

# Herbal Supplements for Diabetes: A Qualitative Review of Current Evidence on Local Indigenous Plants

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**Background:** Herbal supplementation has been used by diabetic patients, unfortunately it has regulatory, safety, and efficacy concerns.

**Objective:** This review was conducted to determine the best evidence in terms of the identified active substance, mechanism of action, pre-clinical and clinical studies of commonly used local herbal preparations.

**Methods:** This is a qualitative review of both local and international published medical literature to identify and summarize information on the use of herbal supplementation in diabetes.

**Results:** After the initial review, the authors identified thirteen herbal preparations that have been investigated for its anti-diabetic properties. Six have extensive studies including randomized controlled trials but cinnamon and fenugreek seed are not readily available locally. Their detailed review eventually focused on four locally available herbal preparations i.e. bitter melon, turmeric, aloe vera and banaba. They decrease glucose absorption and gluconeogenesis, improve glucose utilization and insulin production. Unlike conventional anti-diabetics, herbal preparations also have favorable effect on lipid metabolism and anti-oxidant effect. Bitter melon seems to be the best herbal preparation. But human studies of bitter melon showed it is inferior to conventional anti-diabetic drugs in terms of its anti-diabetic effect but better in terms of its effect on lipid metabolism and anti-oxidant properties. Turmeric, aloe vera and banaba have also been shown to have anti-diabetic effects.

**Conclusion:** In summary, herbal preparation may have multiple beneficial effect for patients with diabetes. Use of combined preparations can produce complementation of the effects and may be a promising approach to the use of herbal supplementation as treatment standard among patients with diabetes.

**Keywords:** diabetes, herbal supplements, herbal preparations

### INTRODUCTION

Diabetes mellitus can be treated and controlled by drugs, regular exercise, diet and change in lifestyle. Currently available anti-diabetic therapies are effective in reducing blood glucose level, but they also have side effects when used in maximum dose and in the long term. As a result, physicians and patients want a safer therapy with less serious side effects.

Herbal supplementation has also been used by patients with diabetes. The most studied herbal plants are *Momordica*

*charantia*, *Allium sativum*, *Gymnema sylvestre*, *Citrullus colocynthis*, *Trigonella foenum graecum*, and *Ficus bengalensis*.<sup>1-2</sup> Based on the World Health Organization data, up to 90% of population in developing countries use plants and its products as traditional medicine for primary health care.<sup>3</sup> Among diabetics, 30-77 percent use herbal medicine.<sup>4</sup>

Unfortunately, the use of herbal supplementation has regulatory, safety, and efficacy concerns. While the active substances from herbal extracts have been identified, their mechanism of actions are not well understood. The scientific

evidence for its efficacy i.e. hypoglycemic effect, carbohydrate absorption inhibition and insulin production is still few and mostly on in-vitro and animal studies. Human studies involved few subjects in contrast to mainstream drug treatment.<sup>5</sup> This review was conducted to determine the most commonly used local indigenous herbal preparation for diabetes and determine which has the best evidence in terms of the identified active substance, its mechanism of action, pre-clinical and clinical studies.

## METHODS

This is a qualitative review of published literature. The authors reviewed both local and international published medical literature to identify, extract and summarize information on the use of herbal supplementation in diabetes. The search and review of published studies were done in two stages. During the first stage, the group searched Pubmed using the free text and MESH terms of "diabetes mellitus" and "herbal medicine". The authors limited their search to "reviews", "clinical trials" and "available full text". They also search Herdin and local publications on herbal medicine. The abstracts of the relevant publications were retrieved. Three reviewers evaluated the retrieved abstracts and full text of the publications. The reviewers evaluated the current evidence as in-vitro, pre-clinical or clinical studies. The merits of the available evidence, local availability of the preparation and local anecdotal experience were discussed. From this discussion, four local indigenous herbal preparation (bitter melon, turmeric, aloe vera and banaba) were found to have good evidence of efficacy from pre-clinical and clinical studies and were considered for further review.

From the initial review, the group conducted the second stage of literature search using the free text search of the scientific names of the identified preparation i.e. "Mamordica charantia", "Curcuma longa", "Aloe vera" and "Lagerstroemia speciose". The abstract and full text articles were retrieved and further reviewed to extract the most appropriate information on the active substance, its mechanism of action and the valid pre-clinical and clinical evidence of efficacy. The full text of the abstracts that contained relevant information were retrieved for further extraction of information and fact checking. The full text was reviewed individually by three reviewers.

