(n = 19): AG powder 3 × 250 mg/daily (12 w)	Starch powder 3 × 250 mg/daily	Reduction in body fat	[35]
Biochemical profile of diabetic patients	59	(n = 29): AG seed extract 4 × 335 mg/daily (4 w)	Placebo 4 × 335 mg/daily	Reduction in FBG, TC, TG, LDL; increase in HDL	[36]

Note: Product standardisation and active-marker content are reported only where specified in the original studies.
Abbreviations: *AG*, *A. graveolens*; d, days; FBG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, number; TC, total cholesterol; TG, triglyceride; w, weeks.

Differences in study design, formulation, dose, treatment duration and product standardisation likely contributed to variability in outcomes. The available clinical evidence supports consideration of these botanicals as adjuncts to conventional care rather than stand-alone therapies. Standardised interventions, outcome measures and direct comparisons of formulations are needed to clarify the magnitude and durability of reported effects.

Available evidence suggests that these botanicals influence glucose homoeostasis, insulin responsiveness, lipid metabolism, oxidative stress and inflammation through diverse but complementary mechanisms. Table 6 summarises the principal bioactive constituents, proposed mechanisms and reported clinical outcomes of the five botanicals.

4.2 | NS (Black Cumin)

Clinical trials generally reported improvements in glycaemic and cardiometabolic outcomes following NS supplementation, although the magnitude of effect varied according to formulation, dose, treatment duration and study design. In a double-blind RCT involving 50 patients with Type 2 diabetes, NS oil (1 g/day for 8 weeks) reduced FBG and HbA1c compared to placebo and produced favourable effects on several lipid parameters, BMI and WC [24]. Similar improvements in glycaemic, lipid, inflammatory and oxidative-stress markers were reported in a second RCT using the same dosage [25].

A 30-day intervention using seed powder (1–3 g/day) also reduced FBG, with the greatest reduction observed at 2 g/day, although lipid changes were not significant [23]. An open-label comparator study reported reductions in HbA1c and FBG with NS oil, although larger reductions were observed with metformin [26]. A factorial study that combined NS supplementation with resistance training reported improvements in glycaemic, lipid, inflammatory and liver-function markers; however, the study design did not allow the independent contribution of NS to be determined [21].

The reported clinical findings are consistent with previous studies describing glucose-lowering, lipid-modulating, antioxidant and anti-inflammatory effects of NS. Variability in formulation, dose, treatment duration and background treatment may have contributed to differences in clinical outcomes across studies. Overall, available evidence suggests beneficial effects on glycaemic control, with additional cardiometabolic benefits reported in several studies. Larger and longer-duration RCTs are required to determine optimal formulations, dosing strategies and clinically relevant outcome measures.

Proposed mechanisms associated with NS are summarised in Table 6. Thymoquinone and related constituents have been linked to improved insulin sensitivity, enhanced glucose uptake, reduced oxidative stress, preservation of β-cell function and modulation of hepatic glucose metabolism [45–48]. These mechanistic observations provide biological context for the clinical findings but do not establish causality in humans.

4.3 | TFG (Fenugreek)

Clinical studies generally report beneficial effects of TFG (fenugreek and TFG) on glycaemic outcomes. The magnitude of effect varies according to formulation, dose, study design and

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TABLE 5 | Study characteristics from articles from *M. koenigii* search.

Investigation	Participants (number of patients)	Treatment group/dose/duration	Comparator/background treatment	Outcomes of interest	References
Glucose profile of diabetic patients	45	(n = 30); two subgroups: dried MK leaf, 45 d; (G1: 5 mg/kg/day; G2: 10 mg/kg/day)	(n = 15): none	Reductions in FBG, RBG and HbA1c	[37]
Body composition of diabetic patients	140	(n = 120); dried MK leaf, 60 d; (G1: 5 mg/day; G2: 10 mg/day)	(n = 40): none	Reductions in body weight, BMI and WC	[38]
Glucose and lipid profile of diabetic patients	60	(n = 30); MK leaf powder 12 g/day in water, 30 days	(n = 30): none	Reductions in FBG, TC, TG, LDL; increase in HDL	[39]

Note: Product standardisation and active-marker content are reported only where specified in the original study.
Abbreviations: BMI, body mass index; d, days; FBG, fasting blood glucose; G, group; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; *MK*, *M. koenigii*; N, number; RBG, random blood glucose; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

study population. Several studies also reported favourable changes in lipid parameters and anthropometric measures.

