MEDI HERB
a phytotherapist's perspective
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Herbs to Support Blood Glucose Regulation

Key Points at a Glance

Nigella

- also known as Black Cumin
- hot and peppery tasting seed used in cooking and traditionally for a wide range of applications including indigestion and diabetes
- clinically demonstrated:
  - hypoglycaemic effect in type 2 diabetic patients with poor glycaemic control (0.7-2 g/day)
  - hypoglycaemic effect in metabolic syndrome (mixed results)
  - to reduce lipids in diabetes and metabolic syndrome (0.5-3 g/day)

Fenugreek

- whole seed used in cooking and extensively in traditional medicine
- whole seed has a range of constituents including steroidal saponins, a substantial quantity of carbohydrates and 4-hydroxyisoleucine (4-HIL; a non-protein amino acid)
- 4-HIL found to stimulate glucose-dependent insulin secretion *in vitro*; hypoglycaemic and antiobesity effects in experimental models for high oral doses
- clinically demonstrated hypoglycaemic and hypolipidaemic effects in type 2 diabetics for aqueous alcoholic extracts (dried herb equivalent unknown)
- clinically demonstrated:
  - hypoglycaemic and hypolipidaemic effects in type 2 diabetics for aqueous alcoholic extracts (dried herb equivalent unknown)
  - to provide some benefit to poorly-controlled type 2 diabetics (Fenugreek, filtered decoction from 15 g/day seed + Cinnamon (3 g/day))
  - to reduce consumption of fat in healthy overweight and normal-weight participants (extract standardised for steroidal saponins, trigonelline and 4-HIL (dose provided 17 mg/day of 4-HIL))

Bitter Melon

- commonly used as a vegetable
- traditionally used in Ayurveda for tonic and digestive applications
- variation in response to Bitter Melon is possible; single-dose studies suggest improved glucose tolerance in some participants
- some hypoglycaemic effects clinically demonstrated in type 2 diabetic patients (0.5-3 g/day dried herb equivalent of variety of preparations: fruit with and without seed; likely that at least 2 g/day is required)

Cinnamon

- *Cinnamomum verum* and *C. cassia* bark traditionally used, particularly to improve digestion and circulation
- *Cinnamomum verum* and *C. cassia* bark constituent profiles share similarities but notable differences
- MediHerb conducted and commissioned research to develop better methods for quality control of Cinnamon
  - raw materials are not always the species they claim to be
  - the quantity of procyanidins, which are therapeutically-important constituents, varies across species
  - coumarin, a constituent with safety concerns, is naturally lowest in *C. verum*
  - the production of low-coumarin extracts from other species may compromise overall quality
- clinical studies have investigated several species (and in many, the species is not defined); the results suggest:
  - hypoglycaemic activity in type 2 diabetes, especially regarding fasting blood glucose but inconclusive (meta-analysis of 10 trials found significant reduction of FBG (1-14.4 g/day equivalent to dried bark))
  - it is likely that more than 2 g/day is required, although effects not dose dependent at higher doses
  - a lipid-lowering effect was not clearly demonstrated
  - many therapeutic benefits for metabolic syndrome patients, including hypoglycaemic effects (3 g/day)

Nigella

The common name given to Nigella in Arabic means 'seeds of blessing'. Avicenna, a first-century Iranian physician, philosopher and writer of herbal medicine, referred to it as the seed that stimulates the body's energy and helps recovery from fatigue and dispiritedness.[1] There is an Arabic proverb: "In the black seed is the medicine for every disease except death".[2]

Nigella is also known as Black Cumin. The seeds have a hot, peppery taste and are often added to curries, cheeses and breads.[3] Nigella seed is traditionally used in India for indigestion, loss of appetite and fevers. The seeds are medicinally prescribed with other aromatics in the form of confectionery.[4] Nigella seed is used traditionally to treat diabetes and hypertension in south-east Morocco.[5]

Nigella sativa seeds contain protein (20-30%), fat (30-40%) and total carbohydrates (25-40%). It contains about 10% fibre and has a low moisture content (2.5%).[6] Important constituents are the fixed oil and volatile oil (< 2%). Minor constituents include saponins and alkaloids.[7,8] The quantities of the volatile oil constituents vary, although a reliable analysis has thymoquinone (a potentially important active constituent) present in the seed at about 0.1–0.2%.[8]

Although clinical trials have used powdered seed, it is likely that alcoholic extracts would also show efficacy, as studies in animals confirm hypoglycaemic and lipid-lowering activities for ethanol and methanol extracts.[9-11]

Clinical Studies

Hypoglycaemic Activity: Diabetes

A Saudi Arabian study tested several doses of Nigella seed in type 2 diabetic patients with poor glycaemic control (defined as two readings of glycosylated haemoglobin (HbA1c) of greater than 7%, conducted 3 months apart) who were taking oral hypoglycaemic drugs. They received capsules containing powdered seed: 1 g/day, 2 g/day or 3 g/day for 12 weeks. Significant **improvement in glycaemic control** (fasting blood glucose, HbA1c, insulin resistance) was found for the 2-g/day dose. The results were not significant at 1 g/day and no additional improvement was found for the 3-g/day dose. Some minor gastrointestinal discomfort was noted, and was relieved by taking the herb capsules after meals.[12]