The information extracted was discussed by e-mail and face-to-face group meetings. Conflicting information was resolved by discussion and consensus.

## Herbal Preparations

After the initial review, the authors identified thirteen herbal preparations that have been investigated for its anti-diabetic properties

(Table 1). Of the thirteen, two have not been studied on humans. Among the preparations with human studies, six have extensive studies including randomized controlled trials. Unfortunately, cinnamon and fenugreek seed are not readily available locally. This detailed review eventually focused on four locally available herbal preparation i.e. bitter melon, turmeric, aloe vera and banaba.

## Bitter Melon (*Mamordica charantia*)

Bitter melon, bitter gourd or ampalaya (*Momordica charantia*) is widely grown in tropical and subtropical regions and has been used as herbal supplement for diabetes mellitus. There are existing reviews that examined its various extracts and compounds, their properties and how they act to exert their beneficial effects in diabetes.<sup>6</sup>

### Active Substance

Bitter melon contains phytochemicals including proteins, polysaccharides, flavonoids, triterpenes and saponins. They have been demonstrated to have antihyperglycemic, antibacterial, antiviral, antitumor, immunomodulation, antioxidant, antidiabetic, anthelmintic, antimutagenic, antiulcer, antipolytic, antifertility, hepatoprotective, anticancer and anti-inflammatory activities.<sup>7</sup> The fruit is the most common and best source of these phytochemicals. This is based on a study by Mahwish et al, that compared the skin, flesh and whole fruit of bitter melon in controlling hyperglycemia and hyperlipidemia. It revealed that reduction in blood glucose was found in skin of the fruit by 1.06%, flesh of the fruit by 2.65%, and whole fruit by 4.29%. The overall results suggest that the whole fruit, skin flesh and seeds have significant pharmacologic property.<sup>8</sup>

The active phytochemicals extracted from bitter melon are the momordicosides. These are cucurbitane triterpenoid glycosides.<sup>9</sup> These phytochemicals can be extracted with lyophilization/superfine grinding and hot air drying/normal grinding. Further fractionation of these compounds revealed a fraction Mc-3 that showed the maximum anti-hyperglycemic activity and reduced blood glucose levels in experimental diabetic rats.<sup>10</sup> Antidiabetic activity has also been reported for certain saponins isolated from *M. charantia* and may have a different effect than momordicosides.<sup>11</sup> The seed of the fruit also contains alpha-eleostearic acid that has been shown to decrease lipid peroxidation and is a potentially effective antioxidant which may be effective in reducing the risk of coronary heart disease in diabetes mellitus.<sup>12</sup>