In a randomised, double-blind trial involving 62 patients with T2DM, 5 g seed powder twice daily for 8 weeks reduced FBG, HbA1c, BMI, WC and diastolic blood pressure. Quality-of-life scores also improved [30]. Another parallel RCT involving 50 patients receiving standard antidiabetic therapy reported reductions in FBG together with improvements in ALT and ALP following supplementation with fenugreek powder (5 g three times daily) for 8 weeks [29]. A study involving newly diagnosed patients with T2DM reported reductions in TC, TG and LDL-C together with increased HDL-C following administration of a 25-g seed-powder preparation twice daily for 4 weeks [28].

A double-blind RCT in individuals with prediabetes reported reductions in FBG, postprandial blood glucose and TG following supplementation with a hydroalcoholic seed extract (500 mg/day) for 12 weeks. No significant effects were observed for HbA1c, insulin resistance, CRP or cholesterol fractions [31]. Additional studies using whole-seed preparations also reported reductions in blood glucose parameters [27].

The reported clinical findings are consistent with previous studies describing glucose-lowering, lipid-modulating and anti-inflammatory effects of fenugreek. Differences in formulation, dose, treatment duration, background treatment and study population may have contributed to variability in clinical outcomes. Overall, available evidence suggests beneficial effects of fenugreek on glycaemic control, with additional improvements in lipid-related and anthropometric outcomes reported in several studies. Larger standardised RCTs are needed to clarify optimal dosing strategies, formulation-specific effects and clinically relevant outcome measures.

Proposed mechanisms associated with fenugreek are detailed in Table 6. Soluble fibre may delay gastric emptying and reduce intestinal glucose absorption, whereas 4-hydroxyisoleucine has been associated with enhanced insulin secretion. Diosgenin and other bioactive constituents have been linked to modulation of PPARγ signalling, glycogen synthesis and insulin sensitivity. Flavonoids, alkaloids and saponins have also been associated with anti-inflammatory and antioxidant activities [41, 49–52]. These mechanistic observations provide biological context for the clinical findings but do not establish causality in humans.

4.4 | MC (BM)

Clinical studies generally report beneficial effects of MC (BM) on glycaemic outcomes, although the magnitude of effect varies according to formulation, dose, treatment duration and study design. In a randomised placebo-controlled trial involving 96 participants with T2DM, BM extract (2.38 g/day) administered for 12 weeks reduced FBG and improved HOMA-IR compared to placebo. No significant effects were observed for HbA1c or lipid parameters [33].

A second RCT involving 142 participants evaluated a peptide-enriched preparation (mcIRBP-19, 600 mg/day) for 12 weeks. Significant reductions in HbA1c, fasting glucose and TGs were observed, whereas TC, LDL and HDL remained unchanged [32]. Additional studies using dried fruit powder or juice preparations also reported reductions in FBG and HbA1c [34]. Differences in

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TABLE 6 | Principal bioactive compounds, mechanisms and clinical outcomes of the studied plants.

Plant name and parts used	Key bioactive components	Primary mechanisms of action	Metabolic & clinical outcomes	References
N. sativa (black cumin); seeds, oil	Thymoquinone and α-hederin	Activation of AMPK; increased GLUT-4 translocation; increased insulin receptor density; antioxidant effects (reduced oxidative stress, improved β-cell function); decreased insulin resistance; enhanced β-cell proliferation; increased pancreatic insulin secretion; reduced hepatic gluconeogenesis; enhanced glucose uptake	Reductions in FBG and HbA1c; improved insulin sensitivity; reduced oxidative stress	[23–26, 40]
T. foenum-graecum (fenugreek); seeds, leaves	Fibre, diosgenin, 4-hydroxyisoleucine, trigonelline, flavonoids (e.g., isoorientin, orientin, vitexin and isovitexin)	Delayed gastric emptying; reduced intestinal glucose absorption; increased glycogen synthase activity and insulin sensitivity; modulation of PPARγ and inflammatory pathways	Reductions in FBG and HbA1c; improved lipid profile; anti-inflammatory effects	[20, 22, 27–31, 41]
M. charantia (bitter melon); fruit, seeds	mcIRBP-19 peptide, polypeptide-p, charantin, flavonoids, polysaccharides, saponins and vicine	Insulin-mimetic activity via insulin receptor binding; AMPK activation; inhibition of gluconeogenic enzymes (FBPase, G6Pase); inhibition of 11β-HSD1	Reductions in FBG and HbA1c; variable lipid effects; possible weight control	[32–34, 42]
A. graveolens (celery); whole and seeds	Flavonoids (e.g., apigenin and luteolin)	Increased insulin secretion; reduced gluconeogenesis; improved pancreatic β-cell integrity; activation of Nrf2 (enhanced antioxidant defence); inhibition of NF-κB (reduced inflammation); reduced lipid peroxidation	Reductions in FBG, TC, TG, LDL; increase in HDL; reductions in weight and BMI	[35, 36, 43]
M. koenigii (curry); leaves	Carbazole alkaloids, flavonoids, phenolics, oxalic acid, resin and volatile oils	Inhibition of α-glucosidase and α-amylase; antioxidant effects; increased HDL-associated paraoxonase activity; reduced fat absorption; increased fecal fat excretion	Reductions in FBG and HbA1c; improved lipid profile; reductions in weight, BMI and WC	[37, 38, 44]

