Evaluation of clinical trials for natural products used in diabetes
An evidence-based systemic literature review

Rizwan Ahmad, PhD, Lina Hussain AlLehaibi, PharmD, Hind Nasser AlSuwaidan, PharmD, Ali Fuad Alghiryafi, PharmD, Lyla Shafiq Almubarak, PharmD, Khawlah Nezar AlKhalifah, PharmD, Hawra Jassim AlMubarak, PharmD, Majed Ali Alkhathami, PharmD

Abstract

Background relevance: A plethora of literature is available regarding the clinical trials for natural products however; no information is available for critical assessments of the quality of these clinical trials.

Aim of study: This is a first time report to critically evaluate the efficacy, safety and large scale applications of up-to-date clinical trials for diabetes, based on the three scales of Jadad, Delphi, and Cochrane.

Methodology: An in-depth and extensive literature review was performed using various databases, journals, and books. The keywords searched included, “clinical trials,” “clinical trial in diabetes,” “diabetes,” “natural products in diabetes,” “ethnopharmaceutical relevance of natural products in diabetes,” etc.

Results: Based on eligibility criteria, 16 plants with 74 clinical trials were found and evaluated. Major drawbacks observed were: “non-randomization and blindness of the studies,” “non-blindness of patients/healthcare/outcome assessors,” “lack of patient compliance and co-intervention reports,” “missing information regarding drop-out/withdrawal procedures,” and “inappropriate baseline characteristics.” Principal component analysis and Pearson correlation revealed four components with %variability; PC1: 23.12, PC2: 15.83, PC3: 13.11, and PC4: 11.38 (P < .000). According to descriptive statistics, “non-blinding of outcome assessors” was the major drawback (82%) whereas, “not mentioning the timing of outcome assessment” was observed lowest (6.8%). An in-house quality grading (scale 0–24) classified these clinical trials as; poor (67.6%), acceptable (19.9%), and good quality trials (13.5%).

Conclusion: Proper measures in terms of more strict regulations with pharmacovigilance of plants are utmost needed in order to achieve quality compliance of clinical trials.

Abbreviations: A-FABP = adipocyte-fatty acid binding protein, ATP = Adenosine triphosphate, AUC = Area Under The Curve, BG = Blood glucose, BMI = Body mass index, CSQS = clinical symptomatic quantitative scores, DM = Diabetes Mellitus, DSR = division of scientific research, FBG = fasting blood glucose, FDA = Food and Drug administration, FFA = Free fatty acids, GLUT4 = Glucose transporter type 4, GSH = Glutathione, HbA1c = Glycated Hemoglobin, Glycated Hemoglobin, Glycohemoglobin, HDL = High-density lipoprotein cholesterol, Good cholesterol, HOMA-IR = Homeostatic Model Assessment of Insulin Resistance, IDDM = Insulin dependent diabetes mellitus, IDF = International Diabetes Federation, IGF-1 = insulin-like growth factor 1, IRB = Institutional Review Board, KMO = Kaiser-Meyer-Olkin, LDL = Low-density lipoproteins cholesterol, Bad cholesterol, MC = Momordica charantia, Mg = magnesium, MMP = maitake mushroom polysaccharides, NIDDM = non-insulin dependent diabetes mellitus.
1. Introduction

“Diabetes Mellitus,” a term coined from Greek language where “Diabetes” stands for “a passer through” and “Mellitus” for “sweet.”[1] Diabetes mellitus (DM) is a metabolic disorder which leads to chronic hyperglycemia, the pathogenesis for which may include defects in insulin secretion, action or both.[2] Chronic autoimmune disease is considered a dominant cause behind insulin-dependent diabetes (IDDM) which selectively destroys insulin secreting pancreatic β-cells and is treated by insulin. Non-insulin dependent diabetes mellitus (NIDDM) or type 2 diabetes is caused; due to insufficient insulin secretion via dysfunctional pancreatic β-cell, or insulin dysfunction due to decreased insulin sensitivity. First line treatment for NIDDM includes diet control and lifestyle modification; however, in case the diseases progresses, the use of oral hypoglycemic drugs is considered the next approach for treatment.[3,4] According to International Diabetes Federation (IDF) report in 2019; the estimated population with diabetes was 463 million adults which has been projected to raise up to 578M adults by 2030 and 700M by 2045.[5] This urges a proper treatment plan in order to lessen the prevalence of diabetes. The researchers are focusing more on natural products strategies in order to find an appropriate cure for diabetes. Several natural products have been successfully utilized to reduce the blood glucose level in the shape of pre-clinical and clinical studies.[6] For instance, Magnesium (Mg) has been applied to recover Mg deficiencies and help relieve insulin resistance,[7] cinnamon (known for insulin-like effect) has been reported to decrease blood sugar,[8] and zinc has been studied to regulate insulin receptors and extend insulin action.[9] Likewise, numerous plants have been observed with prominent folklore applications in various communities such as; bitter melon is considered a traditional plant to treat diabetes in Asia, South America, India, the Caribbean and East Africa,[10] and fenugreek is used since long to cure diabetes in Mediterranean, Asian, North African, and European communities.[11] Clinical research is a wide term that describe studies or trials conducted in various community, were extracted. The inclusion criteria consisted of; “studies reported in English language only and reporting the natural products clinical trials for diabetes humans,” “natural products with established folklore uses and applied practically in diabetes trials,” “any clinical trial for diabetes using natural products irrespective of randomization, blinding, phase (I–V) applied, statistical model used, outcome and assessor blinding, and negative or positive outcomes,” “clinical trials reporting the use of natural products alongwith conventional medications.” For ethnopharmacological relevance, a list of natural products was collected and final selection was based on the ethnopharmacological uses of these natural products. The relevant reports, based on community surveys, interviews, and collection of data from local inhabitants and healers in that particular community, were extracted.
2.4. Exclusion criteria
The criteria for literature exclusion was; “any study reporting diabetes clinical trials without application of natural products,” “clinical studies reported in diabetes using natural products with lack of any prior ethnopharmacological or folklore use,” “natural products with established ethnopharmacological uses in diabetes; however, yet to be evaluated in a proper clinical trial for diabetes,” “any preclinical, duplicated, and incomplete clinical trial,” “Phase-0 clinical trials,” and “clinical trials in diabetes using minerals, vitamins, or conventional drugs only.”

2.5. Review period
An extensive literature search strategy was applied which started in September 2018 and continued till February 2020. The literature was updated on regular basis, for any new information added to database, till final preparation of manuscript.

2.6. Ethical review
The ethical approval was not necessary as the study did not include any animal or human subjects.

2.7. Patient consent
The study did not involve any patients and no consent form was required.

2.8. Search result
The literature search resulted a total of 1073 articles which were confined to 74 studies, following a proper scrutiny of the eligible articles as per pre-defined criteria (Fig. 1).

3. Literature search
The selected literature was downloaded, properly arranged, and studied in-depth for extraction of the relevant data. The bulk of this literature with relevant data is arranged in proper sections as mentioned below;

3.1. Ethnopharmacological relevance and evidence of the plants used in diabetes
Plants with ethnopharmacological relevance, part/s used for folklore purposes, and the community where the plants were applied for the treatment of various ailments have been reported in detail in Table 1.

3.2. Clinical trials of plants used for diabetes
This section describes in detail, the clinical trials reported for natural products in diabetes. A comprehensive information regarding the part of the plant used in the study, mechanisms of action reported, and final results observed are given in Table 2.

Figure 1. PRISMA flow-diagram for literature search and selection.
3.3. Evaluation of clinical trials based on various scales

Jadad scale, is a tool used to assess the quality of clinical trials based on the three key features of randomization, masking, and accountability of all patients including the withdrawals. The Jadad system evaluates and scores a study on a scale of 0 to 5, based on the pre-defined factors as mentioned in Jadad scale (Table 3). Delphi uses nine designated items to measure the quality of a clinical trial. Though a deficiency of a numerical scale for calculation of final score do exist in this system, yet it is widely implemented scale in most of the studies. Delphi uses nine designated questions in order to count the number of positive responses (Table 3). Cochrane back review group developed a scale which is considered the most comprehensive and uncritical among all the available scales. It is considered a quality rating standard scale, followed in most of the review studies for evaluation of the clinical trials. This system also has a lack of numerical scale needed to finalize a value for a clinical trial. As evident from Table 3, few of the points in the three mentioned scales are overlapping. In addition, each scale do possess positive and negative aspects hence, it becomes difficult to decide a best-fit scale for evaluation. To overcome the loopholes present in these scales the authors utilized a novel approach i.e. to apply the three scales together for evaluation of the quality of each clinical trial on individual basis. To maintain uniformity and ease of application in calculating the individual and final scores for each clinical trial, herein we calculated the responses from these two scales in terms of numerical values 0 to 9 (Delphi system) and 0 to 10 (Cochrane based review scale) which sum up to a final value of 0 to 24 points. The scales are applied to evaluate each individual trial and the drawbacks observed per each scale are reported given in Table 4.

3.4. Statistical analysis

For principal component analysis (PCA), four components (scree plot Fig. 2) were observed with %variability (individual and total); PC1: 23.12 (23.12), PC2: 15.83 (38.96), PC3: 13.11 (52.07), and PC4: 11.38 (63.45). A total of 63.45% variability was observed for the drawbacks; “non-randomized and non-blinded studies,” “lack of patient and care provider blinding,” “concealed treatment allocation,” and “lack of proper drop-out procedures mentioned in the studies.” Whereas 15% variation was due to; “lack of/no compliance report for patients” and “no information about co-interventions applied in the study.”