**Table 1.** Herbal preparations with anti-diabetic properties

Common name	Scientific name	Best available evidence	References
Bitter melon (ampalaya)	Momordica charantia	RCT	Inayat U Rahman et al, 2015; Tsai. et al. 2012; Fuangchan, et al. 2011; Inayat U Rahman et al, 2009; Dans, et al. 2007; Tongia, et al. 2004; John, et al. 2003; Pngnikorn, et al. 2003; Ahmad, et al. 1999; Leatherdale, et al. 1981; Baldwa et al, 1977
Banaba	Lagerstroemia speciosa	RCT	Cicero, et al. 2017; Judy, et al. 2003
Aloe vera	Aloe vera	RCT	Zarvandi, et al. 2017; Devaraj, et al. 2013; Huseini, et al. 2012;
Ginger	Zingber officinale	RCT, Phase 1	Shidfar, et al. 2015; Mozafarri-Kozravi, et al. 2015; Arablou, et al. 2014; Mahluji, et al. 2013; Yu, et al. 2011
Virgin coconut oil	Cocos nucifera	RCT	Trinidad, et al. 2003;
Garlic	Alum sativa	RCT	Sobenin, et al. 2008;
Basil	Ocimum basilicum	Pre-clinical (rat) study	Agrawal, et al. 1996
Cinnamon	Cinnamomum verum	RCT, Phase 1,	Ranasinghe, et al. 2017; Azimi, et al. 2016; Liu, et al. 2015; Mirfeizi, et al. 2016; Bernardo, et al. 2015; Whitfield, et al. 2016; Bejmohun, et al. 2014; Magistrelli, et al. 2012; Lu, et al. 2012; Akilen, et al. 2010; Crawford 2009; Roussel, et al. 2009; Solomon, et al. 2009; Hlebowicz, et al. 2009; Tang, et al. 2008; Solomon, et al, 2007; Suppakitiporn, et al. 2006; Blevins, et al, 2007; Mang, et al. 2006; Khan, et al. 2003;
Cardamon	Elettaria cardamomum	RCT protocol	Aghasi, et al. 2018; Daneshi-Maskooni, et al. 2017; Kazemi, et al. 2017;
Capsicum	Capsicum annum	RCT	Nagasukeerthi, et al. 2017; Yuan, et al. 2016; Chaiyasit, et al. 2009; Kim, et al. 2006; Kim and Nam 2006; Ahuja, et al. 2006;
Turmeric	Curcuma longa	Meta-analysis, RCT, Phase 1,	Gopi, et al. 2017; Cicero, et al. 2017; Amin, et al. 2015; Patti, et al. 2015; Panahi, et al. 2015; Panahi, et al. 2014; Kurian, et al. 2014; Jager, et al. 2014; Chuengsamarn, et al. 2014; Schiborr, et al. 2014; Appendino, et al. 2011; Khajehdehi, et al. 2011; Wickenberg, et al. 2010; Tang, et al. 2008; Lao, et al. 2006; Joshi, et al. 2003
Fenugreek seed	Trigonella foenum-graecum	RCT, Phase 1	Kiss, et al. 2018; Zarvandi, et al. 2017; Robert, et al. 2016; Rafraf, et al. 2014; Losso, et al. 2009; Kassaian, et al. 2009; Lu, et al. 2008; Gupta, et al. 2001; Abdel-Barry, et al. 2000; Sharma, et al. 1990; Madar, et al. 1988
Malunggay	Moringa oleifera	Phase 1	Anthanont et al, 2016;

### *Mechanism of Action*

Bitter melon extract lowers blood glucose by several mechanisms. First, the protein extract inhibits the activity of

$\alpha$ -amylase and  $\alpha$ -glucosidase through competitive inhibition resulting to decrease glucose absorption in the gastrointestinal tract. This effect is at par with acarbose.<sup>13</sup> This was confirmed in one study where bitter melon inhibits significantly ( $p < 0.05$ )

$\alpha$ -glucosidase activity resulting to decrease postprandial blood sugar.<sup>14</sup> Second, it prevents gluconeogenesis by depressing glucose-6-phosphatase and fructose-1,6-bisphosphatase and on the other by enhancing glucose oxidation by the shunt pathway through activation of its principal enzyme G6PDH.<sup>15</sup> Third, it stimulates AMP-activated protein kinase (AMPK) and GLUT4 translocation in cell membrane promoting glucose entry into the cell.<sup>16</sup> Lastly, it raised plasma insulin concentrations in a perfused rat pancreas. Momordicosides bind with pancreatic L-cell resulting to elevation of intracellular  $Ca^{2+}$  and GLP-1 concentration. This in turn elevates beta-cell proliferation and insulin secretion.<sup>17</sup>

Bitter melon has lipid lowering effect in diabetic animal models as well. Preadipocytes treated with varying concentrations of bitter melon during differentiation demonstrated significant reduction in lipid content. This is due to reduction in mRNA expression of adipocyte transcription factors resulting to inhibition of lipogenesis. Similarly, there is increased lipolysis as evidenced by the release of glycerol.<sup>18</sup>

Also, administration of bitter melon significantly decreased lipid peroxidation ( $p < 0.001$ ) and significant increase in the activities of key antioxidant enzymes such as superoxide dismutase, catalase, glutathione-s-transferase and reduced glutathione contents in heart tissue of diabetic rats.<sup>19</sup> Treatment with bitter melon may effectively normalize the impaired oxidative stress in streptozotocin induced-diabetes which may be considered an advantage over glibenclamide treatment.<sup>20</sup>

#### *Pre-Clinical Studies*

Both aqueous and methanol extract of bitter melon have been investigated for its anti-diabetic property in diabetic animal models. In a study on in KK-Ay mice, an animal model with type 2 diabetes, the aqueous extract with exercise significantly reduced the blood glucose and plasma insulin after 5 weeks of oral administration. The study result however may have been affected by the exercise component.<sup>21</sup> The methanol fruit extract was also shown to have beneficial effect alloxan-induced diabetic rats. Significant reduction in fasting blood glucose was observed after 2 hours for both 125mg/kg and 375mg/kg dose. The effect was similar to metformin. The maximum reduction was noted between 3 and 12 hours after intake.<sup>22</sup> The anti-diabetic effect was also observed with sub-chronic intake. After a month of administration in alloxan-induced diabetic Wistar rats, bitter melon resulted to lowering blood glucose and percent glycosylated hemoglobin.<sup>23</sup>

