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Scoping Evidence for Herbal Medicine and Type 2 Diabetes (T2D)

Sarah Price MSc PhD Lic.Ac., D CHM and Michael McIntyre MA, DU.

Introduction

The World Health Organization (WHO) reports that diabetes mellitus is the fifth leading cause of death in the world.[1] Globally 285 million people (6.4 % of the world population) currently have diabetes, which is estimated to increase to affect some 439 million people by 2030 (7.7% of the world population).[2] Type 2 diabetes (T2D) is the most common form of diabetes, accounting for over 90% of all cases. [3]

In the UK, diabetes mellitus currently affects 4.5% of the population, approximately 2.9 million people, the majority of whom, in line with worldwide findings mentioned, have T2D and this prevalence is set to rise to 4 million people by 2025.[4] In 2014 the BMJ published research that showed that one in three adults in the UK has signs of prediabetes and is consequently at risk of developing T2D.[5] The researchers commented 'This rapid rise in such a short period of time is particularly disturbing because it suggests that large changes on a population level can occur in a relatively short period of time.' This disastrous rise in the incidence of diabetes makes it imperative that novel and cost effective solutions are found. To this end this literature review explores the potential of herbal medicine to improve glycaemic control of diabetic and prediabetic patients.

Differentiating diabetes

T2D, formerly termed non-insulin-dependent diabetes mellitus (NIDDM) or adult (or late)-onset diabetes, is a metabolic disorder that is characterized by high blood glucose with concomitant insulin resistance and relative (rather than absolute) insulin deficiency. There is β-cell deficiency alongside insulin resistance. This is in contrast to diabetes mellitus type 1 (T1D), in which there is complete insulin deficiency due to autoimmune destruction of islet cells in the pancreas. Prediabetes is deemed a high-risk precursor state for development of T2D. This is a condition in which blood glucose is registered as consistently higher than average, but at lower levels than that diagnostic of diabetes proper.

Risk factors & metabolic syndrome (MetS)

Insulin resistance, the key feature of T2D, starts with impaired glucose tolerance (hyperglycaemia) and impaired fasting glucose (fasting blood glucose level consistently elevated above normal) through to later stages of overt T2D. A crucial aspect of the disease is loss of function and mass of pancreatic β-cells which appears in part to have a genetic component.[6] While healthy adipose tissue secretes beneficial adipokines with hypoglycaemic and anti-inflammatory properties, thereby supporting the body's glucose homeostasis,[7] obesity is a significant risk factor for T2D; 80% of people diagnosed with T2D are obese.[8] However, obesity does not automatically lead to a metabolic disorder with impaired glucose tolerance or insulin resistance.[9] It is apparent that the risk of T2D associated with obesity appears to be influenced by the coexistence of other metabolic abnormalities and poor metabolic health is a more important determinant for the development of T2D than simple obesity.[10]

Metabolic syndrome (MetS) describes a cluster of metabolic abnormalities (e.g. obesity, insulin resistance, hypertension, and dyslipidaemia) the development of which is linked to the onset of T2D.[11] The most important cause of insulin resistance in MetS appears to be a high-fat, refined-

carbohydrate diet combined with physical inactivity exacerbated by genetic predispositions.[12] A large waistline is one of the determining metabolic risk factors of MetS; having an apple shape with excess fat in the stomach area (a sign of visceral fat) is a greater risk factor for T2D than excess fat in other parts of the body, such as on the hips.[13] Adipose tissue in those with MetS is an active endocrine organ that secretes a variety of potent hormones (e.g. C-reactive protein, IL-6, IL-1β, leptin, serum amyloid A, and retinol-binding protein-4) that are biomarkers of insulin resistance and inflammation.[14] These metabolic changes underlie a plethora of pathological processes leading to the well-known complications of diabetes such as cardiovascular disease, nephropathy, retinal blindness, neuropathy, and the development of peripheral ulcers and gangrene as well as mental impairment.[15,16] Aging is also associated with insulin resistance and the onset of T2D; this is likely associated with impaired microvascular responses to insulin in skeletal muscle.[17] While epidemiologic studies and randomized clinical trials show that T2D is largely preventable by means of diet and lifestyle modification, implementing and sustaining effective health promotion strategies remains challenging given modern lifestyles and dietary habits.[18,19]

Phytotherapeutic interventions

Research suggests a number of plausible mechanisms by which medicinal plants may help restore healthy glucose levels and thus help manage T2D. While further research into the use of herbal medicines to manage T2D is required, this Scoping Review demonstrates the significant potential of herbal medicine to help re-establish disturbed glucose homeostasis and treat T2D through a variety of mechanisms.

Method

An initial search of two major databases (Medline and AMED) plus a citation and subject specific journal search with search terms 'diabetes type two' and 'phytotherapy' or 'herb' and 'controlled trial' led to a final number of randomised human studies with more than 60 participants. These are displayed in Table 1 in chronological order. Outcome measures included fasting blood glucose (FBG), postprandial blood glucose (PPG), glycated haemoglobin (HbA1C) - a longer term and more reliable blood-test measure of average blood glucose, triglycerides, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), total cholesterol, body mass index (BMI) and waist circumference.

In order to provide a practical and transparent evaluation of the evidence presented in this review we have adapted the widely used and well-respected GRADE approach (Grades of Recommendation, Assessment, Development and Evaluation) as used by the Cochrane Collaboration.[20] This allows for 4 levels of rating of the research evidence - **High**, **Moderat**e, **Low** and **Very Low**. For the purposes of this review we have amalgamated Low and Very Low grades into a single category of **Preliminary** evidence. This selective review highlights potentially fruitful areas for future research that need to be investigated in more rigorous trials.

Discussion – outcomes and limitations

Most of these studies show positive effects on glucose homeostasis with good safety outcomes. Limitations of these studies relate to the length of time of the study (many were only 8 weeks in duration); to the fact that they included simultaneous lifestyle interventions; that they recruited small numbers with incorrect power calculations; that they contained limited information on the successful blinding of subjects while providing incomplete information on the mechanisms of the herbs used. Consequently, many of these studies can be judged only to demonstrate **Preliminary** effectiveness. Despite this, taking this evidence overall, it is apparent that herbal medicine is a valuable resource that should be fully exploited to help combat the worldwide epidemic level of prediabetes and T2D.

Phytotherapeutic mechanisms

A number of herbs have been investigated for their potential to treat T2D based on the plausibility of their perceived active constituents. However, it should be borne in mind that the supposed active chemical agents are but a fraction of the whole plant used as a herbal medicine and that the action of the whole may exceed that of a single chemical component.[21, 22] This report notes, as an example, research into three specific plant constituents identified as having a regulatory effect on glucose and insulin levels explaining the mechanism by which some medicinal plants may be used to treat T2D.