Another Saudi Arabian trial found Nigella powdered seed (2 g/day) taken for one year improved glucose homeostasis in patients with poorly-controlled type 2 diabetes (two readings, 3 months apart of HbA1c of greater than 7%) who were using oral hypoglycaemic drugs. Treatment resulted in significantly reduced fasting blood glucose (FBG), HbA1c and insulin resistance and **significantly increased beta-cell function** from baseline values. (The latter two parameters were calculated using the FBG and C-peptide levels.) Improvements were also significant at 3, 6 and 9 months. The placebo group did not experience improvements in these parameters or worsened at some time periods. Comparison of parameters between the groups found a significantly lower HbA1c ($p \leq 0.05$) in the Nigella group at 6 and 9 months compared to the control group, and similarly, FBG was significantly lower at 3 and 6 months (despite a substantially higher level at baseline in those receiving Nigella ($p = 0.06$)). No mention was made about the participant's diet and lifestyle throughout the trial.[13] Treatment with Nigella also improved cardiac systolic function in another group of these patients.[14]

A placebo-controlled, crossover trial conducted in Pakistan assessed the effect of capsules containing powdered seed (0.7 g/day) for 40 days in type 2 diabetics. Participants had fasting blood glucose levels greater than normal values, despite taking their usual oral diabetes medications. Significant improvement from baseline was found after treatment with Nigella: fasting blood glucose decreased by 3.69 mmol/L (30.8%) and insulin increased by 1.96 µIU/mL (27.9%). The results reversed significantly by the end of the placebo phase.[15,16]

Treatment with Nigella powdered seed (2 g/day) significantly reduced levels of fasting blood glucose (from a baseline of 14.9 mmol/L) and serum uric acid after 28 and 42 days in poorly-controlled diabetics who were taking oral hypoglycaemic drugs.[17]

An Indian trial found that Nigella significantly improved fasting blood glucose and HbA1c in type 2 diabetic patients with poor glycaemic control (HbA1c > 7%) who were taking metformin. *Nigella sativa* seeds were chewed and consumed in a dose of 2 g/day for 8 weeks. The decreases in FBG (12.8%) and HbA1c (13.8%) from baseline were significant ($p < 0.001$). Significant changes were not observed in the control group who were taking only drug medications. The baseline levels of these parameters were higher in the Nigella group (about 15% higher for FBG).[18]

Hypoglycaemic Activity: Metabolic Syndrome

The addition of Nigella seed (0.5 g/day) to standard drug treatment for 6 weeks in patients with symptoms of metabolic syndrome resulted in a greater improvement in fasting blood glucose than in those not treated with Nigella (decrease from baseline of 28.7% vs 14.8%, respectively; $p = 0.01$). The baseline values were 9% higher in the Nigella group. Patients were advised to adhere to a recommended diet and exercise schedule.[19]

In patients recently diagnosed with metabolic syndrome who were not on any other medication and took Nigella powdered seed at a dose of 1.5 g/day for 8 weeks, the decrease in fasting blood glucose (8.2%) from baseline did not reach statistical significance, but was significant when compared to the placebo group who received 1.5 g/day of psyllium ($p = 0.02$).[20]

For more details of some of these trials see Table 1.

	Parameter	Baseline	After Nigella Treatment (% change)	Ref
Diabetes				
2 g/day powdered seed for 12 weeks; poor glycaemic control[1,2a,3a]	fasting plasma glucose (mmol/L)	12.0	8.9 (-26.0%)*	12
	HbA1c (%)	9.09	7.57 (-16.7%)†	
	insulin resistance index	3.20	2.37 (-25.9%)§	
	beta-cell function (%)	45.03	63.63 (41.3%)‡	
2 g/day powdered seed for one year; poor glycaemic control[1,2b,3b]	fasting plasma glucose (mmol/L) at 3 mo	10.7	9.0 (-16.4%)‡	13
	fasting plasma glucose (mmol/L) at 6 mo	10.7	9.0 (-15.9%)*	
	fasting plasma glucose (mmol/L) at 9 mo	10.7	9.7 (-9.7%)‡	
	fasting plasma glucose (mmol/L) at 12 mo	10.7	9.5 (-11.8%)‡	
	HbA1c (%) at 3 mo	8.6	7.9 (-8.1%)*	
	HbA1c (%) at 6 mo	8.6	7.8 (-9.3%)*	
	HbA1c (%) at 9 mo	8.6	7.9 (-8.1%)‡	
	HbA1c (%) at 12 mo	8.6	8.2 (-4.7%)^	
0.7 g/day powdered seed for 40 days[1,2c,3d]	fasting plasma glucose (mmol/L)	11.96	8.28 (-30.8%)*	16
	insulin (µIU/mL)	7.00	8.96 (28.0%)*	
2 g/day seed for 8 weeks; newly-diagnosed and with poor glycaemic control[1,2d,3c]	fasting plasma glucose (mmol/L)	9.11	7.94 (-12.9%)*	18
	HbA1c (%)	8.11	6.99 (-13.8%)*	
Metabolic Syndrome				
0.5 g/day seed for 6 weeks[1,2d,3c]	fasting plasma glucose (mmol/L)	7.52	5.36 (-28.7%)‡	19
1.5 g/day powdered seed for 8 weeks; recently diagnosed and not drug medicated[2d,3b]	fasting plasma glucose (mmol/L)	6.70	6.15 (-8.2%)**	20

Table 1. Hypoglycaemic activity of Nigella in patients with diabetes or metabolic syndrome.