Aside from its anti-diabetic property, bitter melon has also been shown to have cardiac and kidney protective properties in animal studies. In hypertensive Dahl salt-sensitive

rats, administrations of bitter melon extract produced dose-dependent, significant reductions in systemic arterial blood pressure and heart rates.<sup>24</sup> This was confirmed in another study where oral administration of the extract at 1.5 g/kg resulted to a significant decrease in blood pressure, total cholesterol and triglyceride levels. The study also showed increased aortic tissue nitrous oxide level and decreased malondialdehyde, suggesting vasculo-protective effect. It also reduced morphological damage in cardiac tissue under immunohistochemical staining.<sup>25</sup> Lastly, diabetic rats given bitter melon showed reversal of kidney tissue damage.<sup>26</sup>

#### *Clinical Studies*

Bitter melon has been compared with glibenclamide for the treatment of diabetes mellitus in humans. Ninety-five diabetics were randomized into 3 groups low dose bitter melon extract (2 g/day) and high dose bitter melon extract (4 g/day) and glibenclamide (5 mg/day) for 10 weeks. Compared to baseline, there were statistically significant mean reduction in glycosylated hemoglobin (HbA1-c) at the endpoint in all groups, although more significant in glibenclamide. But the other parameters including blood lipids, atherogenic index, body weight and systolic blood pressure improved among patients given bitter melon but deteriorated among glibenclamide treated patients. This suggests that bitter melon has a weaker hypoglycemic effect but ameliorates the diabetes associated cardiovascular risk factors more effectively than glibenclamide.<sup>27</sup>

#### **Turmeric (*Curcuma longa*)**

Turmeric (*Curcuma longa*) has an active component called curcumin (diferuloylmethane) that can modulate multiple cell signaling pathways. Promising effects have been observed in patients with various diseases including diabetes. It can be used alone or in combination with other herbal preparation and in various formulation.<sup>28</sup>

#### *Active Substance*

Curcumin is the isolated and most studied compound from turmeric. It is a low molecular weight, lipophilic, major yellow natural polyphenolic and the most well-known plant-derived compound.<sup>29</sup> One of its extensively studied effect is on diabetes and diabetes-related disorders, adipocyte dysfunction, neuropathy, nephropathy, vascular diseases, pancreatic disorders, and other complications.<sup>30</sup>

Curcumin and other active substances from turmeric can be extracted in different ways i.e. water, 50% water-alcohol and

96% ethanol. Qualitative analysis of these extracts revealed the existence of certain chemical constituents such as flavonoids, tannins, organic acids and saponin glycosides.<sup>31</sup> Further analysis reveals phenolic compounds like ferulic acid, gallic acid, caffeic acid and coumaric acid, as well as quercetin, kaempferol, apigenin, curcumin, luteolin and esculetin.<sup>32</sup>

The main limitation of the pharmacological and clinical investigations of curcumin is its extremely low solubility in water and in organ fluids. As a result, absorption when orally administered is poor.<sup>33</sup> This feature consequently limits its systemic bioavailability and makes use of curcumin as a therapeutic remedy difficult.<sup>34</sup> However, recent studies have demonstrated increased bioavailability and health-promoting effects of a novel solid lipid particle formulation of curcumin.<sup>35</sup>

#### *Mechanism of Action*

Several reviews have been conducted to explain the mechanism of action of curcumin.<sup>36</sup> It can reduce blood glucose level by reducing the hepatic glucose production, suppression of hyperglycemia-induced inflammatory state, stimulation of glucose uptake by up-regulation of GLUT4, GLUT2 and GLUT3 genes expressions, activation of AMP kinase, promoting the PPAR ligand-binding activity, stimulation of insulin secretion from pancreatic tissues, improvement in pancreatic cell function, and reduction of insulin resistance.<sup>37</sup>