1. **Berberine** is a bitter isoquinoline derivative alkaloid found in a wide range of medicinal plants such as *Berberis vulgaris, Mahonia aquifolium, Hydrastis canadensis, Coptis chinensis* and *Phellodendron amurense*. Berberine's bitter taste may clarify at least in part its hypoglycaemic effect achieved through its activation of bitter taste receptors expressed in gastrointestinal tract.[23] In a recent meta-analysis of studies involving human participants, berberine was found to be better than controls and lifestyle advice alone in lowering FBG, PPG and HbA1C, the hypoglycaemic effect of which was at least as effective as standard oral hypoglycaemic medication.[24] Berberine has been shown to contribute to glycaemic homeostasis through a number of different pathways.[25,26,27,28,29] Berberine displays beneficial effects in the treatment of diabetes and obesity at least in part via stimulation of AMPK (AMP-activated protein kinase) activity.[30] Berberine has also been demonstrated to alleviate insulin resistance via the cholinergic anti-inflammatory pathway in HepG2 cells.[31] In another study berberine increased the number of decreased islets in a dose dependent manner suggesting that in vivo it protects pancreatic islets.[32]

2. **Polyphenols,** ubiquitous in medicinal plants, fruits and vegetables, have demonstrated a significant capacity to protect against diabetes, shielding pancreatic β-cells against glucose toxicity, having anti-inflammatory and antioxidant effects, inhibiting α-amylases or α-glucosidases and advanced glycation end products (AGEs) formation.[33] Those suffering from T2D display features of low-grade inflammation years in advance of the onset T2D; this low-grade inflammation has been proposed to be involved in the pathogenetic processes causing T2D.[34] In the light of this, it is noteworthy that polyphenolic compounds inhibit Interleukin 6 mediated inflammation by direct inhibition of the signal transduction pathway.[35] The hypoglycaemic effect of the polyphenolic flavonoid baicalin, considered one of the main active constituent of *Scutellaria baicalensis*, may be due to increasing the hepatic glycogen content and glycolysis, and reducing the serum levels of TNF-α.[36] Another study reporting on the anti-inflammatory effects of baicalin also reported a reduction in liver steotosis in high-fat diet fed rats and other obesity disorders by targeting liver AMPK.[37] In a smaller study, baicalin increased expression of antioxidant enzyme activities thereby reducing hyperglycaemia-induced oxidative stress through the increased expression of antioxidant enzyme activities. It also demonstrated anti-hyper-triglyceridaemic and anti-hyper-cholesterolaemic properties compared with metformin.[38,39]

3. **Non-starch polysaccharide (NSP),** also known as fibre, is recognised to play an important role in the management of diabetes. It occurs in soluble and insoluble form. Soluble fibre in fruit, vegetables, pulses and oats, legumes and pectin (e.g. apples) and that in root vegetables helps to control blood sugar by delaying gastric emptying, slowing the entry of glucose into the bloodstream, reducing a postprandial rise in blood sugar.[40] Insoluble fibre (includes cellulose, lignins, and also some other hemicelluloses) acts to stimulate the digestive system adding bulk to meals inducing a feeling of satiety.[41] A review of dietary fibre consumption and the incidence of T2D across 8 European countries showed that the intake of total and cereal fibre is inversely

related to the risk of type 2 diabetes.[42] Polysaccharides in medicinal plants such as those found in a variety of medicinal mushrooms[43] e.g. *Ganoderma lucidem* and other medicinal herbs e.g. *Astragalus membranaceus* have demonstrated a variety of beneficial actions relating to diabetes control. *G. lucidum* polysaccharides have been reported to have hypoglycaemic activity by increasing plasma insulin levels and decreasing plasma sugar levels in mice.[44] Astragalus polysaccharide (APS) from *Astragalus membranaceus* induces insulin-sensitizing activity and glycaemic homeostasis partly through reducing endoplasmic reticulum (ER) stress.[45] APS also decreases the expression of protein tyrosine phosphatase 1B (PTP1B), an important therapeutic target due to its role in the negative regulation of insulin signalling.[46] The mechanism by which APS improves glucose toxicity appears to be by increasing liver glycogen synthesis via an AMPK pathway.[47] APS may also restore glycaemic balance through its action on two brain regions known to be involved in glucose-sensing during hypoglycaemia.[48]

Table 1 – Summary of Literature (RCT's with more than 60 participants)[1]

Author and Title	Study Design	Main Findings and Possible Mechanisms	Comments
Anderson RA , Zhan Z et al. 2015. Cinnamon extract lowers glucose, insulin and cholesterol in people with elevated serum glucose. *Journal of Traditional and Complementary Medicine.* doi:10.1016/j.jtcme. 2015.03.005[49]	173 participants (137 completed) were randomised to receive cinnamon or placebo in capsules for 8 weeks. Fasting blood glucose (FBG) and 2-hour postprandial glucose (PPG) as well as insulin resistance were the main outcome measures. BP and serum lipids were also measured along with fructosamine.	The treatment group had significantly lowered fasting blood glucose (FBG) ($p < 0.001$) 8.85 ± 0.36 to 8.19 ± 0.29 mmol/L ($p < 0.005$), compared with 8.57 ± 0.32 to 8.44 ± 0.34 mmol/L in the placebo control group ($p = 0.45$). 2-hour postprandial glucose (PPG) also decreased significantly ($p < 0.0001$) in the treatment group, 15.09 ± 0.57 to 13.3 ± 0.55 mmol/L, compared with the placebo group, 14.18 ± 0.60 to 13.74 ± 0.58 mmol/L. Fasting insulin concentrations decreased significantly and postprandial insulin tended ($p < 0.06$) to be reduced by the cinnamon treatment. Insulin sensitivity, assessed by HOMA-IR, was significantly improved by cinnamon extract as were fructosamine concentrations.	This study was powered to detect differences between groups, and randomisation was described; allocation concealment although described was not assessed at the end of the study. This research provides **moderate** evidence of the effect of cinnamon on the parameters of T2D.
Lian F, Tian J et al. 2015. The Efficacy and Safety of Chinese Herbal Medicine Jinlida as Add-On Medication in Type 2 Diabetes Patients Ineffectively Managed by Metformin Monotherapy: A Double-Blind, Randomized, Placebo-Controlled, Multicenter Trial. *PLOS ONE.* 10 (6): e0130550[50]	186 participants were included in this blinded RCT to receive either Jinlida or an identical placebo for 12 weeks. Participants included those with poorly managed T2D on Metformin. Outcomes included FBG, PPG and HbA1C. Jinlida consists of 17 herbs (*Panax ginseng, Polygonatum odoratum, Atractylodes chinensis, Sophora flavescens (radix), Ophiopogon japonica, Rehmannia glutinosa, Polygonum multiforum, Cornus officinalis, Eupatorium fortunei, Coptis chinenses, Anemarrhena asphodeloides, Epimedium grandiflorum, Salvia miltiorrhiza, Pueraria montana (radix), Lychee chinensis, Lycium chinensis)*	After 12 weeks there were significant differences between the two groups: for HbA1c the level of the Jinlida group was reduced by 0.92 ± 1.09% and that of the placebo group was reduced by 0.53 ± 0.94%. The 95% CI was 0.69 - 1.14 for the Jinlida group vs. 0.34 - 0.72 for the placebo group ($p < 0.01$). There were significant FG and PPG level reductions between the two groups after 12 weeks (both $p < 0.01$). The Jinlida group also showed improved β-cell function with a HOMA-β increase ($p < 0.05$). No statistical significance was observed in the body weight and BMI changes. No serious adverse events were reported	This study provides **moderate** evidence that this combination of herbs improves T2D for patients with poorly managed T2D.
Xu J, Lian F et al. 2015. Structural modulation of gut microbiota during alleviation of type 2	187 T2D participants were randomised to receive either one of three doses of Ge Gen Tang (Pueraria Decoction) or placebo	The moderate to high-dose groups showed significant decrease in FBG and HbA1C compared to the placebo and low dose group. "Pyrosequencing of the V3 regions of 16S rRNA genes revealed a dose-dependent	This study provides **moderate** evidence that GGT improves glycaemic control and the

[1] In the interest of plant identification, where possible, the Latin binomial names are used. Where different parts of the same plant may traditionally be used medicinally, the binomial name is followed by the part of the plant used.

