Annotated Literature Review on 10 Ayurvedic Ingredients for Glycemic Response

Research complied by:

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In my research I found no evidence of harm from any of the ingredients. Any adverse reactions were few and far between - and not indicated as significant by the authors. If used appropriately, I would assert that these herbs are generally safe for human consumption (not to be confused with the FDA "GRAS" status). That is my academic opinion. I also take no responsibility for any adverse event that may occur or for any abuse of said botanicals. Use with appropriate observation from your qualified healthcare professional.

~Stephany Morgan

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Contents

COLOR SCHEME:

Studies related to diabetes or glucose management
Safe for human consumption.
Human studies.
Rat studies.

TURMERIC

1. Gupta, S. C., Patchva, S., & Aggarwal, B. B. (2013). Therapeutic roles of curcumin: lessons learned from clinical trials. *The AAPS journal*, *15*(1), 195–218. doi:10.1208/s12248-012-9432-8 retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3535097/

This literature review looked at clinical trials using curcumin (the active component in turmeric) and/or turmeric. In human trials concerning diabetes types 1 and 2, curcumin/turmeric was taken for varying lengths of time (by both large (largest contained 240 participants) or small groups (smallest was a case study with a single participant). One group was able to manage their diabetic microangiopathy for 5 years without insulin when using a curcumin phytosome product called Meriva. One study reported the use of turmeric for 8 weeks with no negative side effects mentioned. In another study turmeric was assessed for its T2DM preventative actions in prediabetic participants. curcumin was taken for 9 months (1.5 g/day dose). 16.4% of those in the placebo group were diagnosed with T2DM, while none in the curcumin-treated group were diagnosed with T2DM. Participants in a diabetic nephropathy trial in the test group took 500 mg of turmeric 3x daily with meals for 2 months. The authors noted attenuation of TGF-beta and IL-8 and proteinuria, and no adverse effects were noted.

2. Velusami, C. C., Boddapati, S. R., Hongasandra Srinivasa, S., Richard, E. J., Joseph, J. A., Balasubramanian, M., & Agarwal, A. (2013). Safety evaluation of turmeric polysaccharide extract: assessment of mutagenicity and acute oral toxicity. *BioMed research international*, *2013*, 158348. doi:10.1155/2013/158348 retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3877592/

Human safety trials are lacking but this rat study found that, “Overall, results indicated that polysaccharide extract of *C. longa* was found to be genotoxically safe and also exhibited maximum tolerable dose of more than 5 g/kg rat body weight.” The maximum tolerable dose is a massive dose. This would be equivalent to a 150 lb person taking 340 grams daily for 14 days- that is just over half a pound of turmeric daily.

3. Qin, S., Huang, L., Gong, J., Shen, S., Huang, J., Ren, H., & Hu, H. (2017). Efficacy and safety of turmeric and curcumin in lowering blood lipid levels in patients with cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Nutrition journal*, *16*(1), 68. doi:10.1186/s12937-017-0293-y retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5637251/

This looked at 7 studies (649 participants). Although it was reviewing the health benefits and actions of turmeric and curcumin on cholesterol in those with cardiovascular risk factors, it did note that of the 649 participants included in the literature review (varying dose levels and trial lengths) only 6 participants in intervention groups experienced adverse effects. They conclude that, “Turmeric and curcumin appeared safe, and no serious adverse events were reported in any of the included studies.”

4. Poolsup, N., Suksomboon, N., Kurnianta, P., & Deawjaroen, K. (2019). Effects of curcumin on glycemic control and lipid profile in prediabetes and type 2 diabetes mellitus: A systematic review and meta-analysis. *PloS one*, *14*(4), e0215840. doi:10.1371/journal.pone.0215840 retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6478379/

This literature review looked at a total of <1,000 participants combined. All studies were done

in Asian countries (except one from Mexico). 4 of the 12 looked at prediabetics, the rest considered type 2 DM. “The preparation forms of curcumin studied in all trials of both prediabetes and T2DM included curcuminoid extract 300 mg to 1.8 g per day, turmeric powder 1.5 g to 2.4 g per day, curcumin amorphous dispersion 500 mg per day, standardized curcuminoids preparation 600 mg per day, and nano-curcumin 80 mg per day. … Curcumin improves insulin sensitivity by affecting three processes. Firstly, curcumin ameliorates glucose homeostasis by triggering glucokinase activity in the liver. Secondly, it induces lipid metabolism by raising lipoprotein lipase activity to reduce triglyceride. Thirdly, curcumin affects insulin pathway independently by inducing glucose transporter-4 (GLUT4) expression to increase peripheral glucose uptake.” Curcumin significantly reduced HbA1c (hemoglobin linked to glucose that is used to indicate excessive blood sugar and hence, diabetes) in prediabetics. Curcumin also contributed to a significant improvement in glycemic control in T2DM.