Abbreviations: 11β-HSD1, 11β-Hydroxysteroid dehydrogenase type 1; AMPK, AMP-activated protein kinase; BMI, body mass index; FBG, fasting blood glucose; FBPase, fructose 1,6-bisphosphatase; GLUT4, Glucose transporter type 4; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PPARγ, peroxisome proliferator–activated receptor gamma; RBG, random blood glucose; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

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formulation, treatment duration and study design may have contributed to variability in reported outcomes.

The reported clinical findings are consistent with previous studies describing glucose-lowering effects of MC. Variability in formulation, dose, treatment duration and participant characteristics may explain differences across studies. Overall, available evidence suggests beneficial effects on glycaemic control, whereas effects on lipid-related outcomes appear less consistent. Larger and more standardised RCTs are needed to clarify formulation-specific effects, optimal dosing strategies and clinically relevant long-term outcomes.

Proposed mechanisms associated with MC are compiled in Table 6. Peptides such as polypeptide-p and mcIRBP-19 have been associated with insulin-mimetic activity through interaction with insulin-signalling pathways. Additional mechanisms include activation of AMP-activated protein kinase (AMPK), suppression of hepatic gluconeogenesis and modulation of enzymes involved in glucose metabolism [32, 42, 53, 54]. These mechanistic observations provide biological context for the clinical findings but do not establish causality in humans.

4.5 | AG (Celery)

Clinical evidence for AG (celery) remains limited, with only two recent RCTs meeting the inclusion criteria. Different outcomes were reported across the available studies, reflecting differences in formulation, dose, study population and treatment duration. In a triple-blind crossover trial involving 51 participants, supplementation with a seed extract standardised to 3-*n*-butylphthalide (NBP) for 4 weeks reduced FBG, TC, TGs and LDL-C, while increasing HDL-C. Improvements in blood pressure and several liver- and kidney-function markers were also reported. No adverse effects were observed [36].

A second double-blind RCT involving 36 overweight individuals with T2DM evaluated whole celery powder in combination with a hypocaloric diet for 12 weeks. Reductions in body fat percentage were reported; however, no significant between-group differences were observed for fasting glucose, HbA1c, insulin, lipid parameters or oxidative-stress markers [35]. Differences in formulation, treatment duration and study design may have contributed to variability in the reported findings.

The available clinical evidence suggests potential benefits of celery supplementation for glycaemic, lipid-related, anthropometric and cardiometabolic outcomes. The limited number of studies, together with differences in formulation and study design, restricts firm conclusions regarding efficacy. Larger and longer-duration RCTs are needed to clarify formulation-specific effects and clinically relevant outcomes.

Proposed mechanisms associated with AG are outlined in Table 6. Phthalides such as NBP have been associated with vasodilatory, antihypertensive and lipid-modulating effects. Flavonoids including luteolin and apigenin have been linked to antioxidant and anti-inflammatory activities through modulation of Nrf2 and NF-κB signalling pathways [55, 56]. Additional evidence from preclinical studies suggests potential effects on body-weight regulation, lipid metabolism and oxidative stress [55, 57, 58]. These mechanistic observations provide biological context for the clinical findings but do not establish causality in humans.

4.6 | MK (Curry Leaves)

Clinical evidence for MK (curry leaves) remains limited, although available studies report favourable effects on glycaemic, anthropometric and lipid-related outcomes. In a randomised trial involving 160 hypercholesterolaemic women, supplementation with 5–10 g/day dried curry leaf powder for 60 days reduced body weight, BMI, WC, hip circumference and visceral fat [38]. A second randomised trial involving 45 women with T2DM evaluated encapsulated curry leaf extract at doses of 5 or 10 mg/kg/day for 45 days. Both doses reduced FBG, RBG and HbA1c, with larger reductions reported in the higher-dose group [39].