diabetes with a Chinese herbal formula. *The ISME Journal.* 9, 552–562; doi:10.1038/ismej.2014.177[51]	(n=41) for 12 weeks. Outcome measures included FBG and HbA1C; gut microbiota was also compared amongst the four groups. Ge Gen Tang contains four herbs: *Pueraria montana (radix), Scutellaria baicalensis (radix), Coptis chinensis, Glycyrrhiza glabra.*	deviation of gut microbiota in response to GQD treatment. This deviation occurred before significant improvement of T2D symptoms was observed." Physical changes in gut microbiota were observed by GGT that is in enriching the gut in beneficial bacteria which in turn improves glycaemic control.	mechanisms by which it does. The doses of herbs in the high-dose group were above average although few side effects were reported.
Zhang X, Liu Y et al. 2015. Insulin combined with Chinese medicine improves glycaemic outcome through multiple pathways in patients with type 2 diabetes mellitus. *Journal Diabetes Investigation*; 6: 708–715[52]	219 T2D participants were randomised for either insulin monotherapy (110) or insulin combined with Shen Qi Formula (109). Treatment (SQF+Ins) lasted 12 weeks; the main outcomes were changes to FBG, PPG, β-cell function, insulin resistance and blood lipids. Shen Qi Formula consists of 8 herbs (*Panax ginseng, Astragalus membranaceus, Rehmannia glutinosa, Dioscorea opposita, Cornus officinalis, Trichosanthes kirilowii (radix), Salvia miltiorrhiza, Rheum palmatum*).	The FBG was significantly different in the treated group compared to the insulin alone group ($p = <0.05$); PPG was also significantly different ($p = < 0.01$); SQF+Ins significantly decreased the level of HbA1c ($P < 0.05$). Secondary outcomes were also changed (triglyceride levels were significantly decreased ($P < 0.05$) as were beta cell function in the SQF+Ins group which increased but stayed the same in the Insulin alone group ($p=< 0.05$).	This study described in detail the intervention, safety measures, randomisation. Blinding was also described but not assessed. This study provides **moderate** levels of evidence**.**
Mozaffari-Khosravi H, Talaei B et al. 2014. The effect of ginger powder supplementation on insulin resistance and glycaemic indices in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled trial. *Complementary Therapies in Medicine*. 22 (1) :9–16[53]	88 T2D participants were randomised to receive *ginger* (GG) or placebo (PG) groups. The GG received 3 one-gram capsules containing ginger (*Zingiber officinale*) powder whereas the PG received 3 one-gram microcrystalline-containing capsules daily for 8 weeks. FBG, HbA1c, fructosamine, fasting insulin, homeostasis model assessment insulin resistance index (HOMA-IR), β-cell function (β%), insulin sensitivity (S%) and the quantitative insulin sensitivity check index (QUICKI) were assessed before and after the intervention. The study was powered to calculate a difference in mean insulin resistance of 2 units.	81 participants completed. FBG mean showed a decrease of 10.5% ($p = 0.003$) in the GG whereas the mean had an increase of 21% in the PG ($p = 0.01$) (result obtained because differences were substantial to start with the PG Hb1Ac increased significantly from baseline). Variation in HbA1c mean was 8.2 for the GG, but 6.9 for the PG, at baseline). Statistical difference found in the two groups before and after the intervention in terms of median of fasting insulin level, S% and HOMA-IR ($P < 0.005$). Moreover, QUICKI mean increased significantly in the two groups; the mean difference, however, was significantly higher in the GG. Although there were variations in key outcomes, there was no significant difference in the mean insulin resistance and there were substantial differences in the groups for HbA1C at baselines (not fully discussed). There were significant differences for before and after for the insulin resistance indices (QUICKI) but not between the groups	Taking 3g of ginger for 8 weeks demonstrated significant changes in glycaemic control. Although this study shows the promise of ginger for diabetes control the duration of the study was not long enough, and differences not substantial enough for the key outcomes. A properly powered study for a longer period of time is necessary to move forward from these **Preliminary** findings.

Grant SJ, Chang D, et al. 2013. Chinese herbal medicine for impaired glucose tolerance : a randomized placebo controlled trial. *BMC Complementary Alternative Medicine.* 14;13:104. doi: 10.1186/1472-6882-13-104[54]	71 participants with either pre-diabetes or 'controlled' diabetes were randomly selected to receive either Jiangtang Xiaozhi (n = 39) or placebo (n = 32) 16 weeks with a follow up eight weeks later (week 24). Primary outcomes were FBG and HbA1C. The formula Jangtang Xiaozhi consisting of 6 herbs (*Ligustrum lucidum, Astragalus membranaceus, Coptis chinensis, Litchi chinensis, Ecklonia kurome*, *Curcuma longa).*	For FBG was no difference between the two groups. There was a significant difference between the mean levels of fasting insulin (p=0.4 95% CI 11.6 ± 5.5 mmol/L).	The authors suggest this study may have been underpowered to detect a difference between the two groups. This study offers **preliminary** evidence for changes to HbA1C but not FBG. (Chen et al 2012 below also test this combination).
Ji L, Tong XL et al. 2013. Efficacy and Safety of Traditional Chinese Medicine for Diabetes: A Double-Blind, Randomised, Controlled Trial. *PLOS*. 8 (2) e56703[55]	800 participants with poor glycaemic control were randomly assigned in 4 groups. Group 1 to receive Xiaoke Pill (see below); group 2 to receive Glibenclamide (1.25 to 2.5 mg) alone in two study groups called together the 'drug naive group' (n=400). Group 3 patients previously treated with Metformin monotherapy stayed on Metformin and were randomised to either Metformin alone or, as group 4, with additional Xiaoke Pill (called 'Metformin group' n=400). Outcome measures at 48 weeks were incidence and rate of hypoglycaemia, mean difference in HbA1c, and proportion of patients with HbA1c 6.5%. 627 completed the study. The Xiaoke Pill comprised 0.25mg Glibenclamide, *Pueraria montana (radix), Rehmannia glutinosa, Astragalus membranaceus, Trichosanthes kirilowii (radix), Zea mays, Schizanda chinensis, Dioscorea opposita.*	In the drug naive group, the total hypoglycaemia rate and mild hypoglycaemic episodes in the Xiaoke Pill arm were 38% (p = 0.024) and 41% (p = 0.002) less compared to the Glibenclamide arm; in Metformin group, the average annual rate of hypoglycaemia was 62% lower in Xiaoke Pill arm (p = 0.003). The average annual rate of hypoglycaemia was 24% lower in patients treated with Xiaoke Pill [Rate Ratio (95% CI): 0.76 (0.49, 1.18). Respective mean changes in HbA1c from baseline were 20.70% and 20.66% for Xiaoke Pill and Glibenclamide, with a between-group difference (95% CI) of 20.04% (20.20, 0.12) in the drug naive group, and those in Metformin group were 20.45% and 20.59%, 0.14% (20.12, 0.39) respectively. The respective proportions of patients with an HbA1c level of 6.5% were 26.6% and 23.4% in the drug naive group and 20.1% and 18.9% in the Metformin group. No changes were observed in insulin sensitively, beta-cell function or other pathophysiology of diabetes. This is a large scale study with detail provided on attrition which was low given the length of the study. No adverse events were reported.	Xiaoke pill can offer some protection against hypoglycaemia and improved glycaemic control compared with Glibenclamide. This study provides a **moderate to high level** of evidence supporting the safe use of Xiaoke pill for T2D.