Notes: 1: taking oral hypoglycaemic drugs; 2a: maintained diet and lifestyle; 2b: diet and lifestyle not mentioned; 2c: no significant change in diet or physical activity; 2d: advice given on diet and lifestyle; 3a: no placebo or control group; 3b: placebo-controlled; 3c: controlled (drug vs drug + Nigella); 3d: placebo-controlled cross-over study: Nigella then placebo, FBG and insulin results significantly deteriorated after placebo; * $p < 0.001$; † $p < 0.0001$; § $p < 0.01$; ‡ $p < 0.05$; ^ $p = 0.01$; ** not significant

Hypolipidaemic Activity in Diabetes & Metabolic Syndrome

In many of the trials discussed above, treatment with Nigella significantly improved lipid levels in those with diabetes, metabolic syndrome or risk thereof.[16-22] *See Table 2 for additional details.*

In a randomised, single-blind, placebo-controlled trial, Nigella powdered seed (3 g/day) was taken by participants at risk of developing metabolic syndrome (having 3 of the 5 risk factors). At the end of the 12-week treatment, **lipid levels were significantly improved** from baseline ($p \leq 0.001$): total cholesterol (-0.32 mmol/L), HDL-cholesterol (0.24 mmol/L), LDL-cholesterol (-0.22 mmol/L), triglycerides (-0.09 mmol/L). The results were also significant compared to the lipid profile of the placebo group. Food intake and physical activity for those receiving Nigella did not change significantly during the trial.[23]

Supplementation with capsules containing Nigella powdered seed (1 g/day) for 2 months significantly improved lipid levels of menopausal women at moderate risk of hyperlipidaemia who had slightly elevated blood pressure (systolic blood pressure around 130 mmHg). (Total cholesterol and LDL-cholesterol levels were borderline high and high at baseline (approx. 6.1 mmol/L and 4.6 mmol/L, respectively).) Mean total cholesterol of the Nigella group decreased significantly by 16.1% at 2 months of treatment compared to baseline ($p < 0.05$) and the decrease was significantly greater than that of the placebo group ($p < 0.05$). Similarly, the decrease in LDL-cholesterol and triglycerides was significant compared to baseline (27.2% and 22.2%, respectively) and in comparison to the placebo group. HDL-cholesterol was not significantly different. Participants were asked to maintain their diet and physical activity.[24]

	Parameter	Baseline	After Nigella Treatment (% change)	Ref
Diabetes				
2 g/day powdered seed for 12 weeks; poor glycaemic control[1,2a,3a]	total cholesterol (mmol/L)	5.05	4.49 (-11.1%)†	21
	LDL-cholesterol (mmol/L)	3.25	2.71 (-16.8%)†	
	triglycerides (mmol/L)	2.17	1.68 (-22.2%)§	
2 g/day powdered seed for one year; poor glycaemic control[2b,3b]	total cholesterol (mmol/L) at 6 mo	5.02	4.59 (-8.5%)*	22
	total cholesterol (mmol/L) at 9 mo	5.02	4.66 (-7.2%)*	
	total cholesterol (mmol/L) at 12 mo	5.02	4.67 (-7.0%)*	
	LDL-cholesterol (mmol/L) at 3 mo	3.27	2.95 (-9.7%)*	
	LDL-cholesterol (mmol/L) at 6 mo	3.27	2.77 (-15.3%)*	
0.7 g/day powdered seed for 40 days[1,2c,3d]	total cholesterol (mmol/L)	5.14	4.72(-8.1%)^	16
	LDL-cholesterol (mmol/L)	3.14	2.79 (-11.4%)^^	
	HDL-cholesterol (mmol/L)	1.01	1.07 (5.1%)†	
	triglycerides (mmol/L)	2.18	1.90 (-12.9%)^	
2 g/day seed for 8 weeks; newly-diagnosed and with poor glycaemic control[1,2d,3c]	LDL-cholesterol (mmol/L)	4.23	3.05 (-28.0%)^	18
Metabolic Syndrome				
0.5 g/day seed for 6 weeks[1,2d,3c]	LDL-cholesterol (mmol/L)	4.26	3.08 (-27.8%)**	19
	HDL-cholesterol (mmol/L)	1.17	1.57 (34.6%)**	
1.5 g/day powdered seed for 8 weeks; recently diagnosed and not drug medicated[2d,3b]	total cholesterol (mmol/L)	4.77	4.21 (-11.7%)^	20
	triglycerides (mmol/L)	1.91	1.60 (-16.3%)^	

Table 2. Hypolipidaemic activity of Nigella in patients with diabetes or metabolic syndrome.

Notes: 1: taking hypolipidaemic drugs; 2a: maintained diet and lifestyle; 2b: diet and lifestyle not mentioned; 2c: no significant change in diet or physical activity; 2d: advice given on diet and lifestyle; 3a: no placebo or control group; 3b: placebo-controlled; 3c: controlled (drugs vs drugs + Nigella); 3d: placebo-controlled cross-over study: Nigella then placebo, levels of total cholesterol, LDL-cholesterol and triglycerides significantly deteriorated after placebo and the decrease in HDL-cholesterol after placebo was not significant; p values given for difference from baseline, except where noted: † $p < 0.05$; § $p < 0.01$; * significantly lower than placebo group: total cholesterol at 6, 9 and 12 months, $p = 0.007$, $p = 0.05$, $p = 0.02$, respectively; LDL-cholesterol at 3 and 6 months, $p = 0.03$, $p = 0.004$; ^ $p < 0.001$; ^^ $p = 0.001$; ** significantly different from the control group ($p = 0.003$ for both lipids): LDL-cholesterol was lowered by 7.8% in the control group, with baseline values 17.4% higher in the Nigella group, and HDL-cholesterol was raised by 26% in the control group, with similar baseline values