Table 1
Ethnopharmacological relevance of the selected antidiabetic plants.

| Herbs/plants | Botanical name | Synonyms | Part used | Ethnopharmacological relevance |
|--------------|---------------|----------|-----------|--------------------------------|
| Aloe vera    | Aloe barbadensis/chinensis/ elongata/Indica Royale, Aloe | Leaves, dried sap (fluid), gel | Central and south America and Mexican communities, central Uganda[46] |
| American ginseng | Panax quinquefolius | Panax quinquefolius, Panaxis quinquifolius, ginseng | Roots | different parts of the world[47] and Quebec[48] |
| Bilberry | Vaccinium myrtillus | Myrtillus niger and sylvaticus, Vaccinium onorephorum | Fresh fruit | America and Europe[49], Canada[50] |
| Cinnamon | Cinnamomum aromaticum; Cinnamomum longifolium/medium, cinnamom | Bark, leaf | | |
| Fenugreek | Trigonella foenum-graecum | Feonum-graeacum officinale, Trigonella tibetana (Alf.) | Seeds | Iran[52–54] |
| Garlic | Allium sativum | Allium controversum Schrad, Allium longicuspis Regel | Bulb, leaves | [55–58] |
| Gymnema | Gymnema sylvestre | Gummarboos, gummar, periopla | Dried roots and leaves | India and Africa[59], India, America[71] and Canada[48] |
| Jambolan seeds | Syzygium cumini | Calypantheas Caryophyllifolia/ cumini/cuminonada/ jambolana | Fruit, leaves, dried seed and bark | India[60,61], Khulna, Bangladesh[92] |
| Bitter melon | Momordica charantia | Karola, bitter gourd | Fruit, leaf and whole plant | Dhaka, Bangladesh[60], Indian Jodhpur and Rajasthan communities[64] |
| Neem | Azadirachta indica | Neem, neem tree or Indian lilac | Seeds/leaves/bark | Asia[63], China[66] |
| Nopal | Opuntia fulginsosa/ streptacantha | Prickly pear cactus, nopal | Flowers, fruits | India[67–69], Morocco[70], Latinos and Hispanics[71] |
| Onion | Allium cepa | Allium angulense/axtubanum/ cepaum | Leaves, bulb, oil and seeds | Tamilnadu, India[68], Palestine[72] |
| Psyllium | Plantago ovata | Plantago seeds, psyllium husk | Seeds, husk | Mexico[73,74], Canada[48] |
| Siberian Ginseng | Eleutherococcus senticosus; Acanthopanax senticosus | Acanthopanax asperatus, Eleutherococcus asperatus | Bark, roots | |
| Turmeric | Curcuma longa/ domestica; Curcuma aromatica | Amomum curcuma Jaq, Curcuma domestica Valetton, curcumin | Whole plant, fresh rhizome | [67], India[77] |

Ahmad et al. Medicine (2021) 100:16

Medicine
### Table 2
Details regarding plant, its part used, mechanism reported and results observed in clinical trials during diabetes.

| Plant                      | Clinical trail | Part used | Sample size (n) | Intervention method in intervened groups | Period of treatment | Mechanism reported                           | Results                                                                 |
|----------------------------|----------------|-----------|-----------------|-------------------------------------------|---------------------|-----------------------------------------------|-------------------------------------------------------------------------|
| Aloe vera                  | A1             | Juice from gel | 72              | 1 tablespoonful aloe juice BID            | 42 days             | N/A                                           | Blood sugar and triglyceride levels[78]                                 |
|                            | A2             | Juice from gel | 72              | 1 tablespoonful aloe juice BID + glibenclamide (5 mg tablets) | 42 days             | N/A                                           | ↓ Glucose and ↑ triglyceride[78]                                       |
|                            | A3             | Leaves extracted gel powder | 67              | Aloe capsules (300 mg BD)                | 2 months           | ↑ Insulin resistance                          | ↓ HbA1c, LDL, and total cholesterol[81]                                 |
|                            | A4             | Extract as tablet | 44              | Aloe extract tablets (10/00 mg OD)        | 2 months           | N/A                                           | No reduction in fasting blood sugar, HbA1c, total cholesterol, triglycerides, HDL/LDL[81] |
|                            | A5             | Powder of the leaves extracted gel | 90              | First intervention: Group 1: no treatment. Group 2: aloe powder (100 mg Group 3: aloe powder (200 mg) | 3 months           | ↑ Effectiveness of insulin | (Fasting) and post prandial blood glucose and lipid profile[83] |
|                            |                |            |                 | Second intervention: nutrition to group 2 and 3. |                     |                                               |                                                                         |
| American ginseng           | B1             | Opaque gelatin capsule | 39              | Konjac-glucosamin blend fiber (9g/day) + ginseng (3g/day) | 12 weeks + 4 weeks washout period (Crossover) | ↑ Insulin secretion                           | ↓ HbA1c and lipid panel[89]                                           |
|                            | B2             | Ginseng root extract | 74              | Capsules (total 3g/day)                  | 12 weeks           | N/A                                           | Safe in T2DM patient with CVS risk (Mucalo et al., 2014)                |
|                            | B3             | Gelatin capsules | 19              | Ginseng capsules (3g) + oral glucose challenge (25g) in each visit | 4 visits (1 week interval between each visit) | ↓ Digestion and ↑ insulin secretion            | Change in glycemia[89]                                                |
|                            | B4             | Root of American ginseng | 10              | Either placebo or ginseng 3, 6, or 9g randomly/each visit | 16 visits with a 3 days interval | ↑ Digestion and ↑ insulin secretion            | No effect on post prandial glycemia[89]                                |
|                            | B5             | Dried whole root extract | 24              | Ginseng capsules (5g/day)                | 8 weeks + 2 weeks washout period | ↑ Insulin secretion                           | ↑ HbA1c, fasting blood glucose[89]                                      |
| Bilberry                   | C1             | Fruit extract | 8               | 0.47g of Mirtoselect (equal to 50g of fresh bilberries) | Single dose with 2 weeks washout period | ↓ Carbohydrate digestion or absorption | ↑ Postprandial glycaemia and insulin[89]                                |
| Cinnamon                   | D1             | Capsule     | 60              | Cinnamon capsules (500 mg BD)            | 3 months           | NA                                           | No change in glucose and lipid profile[89]                             |
|                            | D2             | Aqueous extract as capsule | 60              | 1, 3, 6g cinnamon daily                  | 40 days            | ↑ Insulin release                             | ↓ Serum glucose and lipid profile[89]                                  |
|                            | D3             | Whole bark extract as capsule | 25              | Cinnamon (150/10mg/day)                 | 6-7 weeks          | ↑ Insulin sensitivity                        | No improvement in glucose[89]                                         |
|                            | D4             | Capsule     | 109             | Cinnamon capsules (1g/day)              | 90 days            | N/A                                           | ↑ HbA1c[89]                                                             |
|                            | D5             | Aqueous cinnamon extract | 79              | Capsule (11.2mg of aqueous cinnamon extract TID) | 4 months           | ↑ Insulin release                             | ↑ Fasting glucose[89]                                                  |
|                            | D6             | Capsule     | 14              | Giving cinnamon capsule 1.5g/day        | 30 days            | NA                                           | ↓ Glucose, triglycerides and cholesterol[89]                            |
|                            | D7             | Bark extract as tablet | 66              | Placebo + Cinnamon extract at 120 or 360g/day | 3 months           | NA                                           | ↑ Fasting blood glucose and HbA1c[89]                                   |
|                            | D8             | Capsule     | 72              | Cinnamon (1g/day)                       | 90 days            | ↑ Insulin stimulated tyrosine phosphorylation | No significant difference in glucose profile or number of hypoglycaemic episodes[89] |
|                            | D9             | Bark extract as capsule | 44              | Cinnamon supplement (3g/day).            | 8 weeks            | ↑ Insulin stimulated tyrosine phosphorylation | No significant difference in glycemic indicators between arms of the study[89] |
|                            | D10            | Bark powder as capsule | 58              | Cinnamon (2g/day)                       | 12 weeks           | ↑ Glucose transporter (GLUT4) and receptor proteins | ↑ HbA1c and blood pressure[89]                                        |
| Fenugreek                  | E1             | Seed extract (Fenfuro-TM) | 174             | Fenugreek capsule (500 mg BD)            | 90 days            | NA                                           | ↑ Post-prandial blood glucose and FBG[91]                              |
|                            | E2             | Seeds soaked in hot water | 60              | Fenugreek seeds soaked in hot water (10g/day) | 6 months           | ↑ Insulin release                             | ↓ Fasting blood glucose levels and HbA1c[91]                            |
|                            | E3             | Dried ripe seed capsule | 69              | Fenugreek saponins 6 capsules (TFGs) TID (0.35g/cap) | 12 weeks           | NA                                           | ↓ Glycemia and CSQS in the treated group[109]                           |
|                            | E4             | Seed powder  | 24              | Powdered fenugreek seeds (10g/day)       | 8 weeks            | ↑ Insulin release                             | ↑ FBS[109]                                                             |
|                            | E5             | Hydro-alcoholic seeds extract | 25              | Hydro-alcoholic extract (1g/ day)        | 2 months           | ↑ Insulin release                             | ↑ HbA1c and insulin resistance[102]                                    |
|                            | E6             | Seed powder  | 80              | Fenugreek powder (25g/day)              | 2 months           | ↑ Insulin release                             | ↓ FBS and HbA1c[109]                                                   |
|                            | E7             | Seed powder  | 30              | Two sachet of Polyherbal formulation (PHF) containing fenugreek 2.5 g | 40 days           | ↑ Insulin                                  | ↓ FBS and HbA1c[109]                                                   |
| Garlic                     | F1             | Aged garlic extract (Hydric) | 26              | 1200mg of Aged garlic extract daily      | 4 weeks with 4 weeks washout | NA                                           | No extra benefit for adding aged garlic[109]                           |
|                            | F2             | Aqueous extract capsule | 32              | Capsules (combination of 200 mg turmeric and 200 mg garlic). Three groups: | 12 weeks           | ↑ Insulin secretion                           | ↑ Glucose profile[109]                                                |