Kianbakht S, Dabaghian FH. 2013. Improved glycaemic control and lipid profile in hyperlipidaemic type 2 diabetic patients consuming *Salvia officinalis* leaf extract: A randomized placebo controlled clinical trial. *Complementary Therapies in Medicine* 21 (5): 441–446[56]	80 T2D participants were randomised to receive *Salvia officinalis (*SO) leaf extract (one 500 mg capsule 3 x a day) or placebo for 3 months. Inclusion criteria HbA1c 7–11% whilst taking 2 x 5mg Glibenclamide and 2 x 500 mg Metformin per day or newly diagnosed patients. Outcome measures were FBG, HbA1c, total cholesterol, triglyceride, LDL-C, HDL-C SGOT (serum glutamic-oxaloacetic transaminase), SGPT (serum glutamic-pyruvic transaminase) and creatinine.	The *S. officinalis* leaf extract lowered FBG, HbA1c, total cholesterol, triglyceride and LDL-C but increased HDL-C compared to baseline at endpoint. Percent difference mean (95% confidence interval) between the extract and placebo groups in terms of effects on FBG 32.2 (26.5, 37.9, p = 0.001), HbA1c 22.7 (16.8, 28.6, P = 0.01), total cholesterol 16.9 (9.7, 24.1, p = 0.01), triglyceride 56.4 (36.1, 76.7, p = 0.009), LDL-C 35.6 (29.9, 41.3, p < 0.001) and HDL-C 27.6 (15.8, 39.4, p =0.008). The extract did not have any significant effects on the other parameters compared to the placebo group at endpoint (P > 0.05). No adverse effects were reported. Mechanisms: Peroxisome proliferator-activated receptors (PPARγ) have an important role in the treatment metabolism of glucose and lipids; and *S. officinalis* leaf extract has been shown *in vitro* to have agonistic activity on PPARγ as well as other effects. More data is needed to elucidate these mechanisms.	In this study *S. officinalis* leaves appear safe and may improve glycaemic control as well as improving the lipid profile in hyper-lipidaemic T2D patients. Given that a large proportion of T2D have Metabolic Syndrome with cardiovascular disease risks, this is a positive outcome. The numbers in this study were small. A longer study with larger numbers is necessary to take forward this promising **preliminary** data.
Kianbakht S, Abasi B et al. 2013. Anti-hyperglycaemic effect of *Vaccinium arctostaphylos* in type 2 diabetic patients: a randomized double-blind controlled trial. *Forsch Komplementmed*. 20 (1): 17-22[57]	88 T2D who were resistant to conventional hyperglycaemic drugs were randomised to receive *Vaccinium arctostaphylos* hydroalcoholic extract (1 capsule = 350 mg 3 x day) in combination with anti-hyperglycaemic drugs or placebo for 2 months. Outcomes were FBG, 2-hour PPG, HbA1c and liver/kidney functions.	74 participants completed the study. The extract significantly lowered FBG, 2-h PPG and HbA1c (p = 0.007, p <0.001, and p = 0.005, respectively) without any significant effects on liver/kidney function (p >0.05) compared with placebo. No adverse effects were reported. This study reports in detail the protocol and the findings showing significant changes in HbA1C, FBG and PPG before and after and compared to the placebo treatment.	This study demonstrates that *Vaccinium arctostaphylos* shows promise and a longer study with bigger numbers is needed to affirm these **preliminary** findings.
Lian F, Li G et al 2013. Chinese herbal medicine Tianqi reduces progression from impaired glucose tolerance to diabetes: a double-blind, randomized, placebo-controlled, multicenter trial. *The Journal of Clinical Endocrinology & Metabolism.* 99 (2): 648-655.[58]	420 participants with impaired glucose tolerance (IGT) were randomly assigned to receive Tianqi (4.8g in capsules) or placebo over the course of a 12-month treatment. This capsule contained *Astragalus membranaceus, Coptis chinensis, Trichosanthes kirilowii (radix), Ligustrum lucidum, Dendrobium nobile, Panax notoginseng, Lycium barbarum cortex radicis), Eclipta prostrata, Galla chinensis, and Cornus*	Of the 420 enrolled subjects with IGT, 389 completed the trial (198 in the Tianqi group and 191 in the placebo group). At the end of the 12-month trial, 36 subjects in the Tianqi group (18.18%) and 56 in the placebo group (29.32%) had developed diabetes (P = 0.01). There was a significant difference in the number of subjects who had normal glucose tolerance at the end of the study between the Tianqi and placebo groups (n = 125, 63.13%, and n = 89, 46.60%, respectively; P = .001). Cox's proportional hazards model analysis showed that Tianqi reduced the risk of diabetes by 32.1% compared with the placebo. No severe adverse events occurred in the trial. There were no statistical differences in body weight and body mass	This study demonstrates **moderate** evidence that improving IGT with Tianqi capsules reduces the risk of developing T2D, and this offers significant potential in the treatment of T2D.

	officinalis. Oral glucose tolerance tests were conducted every 3 months to assess the development of diabetes or restoration to normal glucose tolerance. All subjects received the same lifestyle education. The primary endpoint was the conversion of IGT to T2D. Body weight and BMI were observed. Adverse effects were monitored. The capsule Tianqi was subject to mass spectrometry analysis to explore active compounds such as berberine.	index changes between the Tianqi group and the placebo group during the 12-month trial. This was a properly powered study for impaired glucose tolerance with the main outcome being conversion to T2D. Safety was measured in an earlier study of 300 patients but was also recorded and 26 subjects experienced mild adverse reactions (11 of these from the placebo group). The attrition was low in this study. It would have been of value to see more measures of glycaemic control.	
Tong XL, Wu ST. et al. 2013. The safety and effectiveness of TM81, a Chinese herbal medicine, in the treatment of type 2 diabetes: a randomized double-blind placebo-controlled trial. *Diabetes, Obesity, Metabolism.* 15;448-454.[59]	After a 2-week run-in period, 480 overweight type 2 early-stage diabetic participants were randomised to a TM81 group (n=360) or placebo group (n= 120). The subjects received 6g TM81 or placebo, three times daily for 12 weeks. TM81 consisted *of Coptis chinensis, Paeonia alba, Scutellaria baicalensis (radix), Citrus reticulata and Rheum palmatum.* The authors suggest that C*optis chinensis* is the main active constituent. Outcome measures: change in HbA1c, FBG, PG, β cell function, plus BMI, TG, TC, HDL, LDL, and renal and liver function. Change in Hb1Ac was the primary end point. Homeostatic model assessment (HOMA) was also measured.	There was a small statistically significant difference between the two groups of HbA1C at baseline. After treatment, the HbA1c decrease was 1.02% in the TM81 group versus 0.47% in the placebo group ($p<0.001$). The TM81 was more effective for patients with higher baseline HbA1c levels. 47.6% of the TM81 group had normal HbA1c levels (<6.5%) at the end point. The TM81 group also showed improved β-cell function and increased homeostatic model assessment (HOMA)-β. No difference was found between the groups for changes in insulin resistance (HOMA-IR). In addition, body weight, BMI and waist circumference of subjects in the TM81 group were reduced and the symptoms related to diabetes were improved. There were no significant differences in the types and frequency of adverse reactions between the two groups. There was a substantial discussion on the mechanisms at work and 6 of the most abundant compounds were measured in the formula including berberine, albiflorin, and baicalin. This is a large study, building on previous research. The data showed that TM81 is effective in controlling blood glucose level and is safe to use in patients with early-stage T2D. The study duration was 12 weeks which the authors commentated was short. Attrition was higher in the treatment group (68 compared to 13) although no serious adverse events were recorded such as changes in liver and kidney function.	This study offers **moderate** evidence of the efficacy in improving glycaemic control and also usefully demonstrated that this change took place via improved β-cell function despite there being no change in insulin resistance.