Curcumin also improves lipid metabolism. Using 3T3-L1 cells, Curcumin was shown to inhibit mitogen-activated protein kinase (MAPK) phosphorylation that was associated with differentiation of 3T3-L1 cells into adipocytes.<sup>38</sup> In an in vitro evaluation, the extract stimulated human adipocyte differentiation in a dose-dependent manner and showed human peroxisome proliferator-activated receptor (PPAR)-gamma ligand-binding activity in a GAL4-PPAR-gamma chimera assay.<sup>39-40</sup>

Curcumin has also been shown to have anti-oxidant properties. It abolishes both phorbol-12 myristate-13 acetate and thapsigargin-induced ROS generation in cells from control and diabetic subjects. The pattern of these ROS inhibitory effects as a function of dose-dependency suggests that curcumin mechanistically interferes with protein kinase C (PKC) and calcium regulation.<sup>41</sup>

#### *Pre-clinical Studies*

In high-fat diet-induced obese mice, treatment with the extract (50 or 100 mg/kg/day) significantly decreased fasting and postprandial blood glucose levels. It also lowered insulin, glucose, free fatty acid, and triglyceride levels in serum. Regarding its effect on obesity, it was shown to decrease epididymal fat

pad and adipocyte size by 25.8% and 22.5% and decrease liver fat accumulation.<sup>42</sup> Sub-chronic intake of curcumin at a concentration of 150 mg/kg body weight/rat/d for 45 days also exerted hypoglycemic effect and was found to be safe. Significant reduction in blood glucose, HbA1c, and lipid profile parameters with improvement in plasma insulin levels were observed. There was also reduced activities of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea and creatinine.<sup>43</sup>

#### *Clinical Studies*

Curcumin combined with other herbal preparation has been studied in type II diabetic patients. After three months of treatment, mixed herbal preparation in tablet form containing turmeric showed significant antidiabetic, hypolipidemic and antioxidant effects. In addition to that significant ameliorating effects on the elevated serum AST and ALT activities were also demonstrated by the treatment.<sup>44</sup> But, because of low bioavailability, the hypoglycemic effect of curcumin per se as single preparation showed varying results. In a crossover trial of healthy subjects, using standard 75 g oral glucose tolerance test (OGTT), the ingestion of 6 g *C. longa* had no significant effect on the glucose response but the change in insulin was significantly higher 30 min and 60 min after the OGTT.<sup>45</sup>

#### *Aloe vera*

Aloe vera is a popular herbal treatment for constipation, colic, skin diseases, worm infestation, and infections. It is also used for hypertension and diabetes. In the UK, the juice preparation is a popular supplement for diabetes.<sup>46</sup>

#### *Active Substance*

Aloesin, a chromone in Aloe contain Loesyn, which showed significant impact in reducing glycosylated hemoglobin, fasting blood glucose, fructosamine and plasma insulin level in humans. Radical scavenging activities of chromones and polysaccharides from Aloe have also been reported. Based on spectrophotometry the extract contains organic acid, polyphenols/phenolic acid, alcohol, aldehyde, ketone, alkane, pyrimidine, indole, alkaloid, phytosterol, fatty acid and dicarboxylic acid contents. It also has flavonoid contents.<sup>47</sup> The 95% aqueous ethanol is the more appropriate extraction for concentrating selective groups of health-related compounds in aloe vera.<sup>48</sup>

#### *Mechanism of Action*

In vitro studies showed that the gel preparation of aloe vera inhibited pancreatic lipase. This may decrease glucose

metabolism and absorption, an effect similar to Orlistat.<sup>47</sup> In the tissues, it enhances plasma adiponectin levels and insulin sensitivity in muscles and decreased the mRNA, protein of PPAR and scavenger receptors in white adipose tissue. Both of which are important peripheral tissues affecting insulin resistance.<sup>49</sup> It also decreased obesity-induced inflammatory cytokines and protein and macrophage infiltration.<sup>50</sup>

#### *Pre-clinical Studies*

In male obese mice fed a high-fat diet, supplementation of Aloe vera was compared to pioglitazone and metformin. Aloe vera lowered body weight, fasting blood glucose, plasma insulin, and leptin levels, and markedly reduced the impairment of glucose tolerance in obese mice similar to pioglitazone and metformin.<sup>49</sup> Similar favorable effect was noted in streptozotocin-induced type 2 diabetic model rats.<sup>51</sup>

Purified Aloe vera extract was also shown to be effective with sub-chronic use. After administration of the phytosterols for 28 days, fasting blood glucose levels as well as HbA1c decreased significantly.<sup>52</sup> In another animal study, the improvement in blood glucose clearance was associated with improvement in plasma insulin level.<sup>53</sup>