(continued)
| Plant | Clinical trial | Part used | Sample size (n) | Intervention method in intervened groups | Period of treatment | Mechanism reported | Results |
|-------|----------------|-----------|----------------|----------------------------------------|--------------------|-------------------|---------|
| F3    | Garlic powder tablets (Allicor) | group 1 (1.2g), group 2 (1.6g) and group 3 (2.4g) daily | 300mg Allicor/day | Insulin secretion | ↑ Blood glucose, ↓ Glycemic level | ↑ Insulin secretion, ↓ Blood glucose, ↓ Glycemic level |
| F4    | Bulb extract (Lasuna) capsule | 60 | Garlic capsules (250mg BD) added to standard therapy | 12 weeks | Insulin secretion and sensitivity | ↓ Insulin secretion and sensitivity |
| F5    | N/A             | 96 | Capsules (50 mg/day) added to standard medication | 12 weeks | N/A | N/A |
| F6    | Garlic (KWAi) tablet | 60 | Tablets (300mg TD) | 24 weeks | ↑ Insulin secretion | ↑ Insulin secretion |
| F7    | Garlic tablet   | 210 | 5 groups received garlic (300, 600, 900, 1200, and 1500 mg/day), one took metformin and one was placebo | 24 weeks | N/A | N/A |
| F8    | Kyolic aged garlic extract | 48 | Extract (3g/day) | 3 months | ↑ Insulin secretion | ↑ Insulin secretion |
| F9    | Bulb extract (Lasuna) capsules | 60 | Garlic powder tablets (Allicor) 60 | 12 weeks | ↑ Insulin secretion | ↑ Insulin secretion |
| Gymnema | Water-soluble leaves extract | 60 | Capsules daily (200mg/cap) | 2–30 months | ↓ Endogenous insulin | ↓ Endogenous insulin |
| G2    | Water-soluble leaves extract | 47 | Capsules (400mg/cap) | 12–18 months | Beta cells regeneration | Beta cells regeneration |
| G3    | Beta Fast GXR (leaves extract) | 100 | Tablets (400mg/BID) | 90 days | ↓ Insulin levels due to regeneration of the pancreatic beta cells | ↓ Insulin levels due to regeneration of the pancreatic beta cells |
| G4    | Om Santal Adivasi (OSA) | 60 | Capsules (250mg BID) + metformin. | 12 weeks | ↑ Insulin secretion | ↑ Insulin secretion |
| G5    | Leaves powder   | 20 | Powder (3g/day) | 1 month | ↑ Insulin secretion | ↑ Insulin secretion |
| Jambolan | Dried leaves tea | 27 | Group 1: Syzygium cumini leaves tea (2g/day) | 28 days | ↑ Blood glucose and HbA1c | ↑ Blood glucose and HbA1c |
| G2    | Water-soluble leaves extract | 47 | Capsule (400 mg/day) | 18–20 months | Beta cells regeneration | Beta cells regeneration |
| G3    | Beta Fast GXR (leaves extract) | 100 | Tablets (400mg/BID) | 90 days | ↓ Insulin levels due to regeneration of the pancreatic beta cells | ↓ Insulin levels due to regeneration of the pancreatic beta cells |
| G4    | Om Santal Adivasi (OSA) | 60 | Capsules (1g/cap) | 6 days | ↑ Insulin secretion | ↑ Insulin secretion |
| G5    | Leaves powder   | 20 | Powder (6g/day) | 1 month | ↑ Insulin secretion | ↑ Insulin secretion |
| Jambolan | Dried leaves tea | 27 | Syzygium cumini leaves tea (2g/day) | 28 days | ↑ Blood glucose and HbA1c | ↑ Blood glucose and HbA1c |
| G2    | Water-soluble leaves extract | 47 | Capsule (400mg/cap) | 12–18 months | Beta cells regeneration | Beta cells regeneration |
| G3    | Beta Fast GXR (leaves extract) | 100 | Tablets (400mg/BID) | 90 days | ↓ Insulin levels due to regeneration of the pancreatic beta cells | ↓ Insulin levels due to regeneration of the pancreatic beta cells |
| G4    | Om Santal Adivasi (OSA) | 60 | Capsules (250mg BID) + metformin. | 12 weeks | ↑ Insulin secretion | ↑ Insulin secretion |
| G5    | Leaves powder   | 20 | Powder (3g/day) | 1 month | ↑ Insulin secretion | ↑ Insulin secretion |
| Jambolan | Dried leaves tea | 27 | Group 1: Syzygium cumini leaves tea (2g/day) | 28 days | ↑ Blood glucose and HbA1c | ↑ Blood glucose and HbA1c |
| G2    | Water-soluble leaves extract | 47 | Capsule (400mg/cap) | 12–18 months | Beta cells regeneration | Beta cells regeneration |
| G3    | Beta Fast GXR (leaves extract) | 100 | Tablets (400mg/BID) | 90 days | ↓ Insulin levels due to regeneration of the pancreatic beta cells | ↓ Insulin levels due to regeneration of the pancreatic beta cells |
| G4    | Om Santal Adivasi (OSA) | 60 | Capsules (1g/cap) | 6 days | ↑ Insulin secretion | ↑ Insulin secretion |
| G5    | Leaves powder   | 20 | Powder (6g/day) | 1 month | ↑ Insulin secretion | ↑ Insulin secretion |
| Jambolan | Dried leaves tea | 27 | Syzygium cumini leaves tea (2g/day) | 28 days | ↑ Blood glucose and HbA1c | ↑ Blood glucose and HbA1c |
| G2    | Water-soluble leaves extract | 47 | Capsule (400mg/cap) | 12–18 months | Beta cells regeneration | Beta cells regeneration |
| G3    | Beta Fast GXR (leaves extract) | 100 | Tablets (400mg/BID) | 90 days | ↓ Insulin levels due to regeneration of the pancreatic beta cells | ↓ Insulin levels due to regeneration of the pancreatic beta cells |
| G4    | Om Santal Adivasi (OSA) | 60 | Capsules (1g/cap) | 6 days | ↑ Insulin secretion | ↑ Insulin secretion |
| G5    | Leaves powder   | 20 | Powder (3g/day) | 1 month | ↑ Insulin secretion | ↑ Insulin secretion |
| Jambolan | Dried leaves tea | 27 | Syzygium cumini leaves tea (2g/day) | 28 days | ↑ Blood glucose and HbA1c | ↑ Blood glucose and HbA1c |
| G2    | Water-soluble leaves extract | 47 | Capsule (400mg/cap) | 12–18 months | Beta cells regeneration | Beta cells regeneration |
| G3    | Beta Fast GXR (leaves extract) | 100 | Tablets (400mg/BID) | 90 days | ↓ Insulin levels due to regeneration of the pancreatic beta cells | ↓ Insulin levels due to regeneration of the pancreatic beta cells |
| G4    | Om Santal Adivasi (OSA) | 60 | Capsules (1g/cap) | 6 days | ↑ Insulin secretion | ↑ Insulin secretion |
| G5    | Leaves powder   | 20 | Powder (6g/day) | 1 month | ↑ Insulin secretion | ↑ Insulin secretion |
| Jambolan | Dried leaves tea | 27 | Syzygium cumini leaves tea (2g/day) | 28 days | ↑ Blood glucose and HbA1c | ↑ Blood glucose and HbA1c |
| G2    | Water-soluble leaves extract | 47 | Capsule (400mg/cap) | 12–18 months | Beta cells regeneration | Beta cells regeneration |
| G3    | Beta Fast GXR (leaves extract) | 100 | Tablets (400mg/BID) | 90 days | ↓ Insulin levels due to regeneration of the pancreatic beta cells | ↓ Insulin levels due to regeneration of the pancreatic beta cells |
| G4    | Om Santal Adivasi (OSA) | 60 | Capsules (1g/cap) | 6 days | ↑ Insulin secretion | ↑ Insulin secretion |
| G5    | Leaves powder   | 20 | Powder (6g/day) | 1 month | ↑ Insulin secretion | ↑ Insulin secretion |

(continued)
| Plant | Clinical trial | Part used | Sample size (n) | Intervention method in intervened groups | Period of treatment | Mechanism reported | Results |
|-------|----------------|-----------|-----------------|-------------------------------------------|-------------------|--------------------|---------|
|      |                |           |                 | Group 1: broiled nopal stems (500 g), group 2: only water (400 mL), Group 3: nopal, water and broiled squash | Single dose, 1 week washout between each intervention. |                    | ↓ Serum glucose and insulin[132] |
| L3   | Stems          | 28        | 500 g of nopal  | Single dose                                | N/A               |                    |         |
| L4   | Dehydrated extract, capsulated | 6 | 30 capsules of dehydrated nopal extract (10.1 g) | Single dose | N/A | No hypoglycemic effects observed[132] |
| L5   | Heated blended crude stem | 8 | 5 interventions; 4 for nopal stems (entire broiled, blended broiled, blended crude, and heated blended) and 1 water as placebo. | 5 separate interventions (72hs between them) | N/A | ↓ Serum glucose[132] |
| L6   | Dried, capsulated | 10       | 30 nopal capsules | Single dose                                | N/A               | No hypoglycemic effect observed[132] |
| Onion | M1            | Fresh onion cut into slices | 84 | Crude fresh slices (100 g), standard diabetic treatment, or 15 ml of water. | Single dose, 1 week washout | Improved and regenerated cells | ↓ Blood glucose and FBG[133] |
| Psyllium | N1          | Psyllium pre-mixed in cookies | 77 | Cookies containing either flaxseed/psyllium/placebo (10 g/day) | 12 weeks | N/A | ↓ FBG and HbA1c[134] |
|       | N2          | Psyllium pre-mixed in cookies | 51 | cookies containing either flaxseed/psyllium/placebo (10 g per day) | 12 weeks | N/A | ↓ FBG and HbA1c[135] |
|       | N3          | Fiber psyllium (Metamucil) | 37 | Psyllium (3.4 g), psyllium (6.8 g BID) or placebo. | 12 weeks | ↓ Carbohydrate absorption | ↓ FBG and HbA1c[136] |
|       | N4          | Soluble fiber | 40 | Soluble fiber (10.5 g) daily | 8 weeks | ↓ CHO absorption/digestion | ↓ Glucose levels[137] |
|       | N5          | Psyllium fiber | 18 | 6.8 g psyllium twice in the first visit and placebo in the crossover visit. | One day of treatment for each group (crossover) | ↓ Access of glucose to the gut | ↓ FBG and insulin concentrations[138] |
| Siberian ginseng | O1      | Purified solution of extract | 75 | Extract of Siberian ginseng (480 mg/day), American ginseng (480 mg/day), or placebo. | 3 months | ↓ Glucose induced insulin secretion | ↓ Fasting and post prandial blood sugar[139] |
| Turmeric | P1             | (Sina Curlcumin) | 70 | Curcumin (80 mg/day) | 3 months | N/A | ↓ HbA1c, FBG, TG, and Bld[140] |
|       | P2             | Capsule    | 100 | Curcuminoids capsule (150 mg BID) | 3 months | ↓ Serum A-FABP levels | ↓ Blood glucose with anti-diabetic effects[141] |
|       | P3             | Rhizomes   | 60 | 2 g turmeric + standard metformin therapy | 4 weeks | ↓ Beta cell stimulation | ↓ Fasting plasma glucose[142] |
|       | P4             | Extracts isolated from rhizome | 100 | Curcuminoids (300 mg/day) | 3 months | ↓ BG and ↑ Insulin resistance | ↓ Fasting blood glucose[143] |
Furthermore, no information about the “intention-to-treat-analysis” and “timing of outcome assessment,” was loaded in PC3 with individual variation of 13.11%. Finally, “non-blindness of the outcome assessor” contributed 11.38% to the total variance (63.435%). A three-dimensional representation of the factors loaded in components is shown in Figure 3.