Tu X, Xie CG et al 2013. Fructus Mume Formula (FM) in the Treatment of Type 2 Diabetes Mellitus: A Randomized Controlled Pilot Trial. *Evidence-Based Complementary and Alternative Medicine*. Article ID 787459. http://dx.doi.org/10.1155/2013/787459.[60]	85 T2D participants were randomised to either FM or Metformin. Outcomes included FBG, PPG, HbA1C, insulin concentrations, blood lipids and BMI. There was no blinding in this trial. FM contains: *Prunus mume, Zingiber officinale, Coptis chinensis, Angelica sinensis, Typhonii gigantei, Zanthoxyli bungeani (pericarpium), Cinnamomum cassia, Panax ginseng, Phellodendron amurense.*	73 participants completed the study. There were significant reductions in all the outcome measures and FM performed as well as Metformin. Mechanisms: numerous studies have demonstrated that berberine can exert beneficial effects on the treatment of diabetes (see discussion above). The potential mechanisms include improving insulin sensitivity, inhibiting gluconeogenesis, stimulating glucose uptake through the AMP-AMPK-p38 MAPK pathway, or correcting lipid disorders. Malonyl ginsenosides (one of the ginseng ginsenosides) could alleviate hyperglycaemia, hyperlipaemia, and insulin resistance of T2 diabetes. This study showed that *Prunus mume* formula is as effective as Metformin in reducing blood glucose levels. Both groups were subject to diet and exercise therapy. There was no blinding in this study. There was one case of moderate side-effects from the FM which disappeared on discontinuation	The study offers promising **preliminary** data.
Chen ZH, Xia CD et al. 2012. Clinical study of Jiangtang Xiaozhi capsule in treating type 2 diabetes mellitus patients. *Zhongguo Zhong Xi Yi Jie He Za Zhi.* 32 (7): 910-3.[61]	73 T2D participants of qi-yin deficiency and inter-obstruction between phlegm and stasis syndrome, were randomly assigned to two groups, the pioglitazone tablet group (36 cases) and the JTXZC group (37 cases) for 8 weeks. Outcomes included FBG, PPG, HbA1c, and blood lipids. The HOMA-IR was also calculated. The safety indices such as liver and renal functions, adverse reactions were also monitored. The contents of the capsule are not reported but this classical formula contains *Ligustrum lucidum, Astragalus membranaceus, Coptis chinensis, Litchi chinensis, Ecklonia kurome*, *Curcuma longa* – as used in another study reported above - Grant et al.	The levels of HbA1c were lowered after treatment in the two groups after 8 weeks of treatment, showing statistical difference when compared with before treatment (-0.59% +/- 1.99% and -0.27% +/- 2.73%, $P < 0.05$). The PPG level also decreased with statistical difference (-1.71 +/- 2.52 mmol/L and -0.72 +/- 4.17 mmol/L, $P < 0.05$), but there was no statistical difference between the two groups. The body weight, BMI, TG decreased ($P < 0.05$). The CM symptoms efficacy and CM symptom scoring were significantly reduced in the two groups ($P < 0.01$). No severe adverse event occurred in either group during the therapeutic course.	This small study offers **preliminary** evidence for the effects of Jiangtang Xiaozhi capsule offering increased glycaemic control. This combination of herbs was also tested by Grant et al (see above).
Huseini HF, Kianbakht S. et al. 2012. Anti-hyperglycaemic and	60 T2D participants with a daily intake of two 5 mg glyburide (Glibenclamide) tablets and two 500 mg	The aloe gel lowered the FBG, HbA1c, total cholesterol, and LDL levels significantly ($p = 0.036$, $p = 0.036$, $p = 0.006$, and $p = 0.004$, respectively) without any significant effects on	The study was of short duration and small numbers and therefore offers

anti-hypercholesterolaemic effects of *Aloe vera* leaf gel in hyperlipidaemic type 2 diabetic patients: a randomized double-blind placebo-controlled clinical trial. *Planta Medica* 78 (4):311-6.[62]	Metformin tablets were randomised to receive aloe gel (one 300 mg capsule every 12 hours for 2 months) or placebo. Outcomes included FBG, HbA1C, and blood lipids.	the other blood lipid levels and liver/kidney function tests ($p > 0.05$) compared with the placebo at the endpoint. No adverse effects were reported. These results show some promise for *Aloe vera* leaf gel being useful in reducing cholesterol and improving glycaemic control in T2D patients with high cholesterol.	**preliminary** findings.
Wainstein J, Gantz T et al. 2012. Olive leaf extract as a hypoglycaemic agent in both human diabetic subjects and in rats. *Journal of Medicinal Food*. 15 (7): 605-10.[63]	79 adults with T2D were randomized to treatment with 500 mg olive leaf extract tablet taken orally once daily or matching placebo. The study duration was 14 weeks. Measures of glucose homeostasis including HbA1C and plasma insulin were measured and compared by treatment assignment.	The participants treated with olive leaf extract exhibited significantly lower HbA1c and fasting plasma insulin levels; however, postprandial plasma insulin levels did not differ significantly by treatment group.	A larger study for longer duration is warranted. This study provides **preliminary** evidence for improving glycaemic control with olive leaf extract.
Akilen R, Tsiami A et al. 2010. 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. *A Journal of the British Diabetic Association* 27 (10):1159-67.[64]	58 T2D participants treated only with hypoglycaemic agents and with an HbA1c more than 7% were randomly assigned to receive either 2g of *Cinnamomum cassia* or placebo daily for 12 weeks. Outcomes included HbA1C, FBG, blood pressure, cholesterol and BMI.	The mean HbA1c was significantly decreased ($P<0.005$) in the cinnamon group (8.22% to 7.86%) compared with placebo group (8.55% to 8.68%). The FBG was also significantly reduced. Mean systolic and diastolic blood pressures (SBP and DBP) were also significantly reduced ($P<0.001$) after 12 weeks in the cinnamon group. The author conducted a review of the mechanisms of cinnamon for T2D.	This small study shows **Preliminary** evidence for the efficacy of *Cinnamomum cassia* in improving glycaemic control and lowering blood pressure. A longer and larger study is called for to build on these findings. See also study by Anderson et al reported above.
Huseini HF, Darvishzadeh F. 2009. The Clinical Investigation of *Citrullus colocynthis* (L.) schrad fruit in treatment of type 2 diabetic patients: a randomized, double blind, placebo-controlled clinical trial. *Phytotherapy Research.*23 (8): 1186–1189.[65]	50 T2D participants under standard antidiabetic therapy received either 100 *mg Citrullus colocynthis* (bitter cucumber) capsules or placebos three times daily, respectively. Outcomes included FBG, HbA1c and blood lipids plus liver and kidney function after 2 months.	The results showed a significant decrease in HbA1C and FBG levels in *C. colocynthis* treated patients both before and after treatment and compared to placebo. There were no adverse events and no changes in liver and kidney function. This is a small feasibility study and the main outcome measure HbA1C was significantly different at the outset between the treatment and the placebo group. *C. colocynthis* treatment appeared to have a beneficial effect on improving the glycaemic control without severe adverse effects in T2D patients	Differences in the two groups and the small numbers reduce the rigour of these findings providing **Preliminary** evidence.