BITTER MELON

1. Efird, J. T., Choi, Y. M., Davies, S. W., Mehra, S., Anderson, E. J., & Katunga, L. A. (2014). Potential for improved glycemic control with dietary Momordica charantia in patients with insulin resistance and pre-diabetes. *International journal of environmental research and public health*, *11*(2), 2328–2345. doi:10.3390/ijerph110202328 retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3945602/

Bitter melon has traditionally been used to treat diabetes/pre-diabetics since the early 1900s in the Dominican Republic, Puerto Rico, and Cuba. In a very small trial in a Puerto Rican clinic, 8 participants were given bitter melon alcoholic extract. Positive effects on blood glucose were observed in two patients, one of which was not diabetic. The literature review also cited a published case study of a woman who was struggling with diabetes despite conventional treatment. The co-administration of bitter melon reduced urine sugar levels and she was able to decrease her dose of chlorpropamide. B. Melon contains polypeptide-p which closely resembles bovine insulin and is colloquially called “plant insulin”. It is believed to be more effective if injected subcutaneously, rather than taken orally. In two small injection trials, blood glucose peaks were delayed (normal insulin peaks 2-3 hours after, plant polypeptide-p administration peaked between 4-12 hours after). “Among non-insulin-dependent diabetics, a water-soluble extract from locally obtained fresh (raw) bitter melon juice has been observed to significantly reduce mean blood sugar levels and correspondingly increase mean insulin levels during a 50 g oral glucose test, compared with standard test of distilled water…. A tea prepared from bitter melon leaves reduced HbA1c levels by 63%.” In another study, bitter melon administered orally significantly decreased HbA1c levels after 4 mo of treatment. It was well tolerated and no differences in liver function were reported between groups. In those with T2DM a single dose was significantly more effective than placebo in reducing mealtime glycemic excursions, and reverted to baseline levels more quickly. To date no deaths have been reported from B. melon, and only mild adverse effects have been observed (diarrhea and abdominal pain which ceases with discontinuation of B. melon). “Rare cases of hypoglycemic coma and convulsions have been reported in children drinking bitter melon tea.” One case report suggests that it may cause paroxysmal atrial defibrillation with a score that suggested it was causative, not correlative. It is contraindicated in pregnancy and its long term use hasn’t been studied.

2. Joseph, B., & Jini, D. (2013). Antidiabetic effects of *Momordica charantia* (bitter melon) and its medicinal potency. *Asian Pacific Journal of Tropical Disease*, *3*(2), 93–102. doi:10.1016/S2222-1808(13)60052-3 retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4027280/

It was first demonstrated and later confirmed that oral administration of B. Melon instigates the secretion of insulin from pancreatic beta cells. The alcoholic extract showed improvement in the islets of Langerhans in rat studies. Other studies have shown it can stimulate insulin production and cause glucose uptake in the liver. A rabbit study showed it can stimulate peripheral cell glucose uptake. This literature review criticizes the existing human studies as being small, poorly designed, having poor methodology, and largely lacking in controls. A human uncontrolled trial with 42 participants taking oral capsules of freeze dried wild B. melon found it was statistically significant for improving metabolic syndrome. It ran 3 months. A 26 subject randomized design trial lasting 4 weeks found statistical significance in improving fructosamine levels when B. melon tablets were given. Another small human trial using methanol whole fruit extract found statistical significance when combined with half doses of metformin or glibinclamide at potentiating hypoglycemia.

3. Dans AM, Villarruz MV, Jimeno CA, Anthony M, Javelosab U, Chuaa J, et al. et al. The effect of *Momordica charantia* capsule preparation on glycemic control in type 2 diabetes mellitus needs further studies. J Clin Epidemiol. 2007;60:554–559 retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17493509

A human trial looking at T2 Diabetics: there was no statistical significance (authors call for a larger participant size) however it ran 3 months and there were only mild adverse events and these were few.

4. Yin, R. V., Lee, N. C., Hirpara, H., & Phung, O. J. (2014). The effect of bitter melon (Mormordica charantia) in patients with diabetes mellitus: a systematic review and meta-analysis. *Nutrition & diabetes*, *4*(12), e145. doi:10.1038/nutd.2014.42 retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4315906/

This one does not support the use of bitter melon: A total of four RCTs, each with 40–66 participants, followed between 4 and 12 weeks were identified in this meta-analysis. Overall risk of bias for each article included was determined to be unclear. In total, 208 participants with type 2 DM (mean age of 56.5 years) were evaluated. Compared with no treatment, bitter melon did not significantly lower A1C (WMD −0.13%, 95% CI −0.41 to 0.16) nor fasting plasma glucose (FPG) 47 (WMD 2.23 mg dl^{-1}, 95% CI −14.91 to 19.37).

5. Mardani, S., Nasri, H., Hajian, S., Ahmadi, A., Kazemi, R., & Rafieian-Kopaei, M. (2014). Impact of Momordica charantia extract on kidney function and structure in mice. *Journal of nephropathology*, *3*(1), 35–40. doi:10.12860/jnp.2014.08 retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3956906/

Although this is a mouse trial, the large doses did not cause kidney problems, but prolonged administration was nephrotoxic, however the doses were quite large. This gives some indication for safety.

I could not find human safety trials specifically.

MELIA AZADIRACHTA

(synonym: Azadirachta indica) https://www.uniprot.org/taxonomy/124943
There are no existing human or safety trials [that I was able to find] upon searching multiple databases both via Google and university library databases.

1. Halim, EM. (2003). Lowering of blood sugar by water extract of Azadirachta indica and Abroma augusta in diabetes rats. *Indian Journal of Experimental Biology,* 41(6), 636-640. Retrieved from http://nopr.niscair.res.in/handle/123456789/23329
Study can also be found here: https://www.ncbi.nlm.nih.gov/pubmed/15266913

This study looked at the effects of the two plants used together. The relevance is that it uses Melia azardirachta, and since your product is a multi-herb formulation, this study suggests promise for the synergistic action of Neem with the other plants which have anti-diabetic action.
"Combination (1:1) of water extract of dried powder of root and leaves (200 mg/kg body wt) of A. augusta and A. indica respectively was administered orally to alloxan diabetic rats once a day for 8 weeks. This treatment caused significant lowering of blood sugar in fasted [*sic]* as estimated by glucose tolerance test. The treatment resulted in a significant reduction in serum lipids. Aqueous extract also decreased the formation of lipid peroxides estimated as thiobarbituric acid reactive substance, (TBARS), and increased antioxidants (superoxide dismutase, catalase, glutathione peroxidase and glutathione transferase) in erythrocytes. There was reduction in LPO as TBARS in heart, liver, kidney, and muscles. It also prevented decrease in body weight. Present study showed that Abroma augusta roots and A. indica leaves when given together as water extract had hypoglycaemic action and had better effect than given alone."