For Pearson’s correlation (Table 6), none of the pair was observed with a negative correlation however, the drawback of “mentioning the baseline characteristics for the groups” was found to have no significant correlation with any other drawback extracted from the study. With the same concept of evidence, PCA showed no loading with significant Eigen value for this drawback. The reason is due to sparse distribution of current drawback in the reported clinical trials. The Pearson’s correlation between “intention-to-treat-analysis” and “outcome assessment method” again confirms the loading for both the drawbacks in PC3, and so on. The descending order of the drawbacks in these clinical trials, based on PCA and Pearson’s correlation may be constructed as;

"Non-randomized and non-blinded,” “concealed treatment allocation,” “non-blindness of patient and care provider,” “lack of drop out procedures” > “[lack of patients compliance and co-interventions reports]” > “[non-inclusion of intention-to-treat-analysis and timing of outcome assessment”] > ["outcome assessor non-blind"] > [missing to mention the baseline characteristics of the groups].

Figure 4 represents the descending order of occurrence for these drawbacks.

4. Scoring of clinical trials (jadad, Delphi, and cochrane scales)

For simplicity and leniency, an internal grading scale (points) was applied; 6 or below (any negative value) “very poor quality clinical trial,” 7 to 12 “poor quality clinical trial,” 13 to 18 “acceptable quality clinical trial,” and 19 to 24 “good quality clinical trial.” Beside the two excellent studies (D10, I8) the percentage for good quality clinical trial observed was 13.5%. The very poor and poor quality clinical trials makes the major proportion (67.6%) of these studies (Table 7).

5. Discussion

This study presents a generalized view of the major drawbacks observed in the clinical trials selected and evaluated. The forthcoming discussion is a section-wise classification with extensive explanation of the drawbacks extracted;

5.1. Selection and identification of the plant source

To commence a clinical trial, the identification and quality of the source (natural product) is utmost important. Sufficient background information regarding the identity of the selected source is very essential. Plants may vary in terms of quality and quantity of the active principles present which is due to variation in geographical origins. Hence, the differences in environment, temperature, irrigation, salinity, stress, altitude, and seasonal variation may affect the composition of plant phytochemicals. A lack of very basic and essential information about the herbs used (family, genus, species and geographical origin, phytochemistry and quantification, and mechanism of actions, etc.) was witnessed in these studies, which are strictly needed for a herb to be worked on as mentioned by Heinrich et al.[20] Such information regarding the species and its phytochemistry may help researchers and stakeholders to dig deeper at mechanistic and molecular level to isolate the compound of interest for an effective control of diabetes and related comorbidities. The proper evidence regarding ethnopharmacological and ethnomedicinal value of the plants reported,[21,22] is of prime importance.
### Table 4

Limitations, individual and total score calculated for each clinical trial based on Jadad, Delphi and Cochrane scales.

| Plant                  | Study # | a | b | c | d | e |
|------------------------|---------|---------|---------|---------|---------|---------|
| Aloe vera              | A1      | X        | X        | X        | X        | X        |
|                        | A2      | X        | X        | X        | X        | X        |
|                        | A3      | X        | X        | X        | X        | X        |
|                        | A4      | X        | X        | X        | X        | X        |
|                        | A5      | X        | X        | X        | X        | X        |
| American ginseng       | B1      | X        | X        | X        | X        | X        |
|                        | B2      | X        | X        | X        | X        | X        |
|                        | B3      | X        | X        | X        | X        | X        |
|                        | B4      | X        | X        | X        | X        | X        |
|                        | B5      | X        | X        | X        | X        | X        |
| Bilberry               | C1      | X        | X        | X        | X        | X        |
|                        | D1      | X        | X        | X        | X        | X        |
|                        | D2      | X        | X        | X        | X        | X        |
|                        | D3      | X        | X        | X        | X        | X        |
|                        | D4      | X        | X        | X        | X        | X        |
|                        | D5      | X        | X        | X        | X        | X        |
|                        | D6      | X        | X        | X        | X        | X        |
|                        | D7      | X        | X        | X        | X        | X        |
|                        | D8      | X        | X        | X        | X        | X        |
|                        | D9      | X        | X        | X        | X        | X        |
|                        | D10     | X        | X        | X        | X        | X        |
| Fenugreek              | E1      | X        | X        | X        | X        | X        |
|                        | E2      | X        | X        | X        | X        | X        |
|                        | E3      | X        | X        | X        | X        | X        |
|                        | E4      | X        | X        | X        | X        | X        |
|                        | E5      | X        | X        | X        | X        | X        |
|                        | E6      | X        | X        | X        | X        | X        |
|                        | E7      | X        | X        | X        | X        | X        |
| Garlic                 | F1      | X        | X        | X        | X        | X        |
|                        | F2      | X        | X        | X        | X        | X        |
|                        | F3      | X        | X        | X        | X        | X        |
|                        | F4      | X        | X        | X        | X        | X        |
|                        | F5      | X        | X        | X        | X        | X        |
|                        | F6      | X        | X        | X        | X        | X        |
|                        | F7      | X        | X        | X        | X        | X        |
|                        | F8      | X        | X        | X        | X        | X        |
| Gymnema                | G1      | X        | X        | X        | X        | X        |
|                        | G2      | X        | X        | X        | X        | X        |
|                        | G3      | X        | X        | X        | X        | X        |
|                        | G4      | X        | X        | X        | X        | X        |
|                        | G5      | X        | X        | X        | X        | X        |
|                        | G6      | X        | X        | X        | X        | X        |
|                        | G7      | X        | X        | X        | X        | X        |
|                        | G8      | X        | X        | X        | X        | X        |
|                        | G9      | X        | X        | X        | X        | X        |
|                        | G10     | X        | X        | X        | X        | X        |
| Jambolan               | H1      | X        | X        | X        | X        | X        |
|                        | H2      | X        | X        | X        | X        | X        |
|                        | I1      | X        | X        | X        | X        | X        |
|                        | I2      | X        | X        | X        | X        | X        |
|                        | I3      | X        | X        | X        | X        | X        |
|                        | I4      | X        | X        | X        | X        | X        |
|                        | I5      | X        | X        | X        | X        | X        |
|                        | I6      | X        | X        | X        | X        | X        |
|                        | I7      | X        | X        | X        | X        | X        |
|                        | I8      | X        | X        | X        | X        | X        |
|                        | I9      | X        | X        | X        | X        | X        |
|                        | J1      | X        | X        | X        | X        | X        |
|                        | J2      | X        | X        | X        | X        | X        |
|                        | J3      | X        | X        | X        | X        | X        |
|                        | J4      | X        | X        | X        | X        | X        |
|                        | J5      | X        | X        | X        | X        | X        |
|                        | J6      | X        | X        | X        | X        | X        |
|                        | J7      | X        | X        | X        | X        | X        |
|                        | J8      | X        | X        | X        | X        | X        |
|                        | J9      | X        | X        | X        | X        | X        |
|                        | J10     | X        | X        | X        | X        | X        |
| Maitake Neem           | K1      | X        | X        | X        | X        | X        |
|                        | K2      | X        | X        | X        | X        | X        |
|                        | K3      | X        | X        | X        | X        | X        |
|                        | K4      | X        | X        | X        | X        | X        |
|                        | K5      | X        | X        | X        | X        | X        |
| Nopal                 | L1      | X        | X        | X        | X        | X        |
|                        | L2      | X        | X        | X        | X        | X        |
|                        | L3      | X        | X        | X        | X        | X        |
|                        | L4      | X        | X        | X        | X        | X        |
|                        | L5      | X        | X        | X        | X        | X        |
|                        | L6      | X        | X        | X        | X        | X        |
| Onion                 | M1      | X        | X        | X        | X        | X        |
|                        | M2      | X        | X        | X        | X        | X        |
|                        | M3      | X        | X        | X        | X        | X        |
|                        | M4      | X        | X        | X        | X        | X        |
|                        | M5      | X        | X        | X        | X        | X        |
|                        | M6      | X        | X        | X        | X        | X        |
|                        | M7      | X        | X        | X        | X        | X        |
|                        | M8      | X        | X        | X        | X        | X        |
|                        | M9      | X        | X        | X        | X        | X        |
|                        | M10     | X        | X        | X        | X        | X        |
| Psyllium               | N1      | X        | X        | X        | X        | X        |
|                        | N2      | X        | X        | X        | X        | X        |
|                        | N3      | X        | X        | X        | X        | X        |
|                        | N4      | X        | X        | X        | X        | X        |
|                        | N5      | X        | X        | X        | X        | X        |
|                        | N6      | X        | X        | X        | X        | X        |
|                        | P1      | X        | X        | X        | X        | X        |
|                        | P2      | X        | X        | X        | X        | X        |
|                        | P3      | X        | X        | X        | X        | X        |
|                        | P4      | X        | X        | X        | X        | X        |
|                        | P5      | X        | X        | X        | X        | X        |

**Jadad deficiencies:** a; randomization mentioned, b; randomization method, c; double blind words, d; double blind method, e; description of withdrawals and dropouts. **Delphi scale deficiencies:** a; randomization performed, b; treatment allocation concealed, c; similarity at baseline, d; eligibility criteria specified, e; outcome assessor blinded, f; care provider blinded, g; patient blinded, h; point estimates and of variability presented for the primary outcome measured, i; intention-to-treat analysis. **Cochrane scale deficiencies:** a; randomization adequate, b; treatment allocation concealed, c; similarity at baseline, d; patient blinded, e; care provider blinded, f; outcome assessor blinded, g; co-interventions avoided or similar, h; compliance acceptable, i; description of withdrawals and dropouts, j; similarity in timing of the outcome assessment.
5.2. Part of natural product used and its phytochemistry

Every individual part of a plant may vary with respect to the other part of the same plant in terms of nature of active ingredients or even the amount of similar active ingredient.\cite{23} For instance, the antidiabetic effect was studied for seeds and leaves of Jambolan in these clinical trials. The seeds were observed with prominent antidiabetic effect whereas, the leaves for the same plant exhibited a lack of activity in diabetes. This is a self-explanatory evidence to choose wisely during selection of plant part as it may vary in phytochemistry.