Bitter Melon

Momordica charantia is a flowering vine in the family Cucurbitaceae, which includes many edible plants such as pumpkin, cucumber and melon. It is a tropical plant that is widely cultivated in Asia, India, East Africa and South America for the fruit which is used in cooking. The fruit is eaten raw, boiled or cooked, for example in curries or with meat. It can be parboiled or soaked in salt water before cooking to reduce the bitter taste.[25-27] The fruit is oblong and resembles a small cucumber. Unripe fruit is green which turns to orange-yellow when ripe,[28] although the size, shape, colour and exocarp characteristics vary depending upon the cultivar and where the plant is grown.[29]

Momordica charantia fruit contains many constituents including bitter and non-bitter cucurbitane triterpenes (momordicosides and momordicines are bitter).[30]

In Ayurveda, Bitter Melon has tonic, stomachic and blood purifier actions, with indications of rheumatism and liver complaints.[4] Although the fruit of *Momordica charantia* is not commonly used in traditional Chinese medicine, there is a reference to it: the sweet(!) pulp of ripe fruit is considered to be cooling and strengthening.[31]

Clinical Studies

The **hypoglycaemic activity of Bitter Melon has been documented** in humans (mostly diabetics). The results have varied, possibly due to small sample sizes, use of varying doses and preparations, as well as the lack of controls.[32,33]

It may be the case that certain patients respond to Bitter Melon. In a 1986 placebo-controlled, crossover study conducted in Sri Lanka, single dose of the juice of deseeded, unripe fruit improved tolerance to glucose in 73% of diabetic participants.[34] In a crossover study conducted in Florida and published in 2017, single dose of Bitter Melon extract produced a reduced postprandial glucose response to oral glucose in 50% of the prediabetic participants. The response rate was not due to individual glucose tolerance.[35] Plasma glucose and insulin levels were not affected in a single-dose, pilot study with non-diabetic, overweight men.[36]

Examples of studies that administered ongoing, moderate doses are outlined as follows and for controlled studies, in Table 3.

Patients	Preparation & Dose	Results	Ref
newly-diagnosed type 2 diabetics; not taking oral hypoglycaemic drugs*	0.5, 1 or 2 g/day of dried unripe deseeded fruit pulp, with a known amount of charantin†; taken for 4 weeks	• serum fructosamine was significantly reduced from baseline for those taking metformin (1 g/day; -5.4%) and for those taking Bitter Melon (2 g/day; -3.1%); results not significant at doses of Bitter Melon lower than 2 g/day • no significant effect on fasting plasma glucose or 2-hour plasma glucose after OGTT for those treated with Bitter Melon	37
type 2 diabetics; not taking oral hypoglycaemic drugs^	2 or 4 g/day of dried unripe deseeded fruit pulp, with a known amount of charantin†; taken for 10 weeks	• HbA1c was significantly reduced from baseline for those taking glibenclamide (2.5 mg/day; -18.3%) and for those taking Bitter Melon (2 g/day: -10.3%; 4 g/day: -13.9%) • fasting blood glucose was significantly reduced from baseline for those taking glibenclamide (2.5 mg/day; -18.5%) and those taking Bitter Melon (2 g/day: -8.4%; 4 g/day: -10.7%) • no effect on 2-hour plasma glucose after OGTT for those treated with Bitter Melon	38
newly-diagnosed type 2 diabetics; not taking oral hypoglycaemic drugs§	2 g/day of dried fruit pulp for 3 months	• HbA1c was significantly reduced from baseline for those taking Bitter Melon (-9.0%) • no effect on fasting blood glucose • significant reduction in 2-hour plasma glucose after OGTT (-22.8%) • results were unchanged in the placebo group	39
type 2 diabetics taking oral hypoglycaemic drugs‡	infusion: 3 g/day of dried fruit with seed for 12 weeks	• HbA1c was significantly reduced from baseline for those taking Bitter Melon (-7.6%); no change in those consuming the control (black tea) • no effect on fasting blood glucose	40

Table 3. Hypoglycaemic activity of Bitter Melon in controlled studies with type 2 diabetes patients.

Notes: * advised about diet and lifestyle modification; † charantin is a steroidal glycoside;[41] ^ managed with diet and exercise only; § participants did not engage in heavy exercise or were sedentary, they maintained their normal physical activity and all received nutritional therapy; ‡ diet and physical activity were maintained throughout the study **Abbrev:** OGTT: oral glucose tolerance test

A randomised, placebo-controlled, crossover study investigated the effect of Bitter Melon in prediabetic individuals. Participants took Bitter Melon (2.5 g/day of dried fruit with skin and seed) and dried cucumber powder (as placebo) for periods of 8 weeks with a washout of 4 weeks. The Bitter Melon and placebo were mixed in water with flavouring and sweetener and consumed after the main meal. After 'treatment' the difference in fasting blood glucose levels between Bitter Melon and placebo was significant (-0.3 mmol/L; $p \leq 0.01$). The change in fasting blood glucose differed between individuals: the decrease was found to be greater in those with a higher baseline fasting blood glucose level. Overall, the change in fasting blood glucose had a range from -1.75 to 0.92 mmol/L. Although participants were screened for prediabetes, some had normal fasting blood glucose levels at baseline. There were no effects found for other glycaemic parameters.[42]