2. Ponnusamy, S., Haldar, S., Mulani, F., Zinjarde, S., Thulasiram, H., & RaviKumar, A. (2015). Gedunin and azadiradione: Human pancreatic alpha-amylase inhibiting limonoids from neem (azadirachta indica) as anti-diabetic agents. *PLoS One, 10*(10) doi:http://dx.doi.org/10.1371/journal.pone.0140113

This one used human cells but it was not a human trial.

"Human pancreatic *α*-amylase (HPA) inhibitors offer an effective strategy to lower postprandial hyperglycemia via control of starch breakdown. Limonoids from *Azadirachta indica* known for their therapeutic potential were screened for pancreatic α-amylase inhibition, a known anti-diabetic target. Studies were carried out to reveal their mode of action so as to justify their hypoglycemic potential. Of the nine limonoids isolated/semi-synthesized from *A.indica* and screened for *α*-amylase inhibition, azadiradione and exhibited potential inhibition… In conclusion, results obtained from this study suggest, azadiradione and gedunin to be lead HPA inhibitory molecules. Thus, the hypoglycemic property exhibited by *A. indica* could be justified by HPA inhibition as it could be one of the mechanisms of action. Moreover, this comprehensive study scientifically validates these natural products thereby enabling a better insight with respect to their structure-activity relationship. The study gains importance as these limonoids could be used to design better drug candidates in development of newer inhibitors of HPA for controlling starch digestion in order to reduce post-prandial hyperglycemia."

3. Martínez, N., Rodríguez, Y., Salguero, O., Requena, D., Triana, L., & Pérez-Ybarra, L. (2014). A study of hypoglycemic effects of azadirachta indica (neem) in human blood

cells. *Emirates Journal of Food and Agriculture, 26*(7), 623-629. Retrieved from https://search.proquest.com/docview/1543803979?accountid=158302

“The test in vitro carried out with the aqueous extract of the plant A. indica in a normoglycemic medium with human blood cells evidenced a hypoglycemic effect”. The application of neem reduced blood glucose levels in the sample compared to controls.

SYZYGIUM CUMINI

Snonyms found from https://www.uniprot.org/taxonomy/260142

Human research is limited, most is outdated (1800’s case studies, early studies that do not meet current clinical guidelines, and very small trials post 1980’s).

1.Claudio, C. T., Weinert, L. S., Daniel, C. B., Ricken, C., & al, e. (2004). Syzygium cumini (L.) skeels in the treatment of type 2 diabetes. *Diabetes Care, 27*(12), 3019-20. Retrieved from https://search.proquest.com/docview/223056198?accountid=158302

This human trial found that tea prepared from the leaves of this plant was “pharmacologically inert” and had no effect on fasting blood glucose. There are a couple problems with this study: one, they used the leaves, not the fruit parts (seed, pulp seed coat, kernel). Two, they used an aqueous tea, not a methanolic extract. Furthermore, they used 2 grams of leaf per liter. Normally, most herbal teas require one gram per cup of water, so their dose was extremely low. This study was designed to fail.

2. Helmstädter. (2008). Syzygium cumini (L.) Skeels (Myrtaceae) against diabetes - 125 years of research, (2), 91–101. https://doi.org/10.1691/ph.2008.7335 retrieved from https://www.ingentaconnect.com/content/govi/pharmaz/2008/00000063/00000002/art00001?crawler=true

“Srivastava et al. (1983) treated 28, not further specified “severe diabetic patients” with 4 to 24 g S. cumini seed powder TDS in gelatine capsules and reported a significant reduction in mean fasting (– 18%) and post-prandial (– 32%) blood sugar levels. Five patients developed adverse drug reactions, including nausea, diarrhoea, and epi- gastric pain.” In a 1993 study, 30 participants with non-insulin dependent diabetes mellitus were given intervention. No control group was mentioned. 12 g seed powder was given. After three months results from glucose tolerance test (GTT) were greatly improved. “One and two hour values were reduced by up to 30% after two months of treatment compared to control. It was concluded that the drug “has definite, moderate hypoglycaemic effect comparable to effect of chlorpropamide”. The seed powder did not show any side effects in this study”. They cited another study that used the leaf (as in the poorly done study above) and that study did not demonstrate any effect on blood glucose. This study was done by the same authors above.

3. Sahana DA, Shivaprakash G, Baliga R, et al. Effect of Eugenia jambolana on plasma glucose, insulin sensitivity and HDL-C levels: Preliminary results of a randomized clinical trial. J Pharm Res 2010;3:1268–1270.

15 patients with type 2 DM (newly diagnosed). The standardized seed powder caused a significant decrease in the fasting blood sugar, insulin resistance, and increase in HDL cholesterol after 3 months (when compared to the baseline). After 3 months and 6 months, there was no significant reduction in the postprandial blood sugar and glycosylated hemoglobin when compared to the baseline. Total cholesterol, triglycerides and LDL did not change.