5.3. Effects of extraction methods, temperatures and solvents upon the final dosage form preparation

The process-selection for dosage form preparation (extract, tea, infusion, essential oil, etc), exerts a subtle difference in the final outcomes of a study. The phenomenon has been mentioned in very detail in previous reports.\cite{24–26} For example, Nopal was applied in the form of steamed as well as broiled steamed dosage form in these reported clinical trials. A proper explanation is missing regarding part, dosage form of Nopal used, and the effect of heat/difference in composition of steamed and broiled steamed

| Table 5 | Principal components loading (PCA) for factors analyzed in clinical studies and KMO and Bartlett’s test. |
| Factors | PC1 | PC2 | PC3 | PC4 |
| (A) Clinical trial was randomized or not? | 0.610 | 0.141 | 0.140 | −0.463 |
| (B) Clinical trial was blinded or non-blinded? | 0.665 | −0.556 | 0.010 | −0.032 |
| (C) Treatment allocation was concealed or not? | 0.806 | −0.141 | −0.213 | 0.123 |
| (D) The outcome assessor was blinded or not? | 0.270 | 0.399 | −0.157 | −0.610 |
| (E) Patient was blinded in the study or not? | 0.866 | −0.286 | −0.217 | 0.125 |
| (F) The care provider was blinded or not? | 0.634 | 0.186 | −0.543 | 0.281 |
| (G) The intention to treat analysis, was mentioned in clinical trial? | 0.416 | −0.066 | 0.602 | −0.197 |
| (H) Proper drop out procedure was mentioned? | 0.640 | 0.249 | 0.320 | −0.098 |
| (I) Was the patient compliance for the clinical trial reported? | 0.285 | 0.624 | 0.328 | 0.206 |
| (J) Was the timing of outcome assessment mentioned? | 0.111 | −0.267 | 0.628 | 0.352 |
| (K) Was the baseline characteristics for the group mentioned? | 0.233 | 0.121 | 0.203 | 0.299 |
| (L) Was any co-interventions mentioned? | 0.168 | 0.654 | −0.068 | 0.356 |
| Variability % | 23.12 | 15.83 | 13.11 | 11.38 |
| Cumulative % | 23.12 | 38.96 | 52.07 | 63.455 |

KMO and Bartlett’s test

| | |
| --- | --- |
| Kaiser–Meyer–Olkin measure of sampling adequacy | 0.659 |
| Bartlett’s test of sphericity | 289.58 |
| Approx. Chi-square | 66 |
| degree of freedom | 0.000 |
| Significance | 0.000 |

Figure 2. Scree plot, representing the number of possible components for factors loading.
Nopal dosage form in terms of active drug amount and therapeutic effects.

5.4. Use of toxic and hazardous solvent for dosage form preparation

The use of toxic and hazardous solvents for extraction may be problematic. One of the clinical trial for fenugreek applied hydro-alcoholic solvent for extract preparation. Another clinical study for bitter melon applied a technique for proper phytochemical screening which is interesting to see however, the same study utilized toxic solvents of carbon tetra chloride and benzene for extraction which are well known to release highly toxic phosgene fumes when heated. Hence, toxicity profile needs to be reported for these extracts in preclinical studies. An effective widely used alternative approach now-a-days is, the use of green solvent and green extraction.[27]

5.5. Clinical phase selection for study (Phase 0-V)

Phase-0 is a preliminary step in any clinical study where sub-therapeutic dosing is tested in about ten individuals in order to determine the pharmacokinetics and pharmacodynamics profile.[28] This supportive data helps to safely administer any herb or

![Component Plot in Rotated Space](image)

Figure 3. Scree plot and component loadings for factors.

**Table 6**

Pearson correlation matrix for factors observed in clinical trials (letter A-L represents the points as mentioned in Table 3).

|   | A   | B  | C  | D  | E  | F  | G  | H  | I  | J  | K  | L  |
|---|-----|----|----|----|----|----|----|----|----|----|----|----|
| A | 1   |    |    |    |    |    |    |    |    |    |    |    |
| B | 0.394* | 1  |    |    |    |    |    |    |    |    |    |    |
| C | 0.305* | 0.459* | 1  |    |    |    |    |    |    |    |    |    |
| D | 0.285* | −0.052 | 0.181 | 1  |    |    |    |    |    |    |    |    |
| E | 0.389* | 0.771* | 0.699* | 0.067 | 1  |    |    |    |    |    |    |    |
| F | 0.157 | 0.176 | 0.056* | 0.207 | 0.600* | 1  |    |    |    |    |    |    |
| G | 0.252* | 0.223 | 0.242* | 0.108 | 0.246* | −0.034 | 1  |    |    |    |    |    |
| H | 0.423* | 0.252* | 0.383* | 0.184 | 0.372* | 0.251* | 0.330* | 1  |    |    |    |    |
| I | 0.222 | −0.076 | 0.105 | 0.063 | 0.043 | 0.155 | 0.149 | 0.343* | 1  |    |    |    |
| J | −0.062 | 0.115 | 0.115 | −0.144 | 0.029 | −0.106 | 0.270† | 0.138 | 0.039 | 1  |    |    |
| K | 0.108 | 0.140 | 0.095 | 0.037 | 0.154 | 0.052 | 0.052 | 0.099 | 0.180 | 0.070 | 1  |    |
| L | 0.087 | −0.151 | 0.012 | 0.081 | 0.077 | 0.261† | 0.013 | 0.154 | 0.278* | −0.051 | 0.080 | 1  |

*Correlation is significant at the .01 level (2-tailed).
†Correlation is significant at the .05 level (2-tailed).
herbal product in human participants, without compromising the subject’s rights and values. The data regarding toxicity and sub-therapeutic dosing, that is, Phase-0, is not included in any clinical trial mentioned here. In addition, the clinical trials in this systemic review are mostly reported at a preliminary level of Phase-I/II which necessitates a major data regarding Phase III–V.

5.6. Blinding and concealment of study

Natural products such as cinnamon, onion, and garlic possess a particular smell/aroma and taste, the masking of which is utmost important to avoid any ambiguities/biasness in a study. Furthermore, to avoid any data manipulation, clinical studies needs to be of double-blind nature where both; the care provider/product administrator and outcome assessor are blinded towards the product used, protocols applied, subjects group assigned, and parameters/data to be studied. Unfortunately, majority of the clinical trials herein were observed to be non-blinded or single blinded on behalf of patients, health care providers or outcome assessors.

5.7. Duration and compliance of clinical trials

The duration for these clinical trials ranged from week to months including 6 (cinnamon) and 20 months (gymnema) which are too lengthy and may be pose risks in certain conditions. No doubt, diabetic patients are asked to continue antidiabetic medications on a regular basis however, the co-administration of a natural product with conventional medication may produce unavoidable circumstance due to potential herb-drug interactions in such chronic used patient. Thus more lengthy studies with frequent dosing may lead to non-compliance which was observed in all of the clinical trials reported here.

5.8. Potential herb–drug interactions

Severe or life threatening adverse effects have been reported when herbs are co-administered with conventional medicines. For example, bitter melon along with oral hypoglycemic may decrease blood glucose level whereas, Aloe vera along with insulin/oral hypoglycemic potentiates the hypoglycemic effect hence, needs a proper caution. These clinical trials were unable to explain; how to co-administer the plant with conventional drugs? What is the half-life, excretion ratio/rate, plasma protein binding, and clearance mechanism for extract/herbs studied? Most of the clinical trials used Metformin (half-life: 6.2 h); however, none of them mentioned the dosage frequency for the natural product, information about co-administration, dosage-gap, half-life of natural products used, metabolic pathways and enzymes involved, as well as any herb-drug interactions for the products studied. For example, clinical trial for turmeric and metformin observed a pronounced effect, yet no any prior information were available for such effect.

Table 7

| Quality of trial based on assigned scale | Frequency (N) | Percent (%) | Cumulative Percent |
|----------------------------------------|--------------|-------------|--------------------|
| Very poor quality clinical trials (6 and below, i.e., negative value) | 25            | 33.8        | 33.8               |
| Poor quality clinical trials[7–12]     | 25            | 33.8        | 67.6               |
| Acceptable quality clinical trials[13–16] | 14            | 18.9        | 86.5               |
| Good quality clinical trials[17–24]    | 10            | 13.5        | 100.0              |
| Total                                  | 74            | 100.0       |                    |
5.9. Dose of the natural product used

A dose of 1 to 6 g/day was observed in most of these clinical trials which apparently seems too high for any health related condition treatment. The question rises of how the powder/extract was converted to tablet/capsule with such a high amount? Based on size availability, “000” capsule is able to encompass a dose up to 1 g (subjected to natural product density as it may can reduce to 700/800 mg in case of dense powders). Above all, administering the allowable powder amount/capsule with a frequency of three time/day is still unable to deliver a dose of 3 g or above whereas, a number of clinical trials reported a dose up to 6 g/day. In particular, patient using conventional drugs (on conventional therapy) were given such high doses 3 to 4 times/day. This is a high risk trial with more chances and risks of life threatening herb-drug interactions. These studies completely skipped/failed to report proper information for managing the high doses/day in capsules, especially cinnamon (6 g), fenugreek (10 g), and nopal (500 g).

5.10. Placebo or psychological effect

Improper masking in some cases may produce psychological effects. One of the reported study using coconut oil for a placebo group observed alike effects in the all groups (37) which was explained due to a psychological phenomenon related to placebo. Most of the clinical trials reported herein were observed with a lack of proper coding/process, for natural products carrying intense smell.