Powder of dried, mature Bitter Melon whole fruit (4 g/day) taken for 21 days significantly reduced postprandial blood glucose levels in 8 type 2 diabetics compared to baseline values. These patients were taking a reduced dose of glibenclamide for the duration of the study. They were also advised about diet and exercise.[43]

The hypoglycaemic effect of Bitter Melon (0.8 or 1.6 g/day) was evaluated during a retrospective study in 42 type 2 diabetic patients who were also taking oral hypoglycaemic drugs. Fasting blood glucose was reduced by 1.63 mmol/L (16.6%) in patients who were taking 1.6 g/day of dried fruit powder, and 1.15 mmol/L (12.8%) among these who received 0.8 mg/day. The results were statistically significant for the total (all patients; -1.48 mmol/L (-14.9%)). Median duration of treatment with Bitter Melon was 35 days. Nineteen patients had their fasting blood glucose levels reduced to meet the target therapeutic level (less than 7.2 mmol/L). Median duration of Bitter Melon use among this group was 189.5 days.[44]

In the two trials that assessed these parameters,[38,39] a lipid-lowering effect was, for the most part not demonstrated, although at a dose equivalent to 4 g/day of dried unripe deseeded fruit pulp, Bitter Melon significantly reduced triglycerides from baseline.[38]

Cinnamon

Several species of Cinnamon are used medicinally, as well as for culinary purposes, throughout the world.

Cinnamomum verum (*C. zeylanicum*) inner bark is traditionally used in Britain for flatulent dyspepsia, anorexia, intestinal colic and worm infestation.[45] The Eclectic physicians considered three species suitable for use as Cinnamon: *Cinnamomum verum*, *C. cassia*, *C. saigonicum*. In addition to the digestive applications listed above, they used it for common cold, influenza, cold extremities, uterine haemorrhage and menorrhagia.[46] Many traditional sources note that the barks of *Cinnamomum verum* and *C. cassia* have similar properties and many of the same uses,[47-49] and they have been used interchangeably,[50] although in early times *C. cassia* was described as a somewhat inferior substitute for *C. verum* (bark and oil) this is not the case more recently.[51]

The bark of *Cinnamomum verum* and *C. cassia* share similarities in chemical composition, but there are also notable differences.

MediHerb® Research: Phytochemistry of Cinnamon Species

Being not only medicinal but also a major spice globally, one might expect that the phytochemistry of the main species of Cinnamon was well known, and this is to a large extent true for the volatile oil, which contains as its main constituent cinnamic aldehyde (cinnamaldehyde), which confers the well-known and characteristic aroma of Cinnamon.

However, when it comes to the non-volatile compounds in Cinnamon, the situation is more complex. Aqueous extracts of Cinnamon contain traces of the aroma components but are rich in procyanidins (condensed tannins), which may be at least partly responsible for the hypoglycaemic activity (*see below*).

MediHerb®'s research team, which include phytochemists and pharmacognosists, worked for two years to unravel some of the complexities of the procyanidins in different species of Cinnamon. This work included:[52,53]

- development of an LC-MS (liquid chromatography-mass spectrometry) method that allows for the identification of *Cinnamomum verum*, *C. cassia*, *C. burmanni* and *C. loureiroi* extracts based on their procyanidin profile;
- LC-MS profiling of volatiles;
- collaborative work with researchers at the University of Reading (United Kingdom) and the University of Mississippi;
- DNA authentication at a leading US laboratory of bark samples (partially successful) and extracts (unsuccessful);
- assessment of a range of raw materials.

A key finding from this work was that some raw materials traded on the international market, in particular extracts and powdered barks, are not derived from the species of Cinnamon they claim to be derived from. Products made from these raw materials could therefore contain other species with different therapeutic properties and/or potential safety concerns.

Another focus of MediHerb®'s work has been the content of coumarin in Cinnamon extracts. Coumarin is a fragrant benzopyrone lactone that occurs naturally in many plants - the compound coumarin *should not* be confused with the entire class of related compounds, known as coumarins. Safety concerns have been raised about coumarin and several jurisdictions limit the amount of coumarin in food and herbal medicines (*see Safety section below*).

MediHerb's work confirmed that *Cinnamomum verum* (synonym: *C. zeylanicum*) is the only widely traded species of Cinnamon that is naturally low in coumarin,[52,53] and therefore the species to use in Cinnamon-containing products to avoid the coumarin-associated potential safety concerns.

In addition, low-coumarin extracts from other species are available but have undergone additional treatment including solvent extraction leaving high residues in some samples.[54] Production steps employed by some extract manufacturers to produce low-coumarin Cinnamon extracts have severely impacted on the procyanidin profile and levels.[53]

Type A procyanidins may be important constituents contributing to a hypoglycaemic activity of Cinnamon. *In vitro* testing found these compounds substantially increased glucose metabolism using the epididymal fat cell assay. Aqueous extracts of bark samples of *Cinnamomum verum*, *C. cassia*, *C. burmanni* and *C. loureiroi*, as well as fractions and isolated compounds (primarily from *C. burmanni*) were evaluated. The ***in vitro* activity of the different species of Cinnamon tested were not significantly different**,[55] suggesting that the different species of Cinnamon, possibly containing similar levels of type A procyanidins, had a similar hypoglycaemic activity *in vitro*.