The reported clinical findings are consistent with previous studies describing beneficial effects of MK on glucose metabolism, body composition and lipid-related outcomes. Evidence remains limited by the small number of clinical trials, relatively short intervention periods and variability in study design, formulation, dose and participant characteristics. Larger and longer-duration RCTs using standardised formulations are needed to confirm efficacy and establish optimal dosing strategies.

Proposed mechanisms associated with MK are presented in Table 6. Bioactive constituents, including flavonoids, carbazole alkaloids, phenolics, tannins and saponins, have been associated with inhibition of α-amylase and α-glucosidase, antioxidant activity and modulation of lipid metabolism [59–61]. Additional experimental evidence suggests potential effects on body-weight regulation, intestinal fat absorption and oxidative stress pathways [55, 57, 58]. These mechanistic observations provide biological context for the clinical findings but do not establish causality in humans.

4.7 | Polyherbal Strategies and Combined Mechanisms

Combining botanicals that act through different pathways represents a plausible strategy for addressing the multifactorial nature of T2DM. However, direct clinical evidence supporting polyherbal approaches remains limited. One clinical study of a polyherbal preparation containing fenugreek reported reductions in FBG, PPBG and HbA1c, together with decreases in proinflammatory markers including TNF-α, MCP-1 and resistin, and an increase in adiponectin [62]. Another RCT combining MK with coriander, holy basil and bunching onion reported a reduction in HbA1c over 90 days without adverse effects on hepatic or renal markers [63]. These findings suggest that polyherbal formulations may influence several metabolic outcomes. However, the formulations used in these studies differed from the five botanical combinations considered in this review and therefore do not establish synergy among the selected botanicals.

Mechanistic evidence provides a rationale for investigating these botanicals in combination. The five plants reviewed, NS, TFG, MC, AG and MK, contain different bioactive compounds that act on several interconnected pathways involved in glucose and lipid metabolism. These mechanistic and preclinical findings are presented to explain the biological rationale for combination strategies and should not be interpreted as evidence of clinical efficacy or synergy.

Black cumin, through thymoquinone, has been associated with improved insulin sensitivity, reduced oxidative stress, enhanced

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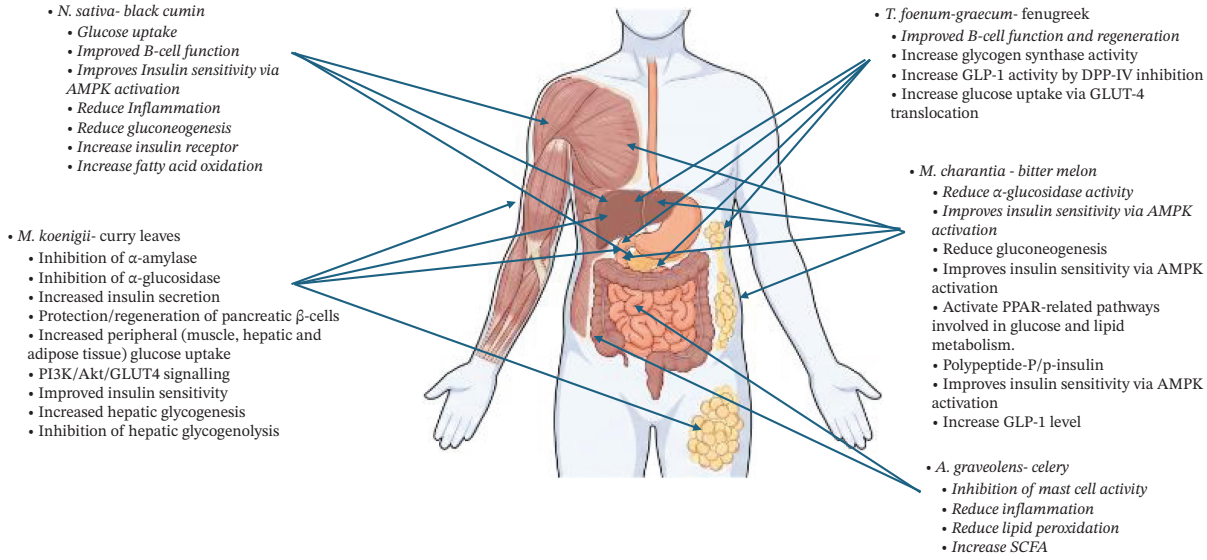