4. Baliga, M. S., Fernandes, S., Thilakchand, K. R., D'souza, P., & Rao, S. (2013). Scientific Validation of the Antidiabetic Effects of Syzygium jambolanum DC (Black Plum), a Traditional Medicinal Plant of India. The Journal of Alternative and Complementary Medicine, 19(3), 191–197. https://doi.org/10.1089/acm.2011.0752 retrieved from: https://pdfs.semanticscholar.org/3c81/799df811e7b2a2f24cf1d999efbc885b4620.pdf

This is a literature review that looks at animal and human trials and discusses the mechanisms of action. They conclude, "This review includes the validated antidiabetic effects of Jamun and some of its compounds. Emphasis is also placed on addressing the various mechanisms of action contributing to the pharmacological effects and the aspects that need future investigations for Jamun to be of clinical use."

Note: I've included this source because the information is good, although it does count as clinical research. It was a source for me because I used their references to help me track down studies. https://www.naturalremedy.com/Syzygium%20cumini.pdf

AMLA

Synonym Emblica officinalis/Indian Gooseberry.
https://www.uniprot.org/taxonomy/296036

1. Akhtar, M. S., Ramzan, A., Ali, A., & Ahmad, M. (2011). Effect of Amla fruit (Emblica officinalisGaertn.) on blood glucose and lipid profile of normal subjects and type 2 diabetic patients. International Journal of Food Sciences and Nutrition, 62(6), 609–616. https://doi.org/10.3109/09637486.2011.560565 retrieved from https://www.researchgate.net/publication/51053902_Effect_of_Amla_fruit_Emblica_officinalis_Gaertn_on_blood_glucose_and_lipid_profile_of_normal_subjects_and_type_2_diabetic_patients

"The present study evaluated the anti-hyperglycemic and lipid-lowering properties of Emblica officinalis Gaertn. fruit in normal and diabetic human volunteers. The results indicated a significant decrease ($P < 0.05$) in fasting and 2-h post-prandial blood glucose levels on the 21st day in both normal and diabetic subjects receiving 1, 2 or 3 g E. officinalis powder per day as compared with their baseline values. Significant ($P < 0.05$) decreases were also observed in total cholesterol and triglycerides in both normal and diabetic volunteers on day 21 that were given either 2 or 3 g E. officinalis powder per day. However, diabetic volunteers receiving only 3 g E. officinalis powder exhibited a significant ($P < 0.05$) decrease in total lipids on day 21. Both normal and diabetic volunteers receiving 2 or 3 g E. officinalis powder significantly ($P < 0.05$) improved high-density lipoprotein-cholesterol and lowered low-density lipoprotein-cholesterol levels." No negative impacts on blood glucose was observed in any of the subjects (diabetic and non-diabetic) at any dose. An added benefit is that the fruit powder, besides being able to maintain a normal range of blood glucose in the participants, can also act as a nutritional supplement that can compensate for mineral deficiencies that occur as a result of diabetic osmotic diuresis. There were 32 subjects in this trial.

2. Chen TS, Liou SY, Wu HC, Tsai FJ, Tsai CH, Huang CY, et al. Efficacy of epigallocatechin- 3-gallate and Amla (Emblica officinalis) extract for the treatment of diabetic-uremic patients. J Med Food;14:718-23.

This study concluded that administration of ECGC with Amla improved diabetic indices and suggested that it is a safe and effective treatment for uremic patients with diabetes. As cited in "Emblica officinalis (Amla) a review of potential therapeutic applications. Retrieved from: https://www.greenpharmacy.info/index.php/ijgp/article/view/272

2. Fatima, N., Hafizur, R. M., Hameed, A., Ahmed, S., Nisar, M., & Kabir, N. (2015). Ellagic acid in Emblica officinalis exerts anti-diabetic activity through the action on β-cells of pancreas. European Journal of Nutrition, 56(2), 591–601. https://doi.org/10.1007/s00394-015-1103-y retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26593435

This is a rat study. It used the methanolic extract of Amla to treat the rats and found a dose-dependent increase in insulin, and an increase in insulin-to-glucose ratio. EO 250 mg per kg increased pancreatic beta cell size, and 500 mg/kg increased the number of pancreatic beta cells. Additionally, Ellagic acid from Amla "stimulated glucose-stimulated insulin secretion from isolated islets and decreased glucose intolerance in diabetic rats".

They conclude “Ellagic acid in EO exerts anti-diabetic activity through the action on β-cells of [the] pancreas that stimulates insulin secretion and decreases glucose intolerance.”

3. Upadya, H., Prabhu, S., Prasad, A., Subramanian, D., Gupta, S., & Goel, A. (2019). A randomized, double blind, placebo controlled, multicenter clinical trial to assess the efficacy and safety of Emblica officinalis extract in patients with dyslipidemia. BMC Complementary and Alternative Medicine, 19(1). https://doi.org/10.1186/s12906-019-2430-y retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30670010 and full text from https://proxy.lirn.net/MuseProxyID=mp01/MuseSessionID=000hege/MuseProtocol=https/MuseHost=search.proquest.com/MusePath/central/docview/2183120927/fulltextPDF/5E212C43129F43AEPQ/1?accountid=158302

Although this study did not set out to evaluate the antidiabetic effects of Alma, they did observe such effects and conclude that Alma may have anti-diabetic properties (however they did not have enough diabetics to make a full conclusion of this action). This study used the fruit and the seeds. I included it for the safety data. Of the 98 subjects, only 4 experienced adverse effects, and those adverse effects were mild and easily “resolved with routine medications”. They conclude that Amla may be “a safer alternative to statins without severe adverse effects”.