Kuriyan R, Rajendran R et al. 2008. Effect of supplementation of *Coccinia cordifolia* extract on newly detected diabetic patients. *Diabetes Care*. 31(2):216-20.[66]	60 recently diagnosed participants with T2D were randomised to two groups of either *Coccinia cordifolia-ivy gourd* (1g per day) or placebo for 90 days. Outcomes included FBG, HBA1c, and blood lipids.	The treatment group had a 16% decrease in FBG and the placebo group a 6% increase at 90 days; similarly, in post-prandial blood glucose the treatment group reduced by 18.5% and the placebo group increased by 7%. The HbA1C level was significantly reduced by 6% in the treatment group but no change in the placebo group. All other outcomes were similar in both groups.	This study provides **preliminary** evidence for *Coccinia cordifolia* aiding hypoglycaemic control in newly diagnosed T2D.
Zhang Y, Li X et al. 2008. Treatment of Type 2 Diabetes and Dyslipidemia with the Natural Plant Alkaloid Berberine. *The Journal of Clinical Endocrinology & Metabolism DOI:* http://dx.doi.org/10.1210/jc.2007-2404.[67]	116 participants with T2D were randomly allocated to receive 1g *berberine* (an alkaloid extracted from medical plants) daily or placebo for 3 months. Outcomes were FBG, PPG and HbA1C, as well as glucose disposal rate and blood lipids.	FBG decreased from 7.0 ± 0.8 to 5.6 ± 0.9 and PPG from 12.0 ± 2.7 to 8.9 ± 2.8 mm/ltr. HbA1c from 7.5 ± 1.0% to 6.6 ± 0.7%.	This study provides **moderate** evidence that the compound *berberine* derived from medicinal plants improves glycaemic control.
Hsu CH, Liao YL et al. 2007. The mushroom *Agaricus Blazei Murill* in combination with Metformin and Gliclazide improves insulin resistance in type 2 diabetes: a randomized, double-blinded, and placebo-controlled clinical trial. *Journal Alternative Complementary Medicine*. 13 (1): 97-102.[68]	72 T2D participants who had T2D for more than a year who had also been taking Gliclazide and Metformin for more than 6 months were randomly assigned to receive either *Agaricus blazei murill* (ABM) 1500g extract or placebo for 12 weeks. Homeostasis model assessment for insulin resistance (HOMA-IR) was used as the major outcome measurement.	At the end of the study, subjects who received supplement of ABM extract (n = 29) showed significantly lower HOMA-IR index (3.60 versus 6.6 p = 0.04) than the control group (n = 31). The plasma adiponectin concentration increased in the ABM group after 12 weeks of treatment, but decreased among those taking the placebo (p < 0.001). Supplement of ABM extract improves insulin resistance among subjects with T2D. The increase in adiponectin concentration after taking AMB extract for 12 weeks might be responsible for the beneficial effect. Safety was not mentioned in the abstract but was referenced as having been previously researched with no serious adverse events.	This small study offers **preliminary** evidence.
Jayawardena MHS, deWis NNW et al. 2005. A double-blind randomised placebo controlled cross over study of a herbal preparation containing *Salacia reticulata* in the treatment of type 2 diabetes. *Journal of Ethnopharmacology*. 97 (2): 215–218.[69]	65 T2D participants were randomised to receive either *Salacia reticulata* (commonly known as Kothala Himbutu tea) or a placebo tea for 3 months followed by placebo in similar tea bags for a further 3 months (n = 28) or in reverse order (n = 23). All patients received detailed advice on diet, exercise and lifestyle modification and maintained their normal diabetic medication. Outcome measures were	The HbA1C at the end of drug treatment was significantly lower than after treatment with placebo P = 0.008). A statistically significant fall in HBA1C was seen with the active drug compared to a rise in HbA1C with the placebo group (0. 54 ± S.D. 0.93) versus −0.3 ± S.D. 1.05; P < 0.001. The daily mean dose of Glibenclamide fell by 1.89 (S.D. 6.2) mg in the active treated group but rose by 2.25 mg in the placebo treated group (P = 0.07). The differences in the Metformin dose were not significantly significant in the two groups. This is a tea preparation widely used for diabetes in Ayurvedic medicine. Blinding is an issue as the participants may have been able to tell the difference between the placebo	This provides **preliminary** data.

	HbA1C at 3 months and on completion of the study at 6 months. Liver and renal functions were assessed.	and real tea. A cross-over trial may be less useful for long term conditions where indices of glycaemic control may change more slowly. It is not clear at what time point (3 or 6 months) the results relate to.	
Liu X, Wei J et al. 2004. Antidiabetic effect of Pycnogenol® French maritime pine bark extract in patients with diabetes type II. *Life Sciences*. 75 (21): 2505–2513.[70]	77 T2D participants were randomised into either 100 mg Pyconogenol® (*Pinus pinaster*) or placebo plus normal diabetic medication for 12 weeks. Outcomes included HbA1C.	Compared to placebo Pyconogenol® significantly lowered plasma glucose levels; HbA1C levels were reduced significantly only for the first month. Endothelin-1 was significantly decreased, while 6-ketoprostaglandin F1a in plasma was elevated compared to placebo suggesting improved endothelial function. The standardised pine tree bark extract Pyconogenol® is a widely used supplement for many ailments and likely works through strong anti-oxidant properties.	This study provides **preliminary** evidence that Pyconogenol® as a supplement to diabetic medication lowers glucose levels.
Ludvik B, Neuffer B, Pacini G. 2004. Efficacy of *Ipomoea batatas* (Caiapo) on diabetes control in type 2 diabetic subjects treated with diet. *Diabetes Care*. 27(2):436-40.[71]	61 participants with T2D were randomly assigned to placebo or 4g *Ipomoea betatas* a day for 12 weeks. Outcomes included FBG and 2-hour glucose, HbA1C and blood lipids.	After 3 months the HbA1C was significantly reduced in the treatment group compared to the placebo group (6.54 to 6.82 p<0.001). The treatment group also saw a significant decrease in FBG and 2 hour PPG at 3 months compared to baseline (p<0.001) with no change in the placebo group.	This study offers **preliminary** evidence that 4g *Ipomoea betatas* offers glycaemic control for patients not yet on diabetic medication.
Khan A, Safdar M et al. 2003. Cinnamon improves glucose and lipids of people with type 2 diabetes. *Diabetes Care*. 26 (12):3215-8.[72]	60 T2D participants were randomised into two groups of cinnamon (1, 2 or 3g) or placebo (1, 2 of 3 capsules) for 40 days. Outcomes were changes to the mean scores of FPG and blood lipids.	The treatment group had reduced mean fasting plasma glucose (18–29%), triglyceride (23–30%), LDL cholesterol (7–27%), and total cholesterol (12–26%) levels. The 6g cinnamon group had significant reductions after 20 days.	This study provides **preliminary** evidence that even small doses of cinnamon can be effective at reducing serum glucose.
Agrawal RP, Sharma A et al. 2002. A randomized placebo controlled trial of Inolter (herbal product) in the treatment of type 2 diabetes. *Journal of the Association of Physicians of India*. 50:391-3.[73]	60 T2D participants were given either Inolter (*Momordica charantis, Trigonella foenum graeceum, Asphaltum punjabianum, Gymnema sylvestre, Eugenia jambolena*) or an identical placebo for three months. Outcome measures were FBG, HbA1c, serum cholesterol, and adverse effect.	Significant reduction in HbA1C mean difference -0.80 (-0.93 to -0.67) and FBG was also significantly reduced compared to the placebo group (-39mg/dl 95% CI: -66 to -12). Changes to cholesterol levels were also noted in the treatment group. There were no adverse effects.	This small study provides good **preliminary** evidence for this combination of traditional medicines to offer improved glycaemic control.
Guo GY, Yan Q, Wang ZC. 1998. Clinical study of Tianyuan Jiangtang Pill for treatment of	130 T2D participants were allocated to one of four groups: to receive either Tianyuan Jiangtang Wan (13 remedies including	Tianyuan Jiangtang Wan plus hypoglycaemic drugs appeared to have significant effects on reducing FBG levels and on HbA1c levels compared with hypoglycaemic drugs alone. FBG -0.72 (-1.40 to -0.04); HbA1C -1.45 (-2.26	This study provides **preliminary** levels of evidence as the blinding was not clear.