6. Future perspectives and recommendations

6.1. Ethnopharmacological relevance of the plant with the study

To conduct a herbal clinical trial, it is essential to know its source (family, genus, species), ethnonotanical/ethnopharmacological relevance with the study, part of the plant used and phytochemical profile, preclinical, and toxicity data available as well as the information regarding the PKs and PDs of the herbal active ingredients, (20-22).

6.2. Identification and geographical information

Geographical location may affect the quality and quantity of active ingredient in a plant thus proper identification of geographical locations along with preliminary quality variation and standardization studies play a vital role for unification of the source intended for any clinical trial. (38,39) The pharmacological activities and toxicity profile must be ensured in animal and in vitro models as this will ease the uniformity of dose applied for an optimum activity of the plant.

6.3. A need for extraction or isolation does exist?

Albeit, it’s a tiresome job with much investment to isolate an active chemical whereas, herbal extract/powders are easy to apply/use which adds an additional advantage of synergism. This made a dogma shift more toward the use of herbs and herbal products. However, when it comes to composition, quantity, mechanism of action, and PKs and PDs of the active drug, its tricky at times to study herbal samples as they are mixture of multicomponent. (40) Thus isolation of active principle is highly recommended as it is far better in order to evaluate the effect of a herbal drug at molecular or genetic level and to market the lead molecule as a potential drug candidate. For instance, the hypoglycemic polypeptide-p or p-insulin in Momordica charantia (41) is yet to be marketed. Likewise, eleutherosides presence makes Siberian ginseng more effective compared to Panax ginseng as a proper mechanism has been proposed for eleutherosides. (42)

6.4. Selection and preparation of final dosage

Due to variation in extraction tools (shorter and greener extraction) and parameters (temperature, solvent, particle size, length of extraction, pressure used during extraction and combination of solvents), the final dosage form may vary in concentration and activity of the active drug. (24-26) Powder samples (more surface area) are known to enhance the solubility, absorption, PKs, and PDs of the herbal drugs or extracts. For example, the clinical trial for psyllium observed a marked difference in activity for soluble fibers Vs whole seeds. Similarly, bitter melon juice showed pronounced effect compared to the fruit powder. For temperature effect, dehydrated Nopal study showed no results whereas, for drying effect, shade dried bitter melon revealed no effect compared to fresh and unripe fruit. Currently, the researchers are focusing to prepare the nanodosage forms (nano-gels, micelles, nanoparticles and nano-emulsions) which are more target-oriented and effective at low doses. Curcumin-nano-micelle in one clinical trial exhibited excellent results.

6.5. Dataset available for clinical phases studied (Phase 0-V)

Proper literature data for Phase 0-V is necessary. Phase-0, though necessary to determine the sub therapeutic/starving dose/toxicity and PKs in human, is often not mandatory for plants with well-known ethnopharmacological background. Thus background information is very important to decide the clinical trials phase. (43)

6.6. Implementation of plan for short duration, multicenter and large scale study

Clinical trials with shorter duration are more effective, particularly in a population where the patient is either asked to pause/drop the conventional therapy during a clinical study or the subjects are maintained on conventional and natural products together. This will avoid unnecessary life threatening consequences due to herb–drug interactions. (29,30)

6.7. Strategy for treating co-markers or stress-related markers in diabetes

A high level of stress prevalence have been reported in diabetic population. Various byproduct such as Amadori, advanced glycation end products (glyoxal, methyl glyoxal, fructosamine, etc), or inflammatory (interleukin-1β, insulin-like growth factor 1 [IGF-1] and monocyte chemoattractant protein 1, etc) and stress-related markers (thioarbituric acid-reactive substances, glutathione, Catalase, Superoxide dismutase, etc) may be interesting and fruitful to study. These clinical trials may help eliminate/reduce the burden of diabetes and its comorbidities. (44,45)
6.8. **Translation of the clinical trials into special populations**

In addition to adult male/female subjects, it would be more helpful to conduct these clinical trials with caution in special population (pregnant, breast feeding women, and geriatric).

6.9. **The need for a mechanistic approach**

The herbs/herbal mixture may be challenging to determine the phytochemical profile hence, isolation is more preferable to overcome this loophole. However, if not required, a proper phytochemistry, suggested mechanism of action, metabolizing enzymes, and clearance pathways are least to be determined for any herbal product to be studied in a clinical trial.

### 7. Conclusion

Apart from the loopholes and drawbacks of the clinical studies reported, the authors worked to add few additional important points (Table 8), which includes; the availability of data regarding ethnopharmacological relevance, pharmacovigilance of medicinal plant (identification of plant and its part to be used with proper phytochemical profile) and intention to focus on co-markers in diabetes. These points may facilitate researchers to plan a clinical trial with high quality and uniformity.

### 8. Final note

The aim of the study was purely to evaluate the quality of reported clinical trials for natural products in diabetes and it does not aim to establish superiority of one clinical trial over the other nor does it intend to provide a comparison for the quality of researchers.

### Author contributions

RA conceived the idea and designed the study with LHA and HNA. RA and all authors conducted literature review and wrote the introduction. RA, LHA, HNA along with MAA wrote the methodology. All the authors contributed in evaluation of each and individual clinical trial and scoring them on an excel sheet. LHA and HNA alongwith AFA, LSA, KNA, and HJA wrote the body parts including; ethnopharmacological relevance, clinical trials evaluation and schedules. RA wrote the discussion and future prospective whereas RA along with LHA and MAA performed statistical analysis. RA edited the final draft and all the authors reviewed and approved the final manuscript.

**Conceptualization:** Rizwan - Ahmad, Lina Hussain AlLehaibi.

**Data curation:** Rizwan - Ahmad, Lina Hussain AlLehaibi, Hind Nasser AlSuwaidan.

**Formal analysis:** Rizwan - Ahmad.

**Funding acquisition:** Majed A Alkhathami.

**Investigation:** Rizwan - Ahmad.

**Methodology:** Rizwan - Ahmad, Ali Fuad Alghirya, Lyla Shafiq AlMubarak, Khawlah Nezar AlKhalifah, Hawra Jassim AlMubarak.

**Resources:** Hind Nasser AlSuwaidan, Ali Fuad Alghirya, Khawlah Nezar AlKhalifah, Majed A Alkhathami.

**Software:** Hawra Jassim AlMubarak.

**Supervision:** Rizwan - Ahmad.

**Validation:** Rizwan - Ahmad.

**Writing – original draft:** Rizwan - Ahmad, Lina Hussain AlLehaibi.

**Writing – review & editing:** Rizwan - Ahmad, Hind Nasser AlSuwaidan, Ali Fuad Alghirya, Lyla Shafiq AlMubarak, Khawlah Nezar AlKhalifah, Hawra Jassim AlMubarak, Majed A Alkhathami.

### References

[1] Piero MN. Diabetes mellitus—a devastating metabolic disorder. Asian J Biomed Pharm Sci 2015;4:1–7.

[2] Ozoegwu O. The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. J Physiol Pathophysiol 2013;4:46–57.

[3] Warjeet Singh L. Traditional medicinal plants of Manipur as anti-diabetics. J Med Plants Res 2011;5:677–87.

[4] A S , M N . A review of types 1 and 2 diabetes mellitus and their treatment with insulin. Am J Ther [Internet] 2006;13:349–61.

[5] Federation ID. IDF Diabetes Atlas—2019. International Diabetes Federation; 2019. 144 p.

[6] Necyk C, Zubach-Cassano L. Natural health products and diabetes: a practical review. Can J Diabetes [Internet] 2017;41:642–7.

[7] Barbagallo M, Dommnguez IJ. Diabetes and clinical research magnesium and type 2 diabetes: an update ClinMed. Int J Diabetes Clin Res 2015;2:1–5.

[8] Medagama AB, Bandara R. The use of Complementary and Alternative Medicines (CAMs) in the treatment of diabetes mellitus: Is continued use safe and effective? Nutr J 2014;13:1–9.

[9] Bjorklund G, Dadar M, Pivina L, et al. The role of zinc and copper in insulin resistance and diabetes mellitus. Curr Med Chem 2020;27:6642–57.

[10] Joseph B, Jini D. Antidiabetic effects of Momordica charantia (bitter melon) and its medicinal potency. Asian Pac J Trop Dis 2013;3:93–102.

[11] Marles RJ, Farnsworth NR. Antidiabetic plants and their active constituents. Phytomedicine [Internet] 1995;2:137–89.

[12] Akhondzadeh S. The importance of clinical trials in drug development. Avicenna J Med Biotechnol 2016;8:4.

[13] Barnes RW. Understanding investigative clinical trials. J Vasc Surg 1989;9:609–18.
[40] Adebajo AC, Iwalewa EO, Obotuo EM, et al. Pharmacological properties of the extract and some isolated compounds of Clausena lancea stem bark: anti-trichomanal, anti-diabetic, anti-inflammatory, hepatoprotective and antioxidant effects. J Ethnopharmacol 2009;122:10–9.

[41] Raman A, Lau C. Anti-diabetic properties and phytochemistry of Monordica charantia L. (Cucurbitaceae). Phytomedicine [Internet] 2009;16:349–62.

[42] Yara-Varón E, Li Y, Balcells M, et al. Vegetable oils as alternative solvents for green oleo-extraction, purification and formulation of food and natural products. Molecules 2017;22:1–24.

[43] World Health Organization (WHO). Operational guidance: information needed to support clinical trials. Geneva: World Heal Organ; 2005, p. 15.

[44] Mooy JM, De Vries H, Grootenhuis PA, et al. Major stressful life events in relation to prevalence of undetected type 2 diabetes: The Hoorn Study. Diabetes Care 2000;23:197–201.

[45] Tian M, Qing C, Cao GX, et al. Differentially expressed genes (DEGs) between cDNA libraries AfD0 and AfR5. J Chem Inf Model [Internet] 2011;51:249–55.

[46] Ssenyange CW, Namulindwa A, Oyik B, et al. Plants used to manage type ii diabetes mellitus in selected districts of central Uganda. Afr Health Sci 2015;15:496–502.

[47] Dey L, Attele AS, Yuan CS. Alternative therapies for type 2 diabetes. Altern Med Rev 2002;7:45–38.