PICRORHIZA KURROA

(watch list potential endangerment)
The call for human studies based on preclinical safety occurred only as recently as 2016. As far as I can find, no human clinical trials have yet been published.

1. Krishna, A. B., Manikyam, H. K., Sharma, V. K., & Sharma, N. (2016). Single dose oral toxicity study of Picrorhiza kurroa rhizome extract in Wistar rats. Fundamental Toxicological Sciences, 3(1), 9–12. https://doi.org/10.2131/fts.3.9 retrieved from https://www.researchgate.net/publication/290510190_Single_dose_oral_toxicity_study_of_Picrorhiza_kurroa_rhizome_extract_in_Wistar_rats

“Picrorhiza kurroa is a well-known ayurvedic or herbal medicine which is used very commonly in the treatment of various diseases. Therefore, we studied the oral toxicity of Picrorhiza kurroa
rhizome extract in rats. A single high dose of the extract at 2000 mg/kg body weight was tested on Wistar rats. Mortality/viability and clinical signs were recorded on test day 0 (prior to administration), 7, 14 and at
death. All animals appeared normal from day one to throughout the experimental procedure.
Picrorhiza kurroa rhizome extract is non-toxic to rats and helped in weight gain with LD
50 > 2000 mg/kg body weight. Oral administration of Picrorhiza kurroa is not connected with any toxicologically significant effects and the data could provide satisfactory preclinical evidence of safety to launch a clinical trial on a standardized formulation of the

plant extracts."
This study is significant because it found no oral toxicity and is the study that found preclinical evidence calling for human trials.

2. Husain, G. M., Rai, R., Rai, G., Singh, H. B., Thakur, A. K., & Kumar, V. (2014). Potential mechanism of anti-diabetic activity of Picrorhiza kurroa. 탕, 4(4), 27.1-27.5. https://doi.org/10.5667/TANG.2014.0013 retrieved from https://www.researchgate.net/publication/268977804_Potential_mechanism_of_anti-diabetic_activity_of_Picrorhiza_kurroa

Dried aqueous extract of P. kurroa was standardized to contain 5% kutkin. It was administered to non-insulin dependent diabetic rats T2DM. It was a randomized, controlled trial. Plasma insulin levels were increased, glucose uptake by skeletal muscles was facilitated, and Pancreatic islet beta cells showed evidence of regeneration.

3. Husain, G. M., Singh, P. N., & Kumar, V. (2009). Antidiabetic activity of standardized extract of Picrorhiza kurroa in rat model of NIDDM. *Drug Discoveries and Therapeutics*, *3*(3), 88–92. Retrieved from https://www.researchgate.net/publication/223976831_Antidiabetic_activity_of_standardized_extract_of_Picrorhiza_kurroa_in_rat_model_of_NIDDM/citations

Glucose tolerance was increased, and fasting blood glucose levels were significantly decreased.
"These findings provide in vivo evidence that standardized extract of Picrorhiza kurroa possess significant antidiabetic activity in streptozotocin-nicotinamide induced type-2 diabetes mellitus in rats."

4. Vaidya AB, Antarkar DS, Doshi JC, et al. *Picrorhiza kurroa* (Kutaki) Royle ex Benth as a hepatoprotective agent—experimental and clinical studies. *J Postgrad Med.* 1996;42:105-108 retrieved from https://www.unboundmedicine.com/medline/citation/9715310/Picrorhiza_kurroa__Kutaki__Royle_ex_Benth_as_a_hepatoprotective_agent__experimental_&_clinical_studies_

Although this trial is not about diabetes, it is included because it is a trial that used human subjects, and no side effects were seen at the doses used, other than laxation which occurred at the higher doses. That is their statement, though they failed to report doses sizes and there were multiple study design flaws (as stated by other source though upon reading it, a major flaw I found was simply lack of pertinent, detailed information). https://www.wkhs.com/health-resources/health-library/article?chunkid=211604&lang=English&db=hlt#ref5

5. Shah BK, Kamat S R, Sheth U K. Preliminary report of use of picrorrhiza kurroa root in bronchial asthma . J Postgrad Med [serial online] 1977 [cited 2019 Sep 25];23:118-20. Available from: http://www.jpgmonline.com/text.asp?1977/23/3/118/42761

(Again, included due to adverse reactions reported). This clinical trial (human)was a small pilot study that had no control group. They reported "On lower dose (320 mg) one patient had headache, abdominal pain, vomiting, increased dyspnoea and giddiness; while on

higher dose (600 mg) three patients had similar symptoms [Table 1]. Only in one it was mild. Thus side-effects seemed significant despite hospitalisation." So significant side effects are possible.

6. Doshi V B, Shetye V M, Mahashur A A, Kamat S R. Picrorrhiza kurroa in bronchial asthma. J Postgrad Med [serial online] 1983 [cited 2019 Sep 25];29:89-95. Available from: http://www.jpgmonline.com/text.asp?1983/29/2/89/5544

This human trial had a very poor study design, but there were more subjects (sample size was larger) and side effects were reported thus: "These were seen in 10 (out of 52; 20%) patients in whom active drug was administered; 4 had vomiting, 1 cutaneous rash, 3 anorexia, 2 diarrhoea, 2 itching and 1 giddiness. Only in one case, vomiting was severe enough to discontinue trial, while in another 5 toxicity was significant."
20% of the patients experienced side effects, however some groups/patients were given antibiotics and steroids in addition to the plant, and they are not differentiated- so it is impossible to know if all of the side effects were due solely to picrorhiza kurroa.