FIGURE 4 | Proposed mechanisms associated with *N. sativa*, *T. foenum-graecum*, *M. charantia*, *A. graveolens* and *M. koenigii* in Type 2 diabetes, highlighting reported effects on glucose uptake, β-cell function, insulin sensitivity, inflammation and oxidative stress. The figure was created using BioRender and assembled by the authors in Microsoft PowerPoint. All pathway information, annotations, labels, arrows and scientific content were developed by the authors. No generative AI tools were used in the creation or modification of this figure.

glucose utilisation and modulation of hepatic glucose metabolism [24–26]. Fenugreek contains soluble fibre and 4-hydroxyisoleucine, which have been linked to delayed carbohydrate absorption, enhanced insulin secretion and modulation of PPARγ-related pathways [28, 31]. BM contains bioactive compounds including charantin, polypeptide-p and mcIRBP-19 that have been associated with insulin-mimetic activity, AMPK activation and reduced hepatic glucose production [32, 33].

Curry leaves contain carbazole alkaloids and flavonoids that have been linked to inhibition of α-amylase and α-glucosidase, antioxidant activity and modulation of lipid metabolism [38, 39]. Celery, particularly seed extracts standardised to NBP, has been associated with improvements in glycaemic and lipid parameters, blood pressure and biomarkers of hepatic and renal function. Proposed mechanisms include calcium-channel modulation together with antioxidant and anti-inflammatory activities mediated by compounds such as luteolin and apigenin [36, 58, 64].

These different but complementary actions provide a biological basis for investigating combination approaches. For example, BM may influence hepatic glucose production, curry leaves may reduce carbohydrate digestion and fenugreek may slow glucose absorption through its fibre content. Black cumin and BM have also been associated with pathways involving AMPK signalling. However, complementary mechanisms alone do not demonstrate greater efficacy, longer-lasting glycaemic control or synergistic effects in humans.

Preclinical findings provide a mechanistic basis for further investigation of these botanicals in combination, but direct clinical evidence remains limited. Figure 4 depicts the principal multi-target mechanisms proposed for the five medicinal plants. Current clinical evidence suggests that polyherbal approaches warrant further investigation, while mechanistic evidence provides biological justification for future combination studies. Direct combination trials are still required to determine whether any benefits are additive, synergistic or greater than those achieved with the individual botanicals. A further limitation is that the review protocol was not prospectively registered, which may introduce potential selection bias despite the use of predefined eligibility criteria and independent full-text screening by two reviewers.

5 | Conclusions and Future Perspectives

This review describes the current clinical evidence for five botanicals, NS, TFG, MC, AG and MK, that have potential to improve different aspects of glycaemic and metabolic control. Fenugreek may delay gastric emptying and enhance glycogen storage. BM contains insulin-mimetic peptides such as polypeptide-p. Black cumin has been associated with improved insulin sensitivity and reduced oxidative stress. Celery may support lipid-related and anthropometric outcomes, whereas curry leaves may reduce carbohydrate digestion through inhibition of α-amylase and α-glucosidase. These different but complementary actions provide a rationale for investigating the botanicals in combination. However, current evidence remains insufficient to determine whether combined administration produces greater or more durable benefits than use of the individual botanicals.

Future studies should employ well-designed multicentre RCTs to evaluate both individual botanicals and defined combinations. Factorial and multi-arm study designs may help determine whether observed benefits are additive or synergistic. Additional priorities include the use of well-characterised and standardised botanical preparations, evaluation of appropriate dose ranges, longer intervention periods and comprehensive safety monitoring. Pharmacokinetic studies are needed to improve understanding of absorption, metabolism and bioavailability and to guide dosing strategies. Comparative studies should also evaluate different delivery formats, including dietary incorporation and standardised nutraceutical formulations. Integration of

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nutrigenomics and personalised nutrition approaches may further refine botanical interventions according to individual genetic, metabolic and microbiome characteristics. These advances may strengthen the evidence base for the use of botanicals as adjunctive strategies in the management of T2DM.

Author Contributions

Mosharraf H. Sarker: conceptualisation, methodology, validation and writing–original draft. Emran Habibi: software, visualisation, writing–original draft and review and editing; Satyajit D. Sarker: writing–original draft and review and editing. Tia Bode: investigation and writing–original draft. Lutfun Nahar: visualisation, writing–original draft and review and editing.

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All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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