[48] Haddad PS, Depot M, Settaf A, et al. Comparative study on the medicinal plants most recommended by traditional practitioners in Morocco and Canada. J Herbs Spices Med Plants 2003;10:25–45.

[49] Tracy TS, Kingston RL. Herbal Products: Toxicology and Clinical Pharmacology. 2nd ed. Germany: Springer Science and Business Media. Humana Press; 2007. XIII, 288 p.

[50] Tarak D, Namsa ND, Tangjang S, et al. An inventory of the ethnobotanicals used as anti-diabetic by a rural community of Dhemaji district of Assam, Northeast India. J Ethnopharmacol [Internet] 2011;138:345–50.

[51] Almubayedh H, Ahmad R, Naqvi AA, et al. Ethnopharmacological uses and public knowledge regarding Cinnamonum zeylanicum in Khober, Saudi Arabia. J Pharm Bioallied Sci 2018;10:159–65.

[52] Mardaninnejad S, Janghorban M, Moradi MT, et al. Traditional uses of medicinal plants to prevent and treat diabetes; an updated review of ethnobotanical studies in Iran. J Nephropathol 2017;6:118–25.

[53] Ahmad M, Khan MA, Arshad M, et al. Ethnophytotherapeutic approaches for the treatment of diabetes by the local inhabitants of District Attock (Pakistan). Ethnobot Res Util 2005;2005:24.

[54] Rachid A, Rabah D, Farid L, et al. Ethnopharmacological survey of medicinal plants used in the traditional treatment of diabetes mellitus in the North Western and South Western Algeria. J Med Plants Res 2012;6:2041–50.

[55] Keter LK, Mutiso PC. Ethnobotanical studies of medicinal plants used by Traditional Health Practitioners in the management of diabetes in Lower Eastern Province, Kenya. J Ethnopharmacol [Internet] 2012;139:59–71.

[56] Eddouks M, Maghrani M, Lemhadri A, et al. Ethnopharmacological survey of medicinal plants used for the treatment of diabetes mellitus, hypertension and cardiac diseases in the south-east region of Morocco (Tafilalet). J Ethnopharmacol 2002;82:97–103.

[57] Leach MJ. Gymnema sylvestre for diabetes mellitus: a systematic review. J Altern Complement Med 2007;13:977–83.

[58] Elavarasi S, Saravanan K. Ethnobotanical study of plants used to treat Diabetes by tribal people of Kolli hills, namakkal district,Tamilnadu, Southern India. Int J PharmTech Res 2012;4:409–41.

[59] Musharaf K. Ethnobotanical studies on plant resources of Sheikh Maltoun, District Mardan, Pakistan. Med Plant Res 2014.
Ahmad et al. Medicine (2021) 100:16

[62] Mahabub Nawaz MD, Hossain AH, Karim M, et al. An ethnobotanical survey of Jessore district in Khulna division, Bangladesh. Am J Sustain Agric 2009;5:328–43.

[63] Ocivirk S, Kistler M, Khan S, et al. Traditional medicinal plants used for the treatment of diabetes in rural and urban areas of Dhaka, Bangladesh— an ethnobotanical survey. J Ethnobiol Ethnomed 2013;9:1–8.

[64] Goyal M. Traditional plants used for the treatment of diabetes mellitus in Sursaang constituency, Jodhpur, Rajasthan - An ethnomedical survey. J Ethnopharmacol [Internet] 2015;174:364–8.

[65] Singh DR. A review on different benefits of mushroom. IOSR J Pharm Biol Sci 2017;12:107–73.

[66] Khutu S. Research on mushroom as a potential source of nutraceuticals: a review on indian perspective. Am J Exp Agric 2012;2:459–67.

[67] Devi S, Kumar P, Singh A, et al. Ethnobotanical survey. J Ethnopharmacol [Internet] 2015;174:364–8.

[68] Atawodi SE, Atawodi JC. Azadirachta indica (neem): a plant of multi biological and pharmacological activities. Phytochem Rev 2009;8:601–20.

[69] Thirumalai T, Beverly CD, Sathiyaaraj K, et al. Ethnobotanical Study of Anti-diabetic medicinal plants used by the local people in Javadih hills Tamlukinda, India. Asian Pac J Trop Biomed 2012;2:910–3.

[70] Tahraoui A, El-Hilaly J, Israili ZH, et al. Ethnopharmacological survey. J Ethnopharmacol [Internet] 2015;174:364–8.

[71] Yadav MK, Pradesh U. Ethno medicinal plants with antidiabetic activity: a review Mukesh Kumar Yadav 1. Gyanendra Tripathi 2 Parul Tripathi 3 2015:64750–8.

[72] Bailey CJ, Day C. Traditional plant medicines as treatments for diabetes. Diabetes Care 1989;12:553–64.

[73] Vanschoonbeek K, Thomassen BJW, Senden JM, et al. Cinnamon supplementation does not improve glycemic control in postmenopausal women with type 2 diabetes. J Nutr Sci Technol 2014;51:90–4.

[74] Crawford P. Effectiveness of cinnamon for lowering hemoglobin A1C in patients with type 2 diabetes: a randomized, controlled trial. J Am Board Fam Med 2009;22:507–12.

[75] Huseini HF, Kianbakht S, Hajiaghaee R, et al. Anti-hyperglycemic and antihyperlipidemic agent in type-2 diabetes- turmeric (Curcuma longa L.) and Garlic (Allium sativum L) extracts as antihyperglycemic, anti-inflammatory and adenosine deaminase-lowering effects of garlic in patients with type 2 diabetes mellitus with obesity. Diabetes Metab Syndr Obes Targets Ther 2013;6:49–56.

[76] Lu FR, Shen L, Qin Y, et al. Clinical observation on trigonella foenum-graecum extract (FenfuroTM) in patients with type 2 diabetes. Food Nutr Res 2016;60:1–8.

[77] Sundaram G, Ramakrishnan T, Parthasarathy H, et al. Fenugreek, an ancient herb: a clinical perspective. J Altern Complement Med 2011;17:503–10.

[78] Lu T, Sheng H, Wu J, et al. Cinnamon extract improves fasting blood glucose and glycosylated hemoglobin level in Chinese patients with type 2 diabetes. Nutr Res [Internet] 2012;32:408–12.

[79] Crawford P. Effectiveness of cinnamon for lowering hemoglobin A1C among adolescents with type 1 diabetes. Diabetes Care 2007;30:813–6.

[80] Vafa M, Mohammadi F, Shidfar F, et al. Effects of a cinnamon extract on plasma glucose, HbA1c, and serum lipids in diabetes melitus type 2. Eur J Clin Invest 2006;36:340–4.

[81] Khan R, Khan Z, Shah S. Cinnamon may reduce glucose, lipid and cholesterol level in type 2 diabetic individuals. Pakistan J Nutr 2010;9:430–3.

[82] Lu T, Sheng H, Wu J, et al. Cinnamon extract improves fasting blood glucose and glycosylated hemoglobin level in Chinese patients with type 2 diabetes. Nutr Res [Internet] 2012;32:408–12.

[83] Bhattacharya B, Basak A, Saha G, et al. Anti-diabetic activity of Aloe vera L. juice II. Clinical trial in diabetes patients. Phytomedicine 1996;3:241–56.

[84] Vyas R, Navshah H, Goyal N, et al. Antidiabetic activity of Aloe vera L. juice. I. Clinical trial in new cases of diabetes mellitus. Phytomedicine 1996;3:241–56.

[85] Lu T, Sheng H, Wu J, et al. Cinnamon extract improves fasting blood glucose and glycosylated hemoglobin level in Chinese patients with type 2 diabetes. Nutr Res [Internet] 2012;32:408–12.

[86] Akilen R, Tsiami A, Devendra D, et al. Glycated haemoglobin and blood pressure-lowering effect of cinnamon in multi-ethnic Type 2 diabetic patients in the UK: a randomized, placebo-controlled, double-blind clinical trial. Diabet Med 2010;27:1159–67.

[87] Verma N, Usman K, Patel N, et al. A multicenter clinical study to determine the efficacy of a novel fenugreek seed (Trigonella foenum-graecum) extract (FenfuroTM) in patients with type 2 diabetes. Food Nutr Res 2016;60:1–8.

[88] Lu FR, Shen L, Qin Y, et al. Clinical observation on trigonella foenum-graecum L. total saponins in combination with sultonylureas in the treatment of type 2 diabetes mellitus. Chin J Integr Med 2008;14:56–60.

[89] Lu T, Sheng H, Wu J, et al. Cinnamon extract improves fasting blood glucose and glycosylated hemoglobin level in Chinese patients with type 2 diabetes. Nutr Res [Internet] 2012;32:408–12.

[90] Akilen R, Tsiami A, Devendra D, et al. Glycated haemoglobin and blood pressure-lowering effect of cinnamon in multi-ethnic Type 2 diabetic patients in the UK: a randomized, placebo-controlled, double-blind clinical trial. Diabet Med 2010;27:1159–67.

[91] Verma N, Usman K, Patel N, et al. A multicenter clinical study to determine the efficacy of a novel fenugreek seed (Trigonella foenum-graecum) extract (FenfuroTM) in patients with type 2 diabetes. Food Nutr Res 2016;60:1–8.

[92] Blevins SM, Leyva MJ, Brown J, et al. Effect of cinnamon on glucose uptake in genetically obese Zucker diabetic rats. J Nutr 2004;134:767–70.

[93] Lu T, Sheng H, Wu J, et al. Cinnamon extract improves fasting blood glucose and glycosylated hemoglobin level in Chinese patients with type 2 diabetes. Nutr Res [Internet] 2012;32:408–12.

[94] Lu T, Sheng H, Wu J, et al. Cinnamon extract improves fasting blood glucose and glycosylated hemoglobin level in Chinese patients with type 2 diabetes. Nutr Res [Internet] 2012;32:408–12.

[95] Akilen R, Tsiami A, Devendra D, et al. Glycated haemoglobin and blood pressure-lowering effect of cinnamon in multi-ethnic Type 2 diabetic patients in the UK: a randomized, placebo-controlled, double-blind clinical trial. Diabet Med 2010;27:1159–67.