These are the only human studies available, and as far as I understand- the only ones which exist. They are all riddled with design flaws, and I have included them for information, but I wouldn't rely solely on them.

SWERTIA CHIRATA

(critically endangered as of 2013) synonyms found here:
https://www.uniprot.org/taxonomy/137887

1. Jauhari, N., Bharadvaja, N., & Sharma, N. (2017). Swertia chirata: A Comprehensive Review with Recent Advances. Current Pharmaceutical Biotechnology, 18(9). https://doi.org/10.2174/1389201018666171026153515 retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29076426

This comprehensive review concluded that S. chirata is a safe and has a positive effect (for specific diseases). I included this one due to the safety conclusion, as tracking down human studies is difficult. The authors write, "It presents many promising prospects for modern medicine, which may be validated after the process of successful in vivo research, clinical studies, and human trials." The last sentence suggests that there haven't been any human clinical trials as of 2017.

2. S, R., Holla, R., Patil, V., S, A., & L, K. (2017). Anti-hyperglycemic effect of Swertia chirata root extract on indinavir treated rats. *National Journal of Physiology, Pharmacy and Pharmacology*, *7*(6), 569–573. doi: 10.5455/njppp.2017.7.0101505022017 retrieved from https://www.ejmanager.com/mnstemps/28/28-1484874316.pdf?t=1569528378

This study looked at several groups of rats to compare the anti-hyperglycemic effects on rats treated with an antiviral for AIDs (indivinar) that can cause diabetes. They found that the ethanol extract of S. chirata root lowered glucose levels, insulin levels, and improved lipid levels- an effect similar to

Metformin and Pioglitazone. They conclude, “In this study, it is proved that *S. chirata* is effective against Indinavir induced hyperglycemia or IR and hyperlipidemia.*S. chirata* root extract known to possess multiple medicinal effect which can be used as an adjuvant in combination therapy for patients having HIV infection AIDS along with other standard drugs such as Indinavir (protease inhibitor).”

3. Gupta, R., & Saxena, A. M. (2012). Assessment of Anti-diabetic Efficacy of Swertia chirayita extracts. *Molecular Biology*. Retrieved from https://www.researchgate.net/publication/317662137_Assessment_of_Anti-diabetic_Efficacy_of_Swertia_chirayita_extracts

In this study, albino mice were treated orally with the methanolic extract of the aerial parts of S. chirayita (250 mg/kg). The plant preparation significantly lowered blood glucose levels in fasted, fed, and alloxan-induced diabetic mice for up to 3-4 hours post administration.

4. Antihyperglycaemic activity of Swertia chirayita in validated animal models of diabetes retrieved from https://www.researchgate.net/publication/261026765_Antihyperglycaemic_activity_of_Swertia_chirayita_in_validated_animal_models_of_diabetes

“An effort was made to establish and confirm the antihyperglycaemic potential of Swertia chirayita (Roxb. ex Fleming) H. Karst. (Gentianaceae) in validated animal models of diabetes. The aqueous extract of S. chirayita (CT-1) decreased blood glucose level in the well studied glucose loaded rats (primary screening in vivo model), streptozotocin-induced diabetic rats as well as animal models of type 2 diabetes and insulin resistance i.e. db/db mice and high fructose enriched diet fed rats. The extract of S. chirayita (CT-1) significantly decreased blood glucose level in both glucose loaded rats and streptozotocin induced diabetic rats. CT-1 also improved glucose tolerance of the hyperglycaemic db/db mice as well as it also improved the insulin resistance in the fructose enriched diet fed rats after subchronic treatment at dose level of 100 mg/kg body weight. In normal rats CT-1 did not cause lowering of the blood glucose below normal level when fed for 30 consecutive days at 100 mg/kg dose. CT-1 was also found to inhibit a-glucosidase enzyme activity in vitro. Present studies thus confirm antihyperglycemic potential in the aqueous extract of Swertia chirayita.”

I was unable to locate any human trials or case series.

TINOSPORA CORDIFOLIA

1.Chandrasekaran, C. V., Mathuram, L. N., Daivasigamani, P., & Bhatnagar, U. (2009). Tinospora cordifolia, a safety evaluation. Toxicology in Vitro, 23(7), 1220–1226. https://doi.org/10.1016/j.tiv.2009.07.030 retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19651204

"Experimental results confirmed that in Ames test up to 5000 microg/plate of TC did not exhibit any mutagenic effect in Salmonella typhimurium mutant strains (TA97a, TA98, TA100, TA102, and TA1535). In CA assay, TC was not clastogenic to human peripheral blood lymphocytes up to a concentration of 3000 microg/ml. In MN and Comet assays, TC was pre-treated for 7 days at three dose levels (150, 200 and 250 mg/kg body weight) orally to male Balb/c mice. The results showed that TC treatment did not display clastogenicity and DNA damaging effect in bone marrow erythrocytes and peripheral blood lymphocytes respectively."

2. Rajalakshmi M. *et al*. 2009, Anti-diabetic properties of *Tinospora cordifolia* stem extracts on streptozotocin-induced diabetic rats. *African Journal of Pharmacy and Pharmacology Vol. 3(5). pp. 171-180, May, 2009.* Retrieved from https://pdfs.semanticscholar.org/222b/9c5e3168cae41ed00e32aa2649408228eff2.pdf

This rat study looked at the antidiabetic effects of TC. They also performed a secondary experiment to test for toxicity of TC at different doses in healthy rats. There was no indication of toxicity, and no mortalities were reported. They concluded that the alcoholic extract of TC was non-toxic. TC does not affect blood glucose in the group of nondiabetic rats. The diabetic rats who had elevated blood glucose were observed to have positive changes of gradually reduced blood glucose over a period of 90 days from TC. "In the TCS treated groups, the insulin and C-peptide levels were improved which shows the regeneration of -cell which secretes insulin, histopathological studies of pancreas of TCS methanol extract treated groups substantiate the regenerating capacity of extract."