Clinical Studies: Diabetes

Cinnamon has been investigated in many clinical trials throughout the world as a support for the treatment of type 2 diabetes. Most often, *Cinnamomum cassia* has been administered, but in many studies the species of Cinnamon is not defined. *The results from clinical trials involving type 2 diabetes patients are summarised in Table 4*. This includes trials where the product was defined as, or was likely to be, dried powder, or the authors provided the dried herb equivalent of the administered extract. (Trials using selective, specialised extracts, or *C. burmanni* are excluded.) Participants were taking hypoglycaemic medications (not insulin) or they were controlled by medications and/or diet, but in many studies, changes to diet and physical exercise were not recorded or taken into consideration in the results. In many trials patients were asked to maintain their normal lifestyle or were advised to make improvements.

The results of 9 of these trials,[56-64] and an additional one (that combined Cinnamon with a small amount of zinc gluconate and tricalcium phosphate)[65] were pooled in a meta-analysis.[66] The 10 controlled trials involved 543 patients, and Cinnamon (mostly *C. cassia*) at doses of 1 to 14.4 g/day equivalent to dried bark,[58,66] taken for periods ranging from 4 weeks to 4 months significantly reduced fasting plasma glucose (-1.35 mmol/L). The authors noted that the results were heterogeneous and publication bias may have occurred. No significant effect on HbA1c was observed.[66] Another meta-analysis,[67] that analysed 6 of these trials,[56,57,59,60,62,63] involving 435 patients also found a significant decrease in fasting blood glucose (-0.84 mmol/L) in comparison to placebo. The decrease in HbA1c was also significant. This analysis also found the results to be heterogeneous, due possibly to the variation in baseline characteristics (e.g. years since diagnosis, baseline glycaemic parameters, BMI). The results of 5 trials were pooled for fasting blood glucose and HbA1c. The dose of *C. cassia* prescribed ranged from 1 to 6 g/day equivalent to dried bark with treatment from 40 days to 4 months.[67]

Cinnamomum verum: 2 trials (2012, 2014)
• Cinnamon (3 g/day, for 8 weeks) produced significant decreases in fasting blood glucose (9%) and HbA1c (6%) from baseline. The reductions were not significant compared to the placebo group.[68] Another trial using the same dose of powder, ingested as an infusion in black tea for the same period, did not have significant effects on these parameters.[69]
Cinnamomum cassia: 11 trials (2003-2015)
• Five trials found a lowering of fasting blood glucose,[56-58,70,71] and in 3 trials, HbA1c was reduced.[58-60] The results were significant compared to baseline values, and in some trials the results were significant compared to placebo/control. The dose ranged from 1.0 to 14.4 g/day (equivalent to dried bark), taken for 40 days to 4 months (5 trials used a dose of 1-3 g/day). • No significant effect was found in 5 trials for fasting blood glucose where Cinnamon was taken at 1-2 g/day (equivalent to dried bark) over periods of 6 weeks to 3 months.[59,61-63,72] No effect was found for HbA1c.[57,61-63,72]
Cinnamon (species not defined): 7 trials (2010-2018)
• Six trials found a lowering of fasting blood glucose from baseline.[64,73-77] In some trials it was noted that the results were also significant compared to placebo.[73,75,77] In the other trial, fasting blood glucose decreased in those treated with Cinnamon, and increased in the placebo group, but the difference did not reach statistical significance (p = 0.06).[78] The dose ranged from 1 to 3 g/day (equivalent to dried bark), taken for 1 to 3 months. • Three trials also measured HbA1c,[74,77,78] and significant effect was found in one trial.[77]

Table 4. Effect of Cinnamon on some glycaemic parameters in people with type 2 diabetes participating in controlled trials.

Although more rigorous trials are needed, the potential hypoglycaemic effect of Cinnamon does not appear to be dose dependent. In two of these trials[56,58] several doses of *C. cassia* were compared and similar activity was demonstrated regardless of dose (*see Table 5*).[56]

Dose (dried herb equivalent; g/day)	Fasting Blood Glucose (mmol/L)	
	Baseline	After Treatment (% change)
Study 1[56]		
1.0	11.6	8.7 (-24.9%) *
3.0	11.4	9.4 (-17.6 %) *
6.0	13.0	9.2 (-29.0%) *
Study 2[58]		
4.8	9.00	7.99 (-11.1%) ‡
14.4	11.21	9.59 (-14.4%) ‡

Table 5. Results for two controlled trials using several doses of Cinnamon in patients with type 2 diabetes.

Notes: No significant changes were observed for the placebo groups at the end of treatment compared to baseline; baseline fasting blood levels ranged from 12.1 to 16.6 mmol/L for the three placebo groups in Study 1, and was 8.9 mmol/L in Study 2. * $p < 0.05$ ‡ $p < 0.01$

A beneficial effect on lipids has not been conclusively demonstrated. Of the 20 trials outlined in Table 4, a lipid-lowering effect was observed for all or some lipids in 8 of the 15 trials that measured these parameters. The results were significant compared to baseline or in comparison with placebo/control.[56,58,64,69,74,75,77,79] One trial produced unreliable results.[76]

Clinical Studies: Metabolic Syndrome

Individuals from northern India with metabolic syndrome were treated with capsules of Cinnamon powder (3 g/day) for 16 weeks in a randomised, double-blind, placebo-controlled trial. By the completion of the trial, 13 of the 116 participants had dropped out. During the run-in period they were advised on diet and exercise and they were not taking hypoglycaemic drugs. At baseline, no significant differences were found between the groups, except that weight and body mass index were significantly higher in the Cinnamon group (82.1 kg vs 89.1 kg and 31.2 kg/m^2 vs 33.6 kg/m^2). Fasting blood glucose and HbA1c were significantly lowered as a result of treatment with Cinnamon, compared to placebo. *See Table 6*.[80] Significantly greater improvements were also found for blood lipids, body weight, adiposity and blood pressure.