non-insulin dependent diabetes mellitus] [in Chinese]. *Hebei Journal of Traditional Chinese Medicine.* 20(3):142-3.[74]	*Rehmannia glutinosa, Cornus officinalis, Angelica sinensis, Bombyx batryticatus, Schisandra chinensis*) or Gliclazide or patients who had previous hypoglycaemic drug treatment were allocated to continue either their original hypoglycaemic drugs treatment alone or hypoglycaemic drugs plus Tianyuan Jiangtang Wan. Outcomes included HbA1C and FBG.	to -0.64).	
Pan MZ, Guo SS et al. 1997. Effect of Xianzhen tablet on Na+-K+-ATPase, Ca+-Mg2+-ATPase, of red blood cell membrane in patients with non-insulin dependent diabetes mellitus. [in Chinese]. *Chinese Journal of Integrated Traditional and Western Medicine*. 17(1):13-6.[75]	72 participants were randomised to either placebo or Xianzhen Pian tablets for two months. Outcomes were FBG, PPG, symptoms and adverse events. (Xianzhen Pian is composed of more than 12 traditional medicinals - (*Astragalus membranaceus, Salvia miltiorrhiza, Rehmannia glutinosa, Ligustrum lucidum, Epimedium grandiflorum , Cuscuta chinensis, Lycium barbarum (fructus), Semen Cassia tora (semen), Anemarrhena asphodeloides, Coptis chinensis, Scutellaria baicalensis (radix), Hirudo seu whitmania*).	Xianzhen Pian pills had better effects at normalising FBG (RR 2.5 95% CI 1.38 to 4.54) and a reduction in FBG (WMD -0.85 mmol/L; 95% CI -1.64 to - 0.05).	This study shows **preliminary** levels of evidence
Vray M, Attali JR. 1995. Randomized study of Glibenclamide versus traditional Chinese treatment in type 2 diabetic patients. *Diabetes and Metabolism*. 21(6):433-439.[76]	216 participants were randomised into 4 groups; (placebo = P & traditional Chinese treatment = TCT). Groups were A = P TCT + P glibenclamide; B = P TCT + verum glibenclamide; C = verum TCT + P glibenclamide; D = verum TCT + verum glibenclamide. Outcome measures were FBG, HbA1c, plasma insulin, weight and adverse effects. Capsules - *Astragalus membranaceus, Coptis chinensis, Lonicera japonica*	The intervention reduced FBG -0.22 (95% CI -0.36 to -0.08) and HbA1C -0.64 (95% CI -0.76 to -0.52) compared with placebo.	This study showed **moderate levels of** evidence.

Table 2 - Systematic Reviews of herbs for T2D or Prediabetes

7 Systematic reviews are included, some of which offer only preliminary evidence. However, for some herbs such as *Aloe vera, Zingiber officinale* and *Cinammomum cassia* the evidence is more substantial.

Authors	Methods	Findings	Comments
Suksomboon N, Poolsup N, Punthanitisarn S. 2016. Effect of *Aloe vera* on glycaemic control in prediabetes and type 2 diabetes: a systematic review and meta-analysis. *Journal of Clinical Pharmacy and Therapeutics.* 41 (2): 180–188.[77]	8 RCTs were included in this search resulting in 470 prediabetes (235) or T2D participants. The outcome measures were changes to the mean of FBG and HbA1C.	Aloe vera significantly changed FBG (mean difference −0·22 mmol/L, 95% CI −0·32 to −0·12 mmol/L, P < 0·0001) for prediabetes but not HbA1C. Conversely for T2D Aloe vera improved glycaemic control with changes to the mean of HbA1C (mean difference −11 mmol/mol, 95% CI −19 to −2 mmol/mol, P = 0·01) and a modest but significant change to FBG (mean differences −1·17 mmol/L, 95% CI −2·3 to 0·00 mmol/L, P = 0·05)	This meta-analysis demonstrates **moderate** evidence of *Aloe vera* offering improved glycaemic control for pre-diabetes and T2D.
Daily JW, Yang M et al. 2016. Efficacy of ginger for treating Type 2 diabetes: A systematic review and meta-analysis of randomized clinical trials. *Journal of Ethical Foods.* DOI: http://dx.doi.org/10.1016/j.jef.2015.02.007.[78]	5 RCT's were included with 318 participants. FBG and HbA1C levels were the main outcome measures.	HbA1c levels were significantly decreased in all four RCTs in which the levels were measured. The 95% CI of mean difference of four RCTs were [−2.04, −1.29] (p < 0.001) suggesting that ginger had a long-term serum-glucose lowering effect. The authors conclude that it is possible that ginger improves fasting serum glucose levels and HbA1c by decreasing insulin resistance inT2D.	This meta-analysis provides **moderate** evidence that ginger (*Zingiber officinale*) Improves glycaemic control.
Akilen R, Tsiami A et al. 2012. Cinnamon in glycaemic control: systematic review and meta-analysis. *Clinical Nutrition.* 31(5):609-15[79]	This systematic review and meta-analysis included 6 trials with 435 participants. The dose of *Cinnamomum* spp. ranged from 1 to 6g per day from 40 days to 4 months.	The meta-analysis showed a significant decrease in mean HbA1c (0.09%; 95% CI was 0.04-0.14) and mean FPG [0.84 mmol/l;95% CI was 0.66-1.02).	The meta-analysis provides a **moderate** level of evidence; it showed a demonstrable benefit for the short term use of *Cinnamomum spp.* to improve glycaemic control.
Sridharan K, Mohan R et al. 2011. Ayurvedic treatments for diabetes mellitus. *Cochrane database of systematic reviews (Online), (12), CD008288.*[80]	This systematic review included 6 RCTs involving 354 subjects. The treatment duration was between 3 and 6 months. Proprietary herbal mixtures based on Ayurvedic tradition were main interventions.	**Diabecon tablets** (*Balsamodendron mukul, Gymnema sylvestre, Glycyrrhiza glabra, Casearia esculenta, Eugenia jambolana, Asparagus racemosus, Boerhavia diffusa, Sphaeranthus indicus, Tinospora cordifolia, Swertia chirata, Tribulus terrestris, Phyllanthus amarus, Gmelina arborea, Gossypium herbaceum, Berberis aristata, Aloe vera, Asphaltum punjabianum)* **Inolter capsules***(Momordica charantia, Trigonella foenum-graecum, Asphaltum punjabianum , Gymnema sylvestre, Eugenia Jambolina)*	Although three interventions showed great promise in reducing HbA1C levels, the numbers were not large enough to offer anything above **preliminary** evidence.

		Cogent DB *(Azadirachta indica, Phyllanthus emblica, Circuma longa,Trigonella foenum-graecum, Syzygium cumini,Tribulus terrestris, Terminalia bellirica, Terminalla chebula, and Rotula aquatica*) significantly lowered glycosylated haemoglobin A1c (HbA1C) levels compared to controls (Diabecon, MD-1% (95% CI, -1.9 to -0.1); Inolter, MD -0.8% (95% CI, -0.9 to -0.7); Cogent DB, MD -2.1(95% CI, -3.3 to -1)	
Davis PA, Yokoyama W. 2011. Cinnamon intake lowers fasting blood glucose: meta-analysis. ***Journal of Medicinal Food.*** **4:1-6.**[81]	This was a systematic review and meta-analysis of 8 trials for cinnamon (the dry bark and twig of *Cinnamomum* spp) and cinnamon extract including 369 subjects. The intervention was given for 4 to 16 weeks.	The analysis showed a modest but significant reduction in FBG (–0.49–0.2mmol/L P=0.025)	This study provides **moderate** evidence of the effect of Cinnamon in improving glycaemic control.
A Shojaii, A Goushegir et al. 2011. Herbs and herbal preparations for glycaemic control in diabetes mellitus (a systematic review) ***Journal of Medicinal Plants Research.*** **5 (16), 3846-3855.**[82]	This review included 38 RCT's, most of which had very small numbers and were not blinded.	Among the RCT studies, evidence for glycaemic control was found for Citrullus *colocynthus*, *Ipomoea betatas*, and *Silybum marianum. Citrullus colocynthis* and *Ipomeao betatas* showed stronger evidence but this is still ranked preliminary due to the methods used for testing.	This review showed only **preliminary** evidence for individual herbs due to poor methodology.
Grant SJ, Bensoussan A et al. 2010. Chinese herbal medicines for people with impaired glucose tolerance or impaired fasting blood glucose. ***Cochrane Database of Systematic Reviews*****. DOI: 10.1002/14651858.CD006690.pub2.**[83]	This review included 16 trials for 15 different Chinese herbal medicines in eight comparisons with pooled data allowing a meta-analysis. There were 1391 participants with trials lasting from 4 weeks to two years with 13 of the trials lasting more than a year.	The results suggest that those taking Chinese herbal medicine combined with lifestyle changes were more than twice as likely to have normal glycaemic control (for instance fasting plasma glucose <7.8 mmol/L and 2hr blood glucose <11.1 mmol/L) compared to lifestyle modification alone (RR 2.07; 95% confidence interval (CI) 1.52 to 2.82). Those taking Chinese herbal medicine had a reduced risk of developing diabetes (RR 0.33 95% CI 0.19-0.58). No adverse events were reported.	Results have to be interpreted with caution due to methodological limitations such as selection and blinding bias. This review suggests **preliminary** levels of evidence and more research is warranted.
Liu JP, Zhang M et al. 2004. Chinese herbal medicines for type 2 diabetes mellitus. ***Cochrane Database of Systematic Reviews*** **Issue 3. Art. No.: CD003642. DOI: 10.1002/14651858.CD003642.pub2**[84]	This review includes mainly Chinese language studies of 65 randomised controlled trials and 8302 participants. A wide range of designs including comparison of single herbs or combinations of herbs (69 different herbs altogether) with placebo	Compared with placebo, Holy basil leaves, Xianzhen Pian, Qidan Tongmai, traditional Chinese formulae (TCT), Huoxue Jiangtang Pingzhi, and Inolter showed significantly improved hypoglycaemic response. Compared with hypoglycaemic drugs including Glibenclamide, Tolbutamide, or Gliclazide, seven herbal formulae demonstrated a significant better metabolic control, including Bushen Jiangtang Tang, Composite	This review has not been updated for many years. Despite the methodological limitations of many of the included studies, there were demonstrable hypoglycaemic