3. Rege NN, Thatte UM, Dahanukar SA. 1999 Adaptogenic properties of six rasayana herbs used in Ayurvedic medicine. *Phytother Res* 1999; 13:275- 291. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10404532

AND

4. Sipahimalani AT, Noerr H, Wagner H 1994. Phenylpropanoid glycosides and tetrahydrofuran lignan glycosides from the adaptogenic plant drugs *Tinospora cordifolia* and *Drypetes roxburghii*. *Planta Med* ; 60:596-7, 1994 retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17236093

Both of the above studies (3&4) have noted adaptogenic properties in T. cordifolia. An adaptogen modulates and regulates (which would explain why healthy rats in reference #2 saw no changes in blood glucose, but rats with diabetes, given the same extract in the same amount did see a reduction in blood glucose). Adaptogenic herbs are, by definition considered tonic herbs- relatively non-toxic and capable of being taken long term with no ill effects.

5. Karkal YR And Bairy LK, Safety of Aqueous Extract of *Tinospora cordifolia*(Tc) in Healthy Volunteers: A Double Blind Randomised Placebo Controlled Study, *IJPT* , vol. 6, no. 1, January 2007 retrieved from http://ijpt.iums.ac.ir/browse.php?a_code=A-10-100-121&sid=1&slc_lang=en

“To evaluate the safety profile of Tinospora cordifolia in healthy volunteers using a battery of haematological, and biochemical tests and open questionnaire method. Thirty healthy volunteers (males - 22 and females - 8) aged 18 - 30 years (mean 22.5 ± 0.28) who volunteered to participate were studied in a randomized, double - blind, placebo controlled design. The volunteers were provided with 21 days of medication (coded box) containing Tinospora cordifolia 500 mg or matching placebo. One tablet of Tinospora cordifolia of 500mg strength or placebo was taken once daily orally in the morning along with breakfast for 21 days. The safety assessment was done with the help of haematological and biochemical investigations which were assessed before and after the medication. ‘Unpaired t test’ using SPSS computer software package. Analysis of the various lab values between the control and the test group before and after taking the drug/placebo by unpaired ‘t’ test shows no significant difference between the groups (P = > 0.05). Hence it can be concluded that Tinospora cordifolia is safe at a dose of 500 mg per day for a period 21 days in healthy volunteers for the parameters studied.”

GYMNEMA SYLVESTRE

Synonyms found here: https://www.uniprot.org/taxonomy/4068

1. Shanmugasundaram, E. R. B., Rajeswari, G., Baskaran, K., Kumar, B. R. R., Shanmugasundaram, K. R., & Ahmath, B. K. (1990). Use of Gymnema sylvestre leaf extract in the control of blood glucose in insulin-dependent diabetes mellitus. Journal of Ethnopharmacology, 30(3), 281–294. https://doi.org/10.1016/0378-8741(90)90107-5 retrieved from https://www.sciencedirect.com/science/article/pii/0378874190901075

GS4, a water-soluble extract of the leaves of *Gymnema sylvestre*, was administered (400) to 27 patients with insulin-dependent diabetes mellitus (IDDM) on insulin therapy. Insulin requirements came down together with fasting blood glucose and glycosylated haemoglobin (HbAlc) and glycosylated plasma protein levels. While serum lipids returned to near normal levels with GS4 therapy, glycosylated haemoglobin and glycosylated plasma protein levels remained higher than controls. IDDM patients on insulin therapy only showed no significant reduction in serum lipids, HbAlc or glycosylated plasma proteins when followed up after 10–12 months. GS4 therapy appears to enhance endogenous insulin, possibly by regeneration/ revitalisation of the residual *beta* cells in insulin-dependent diabetes mellitus.

2. Baskaran, K., Ahamath, B. K., Shanmugasundaram, K. R., & Shanmugasundaram, E. R. B. (1990). Antidiabetic effect of a leaf extract from Gymnema sylvestre in non-insulin-dependent diabetes mellitus patients. Journal of Ethnopharmacology, 30(3), 295–305. https://doi.org/10.1016/0378-8741(90)90108-6 retrieved from https://www.sciencedirect.com/science/article/pii/0378874190901086

The effectiveness of GS4, an extract from the leaves of *Gymnema sylvestre*, in controlling hyperglycaemia was investigated in 22 Type 2 diabetic patients on conventional oral anti-hyperglycaemic agents. GS4 (400) was administered for 18–20 months as a supplement to the conventional oral drugs. During GS4supplementation, the patients showed a significant reduction in blood glucose, glycosylated haemoglobin and glycosylated plasma proteins, and conventional drug dosage could be decreased. Five of the 22 diabetic patients were able to discontinue their conventional drug and maintain their blood glucose homeostasis with GS4 alone. These data suggest that the *beta* cells may be regenerated/repaired in Type 2 diabetic patients on GS4 supplementation. This is supported by the appearance of raised insulin levels in the serum of patients after GS4 supplementation.