	Cinnamon		Placebo	
	Baseline	After Treatment (% change)	Baseline	After Treatment (% change)
fasting blood glucose (mmol/L)	5.7	5.2 (-8.7%)	5.6	5.5 (-2.0%) †
HbA1c (%)	6.15	5.77 (-6.2%)	6.03	6.04 (0.2%) *

Table 6. Hypoglycaemic activity of Cinnamon in patients with metabolic syndrome.

Notes: † the Cinnamon and placebo group raw results for fasting blood glucose in the intention to treat and the per protocol analyses were the same; in addition, the mean differences were similar when the results were adjusted for baseline BMI and were significant in comparison with placebo (p = 0.001); * raw results significant (p = 0.011), the mean difference was also significant when the results were adjusted for baseline BMI (p = 0.023)

Fenugreek

Whole Fenugreek seed (*Trigonella foenum-graecum*) has been used in a number of traditional systems for a range of applications. Fenugreek is also used as a culinary spice in many cultures.

Constituents of Fenugreek seed include steroidal saponins, flavonoids, lipids (fatty acids), sterols, protein, amino acids, an alkaloid, proteinase inhibitors and carbohydrates.[47,81] Carbohydrates, including fibre and gum, make up a substantial proportion of the constituents (about 50%).[82,83]

The non-protein amino acid 4-hydroxyisoleucine is thought to be one of the major active constituents in whole Fenugreek seed. 4-Hydroxyisoleucine is not found in mammalian tissues, and is only present in some plants,

such as species of *Trigonella* and including the seed of Fenugreek.[84] The amount varies, for example, from 0.015% to 0.6% in dried seed depending upon where the plant is grown.[84,85]

4-Hydroxyisoleucine was shown to stimulate glucose-dependent insulin secretion *in vitro*, having a direct effect on pancreatic islets. It has also been investigated *in vivo* (experimental models): high oral doses of 4-hydroxyisoleucine decreased plasma insulin, glucose and lipid levels, and reduced body weight in obese, insulin-resistant mice.[86]

A 2001 placebo-controlled trial found that aqueous alcoholic extract of Fenugreek seed taken for 2 months significantly improved glycaemic control, particularly fasting blood glucose, insulin resistance and insulin sensitivity, in those with newly-diagnosed type 2 diabetes. About 80% of patients were taking oral hypoglycaemic drugs. Treatment with Fenugreek extract also significantly decreased serum triglyceride levels.[87] Aqueous alcoholic extract of Fenugreek seed significantly improved fasting blood glucose by 24.6% (9.07 to 6.84 mmol/L) and HbA1c by 9.38% (7.93 to 7.18%) after 12 weeks in unmedicated type 2 diabetics. Significant decreases were also observed for total cholesterol, triglycerides and LDL-cholesterol.[88] In both trials, the extract was not defined in terms of the dried herb equivalent of Fenugreek seed.

Fifty-four type 2 diabetic patients not well controlled by oral hypoglycaemic drugs were randomly divided into 4 groups: placebo, Cinnamon, Fenugreek, Cinnamon + Fenugreek, and treated for 40 days. Participants were asked to adhere to a diet program. There were no significant differences between the groups at baseline for age, body weight or time since diagnosis. At the end of treatment, 2 hour-postprandial glucose levels had significantly decreased from baseline for all groups including those receiving placebo. The **decrease in the group receiving the combination of herbs was significant** compared to placebo (-24.8% vs -9.8%; $p < 0.05$). The decreases in this parameter for the Cinnamon and Fenugreek groups were 20.0% and 21.0%, respectively (significant compared to baseline only). Patients took capsules containing powdered Cinnamon bark (3 g/day; species undefined), filtered decoction made from Fenugreek seed (15 g/day) or combination of the two herbs at the same dosage. HbA1c levels were also significantly improved in those receiving Cinnamon and the herbal combination, compared to placebo.[89]

In a randomised, double-blind trial Fenugreek seed extract **reduced spontaneous dietary fat consumption** in healthy overweight volunteers. The aqueous alcoholic extract contained known quantities of steroidal saponins, trigonelline and 4-hydroxyisoleucine, and was taken for 6 weeks. The daily dose of 4-hydroxyisoleucine was 17 mg. Energy intake was assessed from dietary records. At the end of the trial there was a significant difference between the Fenugreek seed extract group compared to those receiving the placebo for dietary fat consumption (expressed as fat-REI/TEE (fat reported energy intake/total energy expenditure): 0.26 vs 0.30, respectively; $p < 0.05$). At the end of the trial the fasting insulin to glucose ratio was significantly lower for Fenugreek extract in comparison to placebo.[90] Dietary fat consumption was also decreased in healthy, normal-weight volunteers who took the same extract at the same dosage for 14 days. Diet and physical activity were assessed before and at the end of treatment, using a 7-day record.[91]

Safety

Nigella

Nigella seed and its constituents have low toxicity, particularly at therapeutic doses.[92,93]