	control or diabetic medication, or herbs with diabetic medications versus these medications alone, or with lifestyle or dietary changes. Methodological limitations suggest caution in interpretation of the findings. Most of these studies used fasting blood glucose or glycaemic control as outcomes. Many of these trials reported improvements in glycaemic control.	Trichosanthis, Jiangtang Kang, Ketang Ling, Shenqi Jiangtang Yin, Xiaoke Tang, and Yishen Huoxue Tiaogan. In 29 trials that evaluated herbal medicines combined with hypoglycaemic drugs, 15 different herbal preparations showed additional better effects than hypoglycaemic drug monotherapy. Two herbal therapies combined with diet and behaviour change showed better hypoglycaemic effects than diet and behaviour change alone. No serious adverse effects from the herbal medicines were reported	responses. The authors conclude **moderate** levels of evidence should lead to further research.

Table 3 - Evidence by sample of individual herbs with references to studies in Table 1

Herb	Study	Findings
Agaricus blazei murill	Hsu et al 2007	Insulin resistance was improved compared to placebo.
Angelica sinensis	Tue et al 2013	In a formula of 9 herbs – reduced FBG, HbA1C, postprandial BG.
	Guo et al 1998	In a formula of 13 herbs – reduced FBG, HbA1C and improved glycaemic control.
Aloe vera	Suksomboon et al 2016	Systematic review.
	Huseini et al 2012	Reduced HbA1C and FBG.
Astragalus membranaceus	Zhang et al 2015	In a formula of 8 herbs – reduced FBG, postprandial BG and HbA1C and improved beta cell function.
	Ji et al 2013	In a formula of 7 herbs – reduced HbA1C and improved glycaemic control and reduced incidence of hypoglycaemia.
	Lian et al 2013	In a formula of 10 herbs – reduces the risk of progressing to diabetes by 32% compared with placebo.
	Grant et al 2009	In a formula of 6 herbs – no difference in FBG or HbA1C compared to placebo but a difference in fasting insulin.
	Vray et al 1995	In a formula of 3 herbs – reduced FBG

		and HbA1C compared with placebo.
***Cinnamomum* spp.**	Anderson et al 2016	Reduced FBG, 2-hour glucose, and insulin compared to placebo.
	Tu et al 2013	In a formula of 9 herbs – reduced FBG, HbA1C, postprandial BG.
	Akilen et al 2010	Reduced FBG, HbA1C compared to placebo.
	Khan et al 2003	Reduced FBG.
	Akilen et al 2012	Systematic review.
	Davis et al 2011	Systematic review.
Cornus officinalis	Lian et al 2015	In a formula of 17 herbs – reduced FBG, HbA1C and PPG and improved beta cell function compared to control group.
	Lian et al 2013	In a formula of 10 herbs – reduces the risk of progressing to diabetes by 32% compared with placebo.
	Ji et al 2013	In a formula of 7 herbs – reduced HbA1C and improved glycaemic control and reduced incidence of hypoglycaemia.
	Guo et al 1998	In a formula of 13 herbs – reduced FBG, HbA1C and improved glycaemic control.
Eugenia jambolena	Agrawal et al 2002	HbA1C and FBG were reduced compared to placebo
Panax ginseng	Lian et al 2015	In a formula of 17 herbs – reduced FBG, HbA1C and PPG and improved beta cell function compared to control group.
	Zhang et al 2015	In a formula of 8 herbs – reduced FBG, postprandial BG and HbA1C and improved beta cell function.
Zingiber officinale.	Daily et al 2016	Systematic review.
	Mozaffari-Khosravi et al 2014	Differences not substantial enough but in a properly powered study might be otherwise.
	Tu et al 2013	In a formula of 9 herbs – reduced FBG, HbA1C, postprandial BG.

Gymnema sylvestre	Agrawal et al 2002	In a formula of 4 herbs – HbA1C and FBG were reduced compared to placebo.
Prunus mume	Tu et al 2013	In a formula of 9 herbs – reduced FBG, HbA1C, postprandial BG.
Rehmannia glutinosa	Lian et al 2015	In a formula of 17 herbs – reduced FBG, HbA1C and PPG and improved beta cell function compared to control group.
	Zhang et al 2015	In a formula of 8 herbs – reduced FBG, postprandial BG and HbA1C and improved beta cell function.
	Guo et al 1998	In a formula of 13 herbs – reduced FBG, HbA1C and improved glycaemic control.
	Pan et al 1997	In a formula of 12 herbs – reduced FBG.
Salvia miltiorrhiza	Zhang et al 2015	In a formula of 8 herbs – reduced FBG, postprandial BG and HbA1C and improved beta cell function.
	Pan et al 1997	In a formula of 12 herbs – reduced FBG.
Salvia officinalis	Kianbakht et al 2013	Reduced FBG, HbA1C.
Salacia reticulata	Jayawardena et al 2005	Reduced HbA1C.
Scutellaria baicalensis	Tong et al	In a formula of 5 herbs – HbA1C was reduced compared to placebo.
	Pan et al 1997	In a formula of 12 herbs – reduced FBG.
Trichosanthes kirilowii	Zhang et al 2015	In a formula of 8 herbs – reduced FBG, postprandial BG and HbA1C and improved beta cell function.
	Ji et al 2014	In a formula of 7 herbs – reduced HbA1C and improved glycaemic control and reduced incidence of hypoglycaemia.
	Lian et al 2013	In a formula of 10 herbs – reduces the risk of progressing to diabetes by 32% compared with placebo.
	Liu et al 2004	Systematic review.
Trigonella foenum-graecum	Agrawal et al 2002	In a formula of 4 herbs – reduced HbA1C and FBG compared to placebo.
Vaccinium arctostaphylos	Kianbakht et al 2013	Reduced FBG, postprandial BG and HbA1C.

Discussion & conclusion

These included studies are a comprehensive, but by no means exhaustive, list of (mostly) blinded, randomised controlled trials. Taken as a whole, they demonstrate the significant potential of herbal medicine for managing T2D and improving glycaemic control. They also provide evidence that herbal medicine may reduce the risk of progression to T2D in those with prediabetes. Plant medicines are relatively cheap to produce and have a low incidence of associated adverse effects. Herbal medicine is a largely untapped and potentially invaluable resource for managing T2D. It will undoubtedly reward investment in further research and should be a major focus of investigation to answer the growing health crisis posed by T2D.

Contact ehpa@globalnet.co.uk

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