3. Gunasekaren, V., Srinivasan, S., & Sudha, S. (2018). Potential antioxidant and antimicrobial activity of Gymnema sylvestre related to diabetes. *Journal of Medicinal Plant Studies*, *7*(2), 5–11. Retrieved from https://www.researchgate.net/publication/331732815_Potential_antioxidant_and_antimicrobial_activity_of_Gymnema_sylvestre_related_to_diabetes

More than 90 years ago, it was observed that Gymnema leaves reduced urine glucose in diabetics. It reduces fat accumulation and weight gain. It enhances glucose reuptake via insulin receptor affinity and altered gene expression. In mice, it increased enzymatic action which catalyzed glucose uptake via insulin dependent pathways.

4. Najm, W. I. (2012). An Overview on Nutraceuticals and Herbal Supplements for Diabetes and Metabolic Syndrome. In Nutritional and Therapeutic Interventions for Diabetes and Metabolic Syndrome (pp. 355–365). Elsevier. https://doi.org/10.1016/b978-0-12-385083-6.00028-0. Retrieved from https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/gymnema

"Gymnema extract appears to be safe. Caution should be used when taken along with antidiabetic medications (additive effect). Caution should be used in pregnant and breastfeeding women since the effects have not been evaluated. A recent case reported toxic hepatitis, in a 60-year-old woman with T2DM, secondary to *Gymnema sylvestre* taken over 10 days, as a tea, three times daily. The exact mechanism of the injury is unknown, although the authors indicate that diabetes and non-alcoholic fatty liver disease could be predisposing factors."

*The case report had confounding factors and the causative agent cannot be ascertained.

Srividiya, A. R., Varma, S., Dhanapal, S. P., Ramachandran, V., & Vajayan, P. (2010). In Vitro and In Vivo Evaluation of Hepatoprotective Activity of Gymnema Sylvestre. *International Journal of Pharmaceutical Sciences and Nanotechnology*, *2*(4), 768–773. Retrieved from https://www.researchgate.net/publication/215485661_In_Vitro_and_In_Vivo_Evaluation_of_Hepatoprotective_Activity_of_Gymnema_Sylvestre

** Furthermore, G. sylvestre has been tested and was found to exhibit liver protective and liver restorative properties.

FENUGREEK

1. Geberemeskel, G. A., Debebe, Y. G., & Nguse, N. A. (2019). Antidiabetic Effect of Fenugreek Seed Powder Solution (Trigonella foenum-graecum L.) on Hyperlipidemia in Diabetic Patients. Journal of Diabetes Research, 2019, 1–8. https://doi.org/10.1155/2019/8507453 retrieved from https://doaj.org/article/7150df75b9824868b4d72d41c28c699c

They concluded that "The present study showed that the administration of Trigonella foenum-graecum seed powder solution had pronounced effects in improving lipid metabolism in type II diabetic patients with no adverse effects. Therefore, Trigonella foenum-graecum seed may provide new alternatives for the clinical management of type II diabetes."

2. Kassaian, N., Azadbakht, L., Forghani, B., & Amini, M. (2009). Effect of Fenugreek Seeds on Blood Glucose and Lipid Profiles in Type 2 Diabetic Patients. International Journal for Vitamin and Nutrition Research, 79(1), 34–39. https://doi.org/10.1024/0300-9831.79.1.34 retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19839001

They found that fenugreek seeds soaked in hot water significantly decreased FBS, TG and VLDL-C. Fenugreek with yogurt caused no change.

3. Ranade, M., & Mudgalkar, N. (2017). A simple dietary addition of fenugreek seed leads to the reduction in blood glucose levels: A parallel group, randomized single-blind trial. *Ayu*, *38*(1-2), 24–27. doi:10.4103/ayu.AYU_209_15 retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5954247/

This study found that fenugreek worked synergistically with medication called OHAs. The added fenugreek significantly reduced HbA1Cs and blood glucose. They conclude "A simple complementary addition of fenugreek seeds can have a synergistic effect along with diet control and exercise on fasting blood glucose and HbA1c but is of delayed occurrence." Human trial.

4. Neelakantan, N., Narayanan, M., de Souza, R. J., & van Dam, R. M. (2014). Effect of fenugreek (Trigonella foenum-graecum L.) intake on glycemia: a meta-analysis of clinical trials. *Nutrition journal*, *13*, 7. doi:10.1186/1475-2891-13-7 retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3901758/

"A total of 10 trials were identified. Fenugreek significantly changed fasting blood glucose by -0.96 mmol/l (95% CI: -1.52, -0.40; I2 = 80%; 10 trials), 2 hour postload glucose by -2.19 mmol/l (95% CI: -3.19, -1.19; I2 = 71%; 7 trials) and HbA1c by -0.85% (95% CI: -1.49%, -0.22%; I2 = 0%; 3 trials) as compared with control interventions. The considerable heterogeneity in study results was partly explained by diabetes status and dose: significant effects on fasting and 2 hr glucose were only found for studies that administered medium or high doses of fenugreek in persons with diabetes. Most of the trials were of low methodological quality.Results from clinical trials support beneficial effects of fenugreek seeds on glycemic control in persons with diabetes…"

5. Kandhare, A. D., Thakurdesai, P. A., Wangikar, P., & Bodhankar, S. L. (2019). A systematic literature review of fenugreek seed toxicity by using ToxRTool: evidence from

preclinical and clinical studies. *Heliyon*, *5*(4), e01536. doi:10.1016/j.heliyon.2019.e01536 retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6482331/

In the present study, toxicological publications on fenugreek seeds that are categorized as 'Reliable without restrictions' can be considered for toxicological risk assessment with reasonable certainty.