[96] Verma N, Usman K, Patel N, et al. A multicenter clinical study to determine the efficacy of a novel fenugreek seed (Trigonella foenum-graecum) extract (FenfuroTM) in patients with type 2 diabetes. Food Nutr Res 2016;60:1–8.

[97] Akilen R, Tsiami A, Devendra D, et al. Glycated haemoglobin and blood pressure-lowering effect of cinnamon in multi-ethnic Type 2 diabetic patients in the UK: a randomized, placebo-controlled, double-blind clinical trial. Diabet Med 2010;27:1159–67.

[98] Crawford P. Effectiveness of cinnamon for lowering hemoglobin A1C among adolescents with type 1 diabetes. Diabetes Care 2007;30:813–6.

[99] Vafa M, Mohammadi F, Shidfar F, et al. Effects of a cinnamon extract on plasma glucose, HbA1c, and serum lipids in diabetes mellitus type 2. Eur J Clin Invest 2006;36:340–4.

[100] Lu FR, Shen L, Qin Y, et al. Clinical observation on trigonella foenum-graecum L. total saponins in combination with sultonylureas in the treatment of type 2 diabetes mellitus. Chin J Integr Med 2008;14:56–60.

[101] Lu FR, Shen L, Qin Y, et al. Clinical observation on trigonella foenum-graecum L. total saponins in combination with sultonylureas in the treatment of type 2 diabetes mellitus. Chin J Integr Med 2008;14:56–60.

[102] Lu FR, Shen L, Qin Y, et al. Clinical observation on trigonella foenum-graecum L. total saponins in combination with sultonylureas in the treatment of type 2 diabetes mellitus. Chin J Integr Med 2008;14:56–60.

[103] Lu FR, Shen L, Qin Y, et al. Clinical observation on trigonella foenum-graecum L. total saponins in combination with sultonylureas in the treatment of type 2 diabetes mellitus. Chin J Integr Med 2008;14:56–60.

[104] Lu FR, Shen L, Qin Y, et al. Clinical observation on trigonella foenum-graecum L. total saponins in combination with sultonylureas in the treatment of type 2 diabetes mellitus. Chin J Integr Med 2008;14:56–60.

[105] Lu FR, Shen L, Qin Y, et al. Clinical observation on trigonella foenum-graecum L. total saponins in combination with sultonylureas in the treatment of type 2 diabetes mellitus. Chin J Integr Med 2008;14:56–60.
[109] Manafikhi R, Kalie L, Laldo R. Effects of garlic supplementation on fasting blood sugar. HbA1c and lipid profile in type 2 diabetics receiving metformin and glyburide 2015;3:11–8.

[110] Ashraf R, Khan RA, Ashraf I. Garlic (Allium sativum) supplementation with standard antidiabetic agent provides better diabetic control in type 2 diabetes patients. Pak J Pharm Sci 2011;24:565–70.

[111] Khan R. Effects of garlic on blood glucose levels and HbA1c in patients with type 2 diabetes mellitus. J Med plant Res 2011;5:2922–8.

[112] Chhatwal S, Sharma R, Sharma G, et al. To study the antihyperglycaemic and lipid lowering effect of garlic as an adjunct to metformin in patients of type 2 diabetes mellitus with obesity. Int J Basic Clin Pharmacol 2012;1:22.

[113] Joffe DJ, Freed SH. Effect of extended release gymnema sylvestre leaf extract (Beta Fast GXR) alone or in combination with oral hypoglycemics or insulin regimens for type 1 and type 2 diabetes. Diabetes Control News 2001;30.

[114] Al-Romaina A, Liu B, Asare-Anane H, et al. A novel Gymnema sylvestre extract stimulates insulin secretion from human islets in vivo and in vitro. Phyther Res 2010;24:1370–6.

[115] Paliwal R, Kathori S, Upadhyay B. Effect of gurmar (Gymnema sylvestre) powder intervention on the blood glucose levels among diabetics. Stud Ethno-Med 2009;3:133–5.

[116] Teixeira CC, Fuches FD, Weintrt LS, et al. The efficacy of folk medicines in the management of type 2 diabetes mellitus: results of a randomized controlled trial of Syzygium cumini (L.) Skeels. J Clin Pharm Ther 2006;31:1–5.

[117] Teixeira CC, Weintrt LS, Barbosa DC, et al. Syzygium cumini (L.) skelms in the treatment of type 2 diabetes [2]. Diabetes Care 2004;27:3019–20.

[118] Akhtar MS. Trial of Momordica charantia linn (Karela) powder in the treatment of type 2 diabetes patients. Pak J Pharm Sci 2011;24:565.

[119] Fuangchan A, Sonthisombat P, Seubnukarn T, et al. Hypoglycemic effect of Momordica charantia administration improves insulin secretion in human islets in vivo. J Clin Epidemiol 2007;60:554–9.

[120] John AJ, Cherian R, Subhash HS, et al. Evaluation of the efficacy of bitter gourd (Momordica charantia) as an oral hypoglycemic agent: a randomized controlled clinical trial [3]. Indian J Physiol Pharmacol 2003;47:363–5.

[121] Tongia A, Tongia SK, Dave M. Phytochemical determination and extraction of momordica charantia fruit and its hypoglycemic potential of oral hypoglycemic drugs in diabetes mellitus (NIDDM). Indian J Physiol Pharmacol 2004;48:241–4.

[122] Rahman IU, Khan RU, Rahman KU, et al. Lower hypoglycemic but higher antiatherogenic effects of bitter melon than gliabenclamide in type 2 diabetic patients. Nutr J 2013;14:1–7.

[123] Baldwa VS, Bhandari CM, Pangaria A, et al. Clinical trial in patients with diabetes mellitus of an insulin-like compound obtained from plant source. Ups J Med Sci 1977;82:39–41.

[124] Cortez-Navarrete M, Martinez-Abundis E, Perez-Rubio KG, et al. Momordica charantia administration improves insulin secretion in type 2 diabetes mellitus. J Med Food 2018;21:672–7.

[125] Dans AML, Villarruz MVC, Jimeno CA, et al. The effect of Momordica charantia capsule preparation on glycemic control in type 2 diabetes mellitus needs further studies. J Clin Epidemiol 2007;60:554–9.

[126] Inayat-ur-Rahman, Malik SA, Bashir M, et al. Serum sialic acid changes in non-insulin-dependant diabetes mellitus (NIDDM) patients following bitter melon (Momordica charantia) and rosiglitazone (Avandia) treatment. Phytomedicine 2009;16:401–5.

[127] Koon S, Tortorelli DG, Fullerton SA, et al. A possible hypoglycaemic effect of maitake mushroom on type 2 diabetic patients [5]. Diabet Med 2001;18:1010.

[128] Kochhar A, Sharma N, Sachdeva R. Effect of supplementation of Turhi (Ocimum sanctum) and Neem (Azadirachta indica) leaf powder on diabetic symptoms, anthropometric parameters and blood pressure of non insulin dependent male diabetics. Snd Ethno-Med 2009;3:5–9.

[129] Kumari DJ. Hypoglycemic effect of Moringa oleifera and Azadirachta indica in type 2 diabetes mellitus. Bioscan 2010;5:211–4.

[130] López-Romero P, Pichardo-Ontiveros E, Avila-Nava A, et al. The effect of Nopal (Opuntia Ficus Indica) on postprandial blood glucose, incretins, and antioxidiant activity in mexican patients with type 2 diabetes after consumption of two different composition breakfasts. J Acad Nutr Diet [Internet] 2014;114:1811–8.

[131] Castillo-Andrade I, Gonzalez-Sanchez J, Frati-Munari AC. Hypoglycemic effect of an Opuntia streptacanta Lemaire dysalate. J Prof Assoc Cactus Dev 1997;2:73–5.

[132] Knishinsky R. Prickly pear cactus medicine: Treatments for diabetes, cholesterol, and the immune system. 144 pages, Published by Inner TraditionsBear & Co; 2004 Jun 7.

[133] Eldin IMT, Ahmed EM, Abd EHM. Preliminary study of the clinical hypoglycemic effects of Allium cepa (Red Onion) in type 1 and type 2 diabetic patients. Environ Health Insights 2010;4:71–7.

[134] Soltanian N, Janghorbani M. Effect of flavaseed or psyllium vs. placebo on management of constipation, weight, glycemia, and lipids: a randomized trial in constipated patients with type 2 diabetes. Clin Nutr ESPEN [Internet] 2019;29:41–8.

[135] Noureddin S, Mohsen J, Payman A. Effects of psyllium vs. placebo on constipation, weight, glycemia, and lipids: a randomized trial in patients with type 2 diabetes and chronic constipation. Complement Ther Med 2018;40:1–7.

[136] Feinglos MN, Gibb RD, Ramsey DL, et al. Psyllium improves glycemic control in patients with type-2 diabetes mellitus. Bioact Carbohydrates Diet Fibre 2013;1:156–61.

[137] Abutarb S, Naser IA, Hamed AT. Soluble fibers from psyllium improve glycemic response and body weight among diabetes type 2 patients (randomized control trial). Nutr J [Internet] 2016;15:1–7.

[138] Pastors JG, Blaisdell PW, Balm TK, et al. Psyllium fiber reduces rise in postprandial glucose and insulin concentrations in patients with non-insulin-dependent diabetes. Am J Clin Nutr 1999;53:1431–5.

[139] Enno F, Gleske J. Siberian Ginseng results in beneficial effects on glucose metabolism in diabetes type 2 patients: a double blind placebo-controlled study in comparison to Panax Ginseng. Int J Clin Nutr [Internet] 2013;1:11–7.

[140] Rahimi HR, Mohammadpour AH, Dastani M, et al. The effect of nano-curcumin on HbA1c, fasting blood glucose, and lipid profile in diabetic subjects: a randomized clinical trial. Avicenna J Phytomed 2016;6:567.

[141] Na LX, Yan BL, Jiang S, et al. Curcuminoids target decreasing serum adipocyte-fatty acid binding protein levels in their glucose-lowering effect in patients with type 2 diabetes. Biomed Environ Sci 2014;27:902–6.

[142] Na LX, Li Y, Pan HZ, et al. Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: a double-blind, placebo-controlled trial. Mol Nutr Food Res 2013;57:1569–77.