Mild gastrointestinal discomfort can occur occasionally, and it may be best taken after meals.[94]

As there are traditional references to Nigella causing terminations when given in high doses, it is contraindicated in pregnancy.[4,95,96] It may also be best avoided in women wishing to conceive: animal studies have demonstrated an antifertility effect (preventing pregnancy),[96,97] although not at lower doses.[98]

Bitter Melon

There are historical references to Bitter Melon fruit being used as an abortifacient, for example, in India.[99,100] Contemporary practitioners of Ayurveda also recommend Bitter Melon fruit not be used in pregnancy (due to the 'bitter and descending effect').[95] Animal studies refer to adverse effects during pregnancy, although the results are not consistent for oral use of the fruit. The constituents most consistently cited for the abortifacient activity are found in the seed (proteins).[101-103] Teratogenic effects have been demonstrated using extract of whole unripe fruit (pulp and seed)[104] and an antifertility effect is suggested by the prolongation of the oestrus cycle and dioestrous phase in mice fed an extract of the fruit.[105] An antifertility effect has been demonstrated in male animals after ingesting fruit juice and extract of deseeded fruit.[106,107]

In two small clinical trials involving people with type 2 diabetes, treatment with Bitter Melon did not significantly alter liver enzymes. Patients received 2 g/day of dried fruit pulp for 3 months or 6 g/day of dried deseeded unripe fruit for 16 weeks.[39,108]

There is a theoretical concern for people with glucose-6-phosphate dehydrogenase deficiency, as the seeds of *Momordica charantia* contain vicine,[109] (a constituent associated with causing favism in this population). (This would not be a concern if deseeded fruit were consumed.)

Cinnamon

Cinnamomum verum bark is traditionally contraindicated in pregnancy,[47,110] perhaps due to its ability to induce uterine contractions,[46,111] although the need for the contraindication has been questioned.[47]

Two animal studies have investigated the effect on adult offspring of the maternal intake of an aqueous extract of Cinnamon during lactation. Some beneficial effects, such as lower visceral fat mass, occurred in one study, although the other study found adverse effects (such as higher visceral fat mass and increased lipid accumulation) when the rats were assessed at an older age.[112,113] Assuming the administered dose (400 mg/kg/day) refers to the dried herb equivalent of the extract, this corresponds to approximately 5.3 g/day for a 70-kg human.

Cinnamon is contraindicated in known allergy/hypersensitivity to Cinnamon or Peruvian balsam.[110]

A review of controlled clinical trials involving people with diabetes found adverse reactions to Cinnamon (predominantly *C. cassia*) were generally mild and infrequent.[114] A few, more serious adverse effects have been reported.[115]

There have been concerns about the safety of coumarin. *Cinnamomum cassia* bark can contain up to 1.2% coumarin, although often lower levels are present. *Cinnamomum verum* contains only a trace amount. In 2004, the European Food Safety Authority recommended a coumarin daily intake limit of 0.1 mg/kg body weight.[116,117] The Australian Therapeutic Goods Administration has imposed a limit of no more than 0.001% (10 ppm) of coumarin in listed (low-risk) medicines.[118] The concern centres around hepatotoxicity which has been demonstrated in animals. In addition, clinical data from patients treated with coumarin have revealed the existence of a subgroup which is sensitive to developing hepatotoxicity. This group may amount to a single-digit percentage of the population.[119] The doses of coumarin utilised in these clinical studies were generally well in excess of the amount of coumarin ingested from Cinnamon in food or herbal medicines. It is advised that for ongoing ingestion, species of *Cinnamomum* with a low coumarin content, such as *Cinnamomum verum*, be used.[118,120]

Fenugreek

Ongoing administration of Fenugreek whole or defatted seed in doses up to 100 g/day in patients and healthy volunteers found no liver or kidney toxicity. Main side effects were transient symptoms of gastrointestinal discomfort.[121,122]

Toxicological studies in animals suggest low acute toxicity for ethanol extracts of Fenugreek and for two isolated constituents (4-hydroxyisoleucine and trigonelline) given orally.[123,124] A Fenugreek seed extract containing 40% 4-hydroxyisoleucine did not exhibit genotoxicity in a standard battery of tests.[125]

Although the animal research is not consistent (in terms of an antifertility effect),[123] it is recommended that Fenugreek not be taken doses in higher than that used in cooking, during pregnancy or in couples wishing to conceive.

Studies are not consistent or conclusive but Fenugreek extracts may have an inhibiting effect on the thyroid. Results include: inhibiting T3 production (but increased thyroxine (T4) concentration) in normal adult mice and rats,[126,127] suppressing the hypothalamic-pituitary-thyroid axis (e.g. decreased TSH, free T3 and free T4 levels and regressed thyroid gland) in normal and type 1 diabetic rats,[127] and decreasing thyroid hormones in hyperthyroid animals.[128] Until further information is available, caution is advised with high doses of Fenugreek seed (> 20 g/day) in patients with low thyroid activity.[129]

Allergy to Fenugreek (powder) has been reported. It may also cause reactions in those with peanut allergy due to cross-reactivity.[130]

Supportive Formulation

These herbs complement each other to support hypoglycaemic and hypolipidaemic actions.

Indications

- Adjunctive treatment for diabetes, metabolic syndrome, glucose fluctuations due to stress, dysglycaemia and prediabetes with an emphasis on early disease stage and/or acute condition.

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