Aloe vera gel extract has antioxidant property as well. Oral administration of the extract at a concentration of 300 mg/kg to diabetic rats reverted to normal levels the lipid peroxidation and hydroperoxides in tissues of diabetic rats. The extract treatment also resulted in a significant increase in reduced glutathione, superoxide dismutase, catalase, glutathione peroxidase and glutathione-S-transferase in the liver and kidneys.<sup>54</sup>

#### *Clinical Studies*

A systematic review of five randomized controlled trials (RCTs) involving 415 participants was already conducted on the use of Aloe vera among patients with pre-diabetes and diabetes. Compared with the controls, aloe vera supplementation significantly reduced the concentrations of fasting blood glucose, glycosylated hemoglobin A1c, triglyceride, total cholesterol and low-density lipoprotein-cholesterol. Aloe vera was superior to placebo in increasing serum high density lipoprotein-cholesterol (HDL-C) levels. Only one adverse event was reported.<sup>55</sup>

### **Banaba (*Lagerstroemia speciosa*)**

The leaves of *Lagerstroemia speciosa* more commonly known as Banaba have been traditionally consumed in various forms by Filipinos for treatment of diabetes and kidney related diseases. This herbal medicine began to attract attention starting in the

1990s. Since then, there have been numerous in vitro and in vivo studies that consistently confirmed its antidiabetic activity.<sup>56</sup>

#### *Active Substance*

The hypoglycemic effect of Banaba was attributed to both corosolic acid as well as ellagitannins and gallotannins. Corosolic acid was isolated from the methanol extract of Banaba and shown to be an active compound. It has low water solubility resulting poor absorption after oral administration. Special drug delivery system is necessary to improve oral absorption.<sup>57</sup> It has been reported to decrease blood sugar and exhibits antihyperlipidemic and antioxidant activities.<sup>58</sup> On the other hand, the water-soluble fraction of the extract led to the discovery of ellagitannin. This extract exhibited an insulin-like glucose transport inducing activity. Coupling HPLC fractionation with a glucose uptake assay further identified gallotannins as components responsible for the anti-diabetic activity, not corosolic acid. Penta-O-galloyl-glucopyranose (PGG) was identified as the most potent gallotannin.<sup>56</sup> Another substance, valoneic acid dilactone was isolated from the leaves of Banaba using bioassay-guided separation. This has been showed to be a potent alpha-amylase inhibitor.<sup>59</sup>

#### *Mechanism of Action*

The beneficial effects of Banaba extract with respect to various aspects of glucose and lipid metabolism appear to involve multiple mechanisms. These include enhanced cellular uptake of glucose, impaired hydrolysis of sucrose and starches, decreased gluconeogenesis and regulation of lipid metabolism.<sup>58</sup> One study showed that administration of the extract led to decreased hydrolysis of sucrose in the small intestine of mice. This suggests that the hypoglycemic activity is due to decreased digestion and absorption of sugars.<sup>60</sup>

#### *Pre-clinical Studies*

As a single preparation, the hypoglycemic effect of Banaba was studied using hereditary diabetic mice. The blood plasma glucose level in non-insulin dependent diabetic mice fed the cellulose as control diet was almost entirely suppressed by addition of Banaba.<sup>61</sup> Pre-clinical and clinical studies on Banaba have also been done in combination with other herbal plant. A standardized extract combination containing Banaba and Cinnamon was seen to increase phosphorylation at the tyrosine residue of the insulin receptor substrate, increased insulin signaling and sensitivity. In addition, glucose transporter 4 protein levels were seen to increase.<sup>62</sup> Another combination of

**Table 2.** Mechanisms of action of the four herbal preparations.

Mechanism	Bitter melon	Turmeric	Aloe vera	Banaba
Decrease glucose absorption	+	-	+	+
Decrease gluconeogenesis	+	+	-	+
Increase glucose utilization/cell entry	+	+	-	+
Enhance insulin production/insulin effect	+	+	+	-
Favorable lipid effect	+	+	+	+
Anti-oxidant properties	+	+	-	-

dried bulbs of *Allium sativum* (Garlic) and leaves of *Lagerstroemia speciosa* (Banaba) was studied to ascertain synergistic therapeutic effect in diabetic state. The results showed that the combination produced synergistic and a dose dependent increase in glucose uptake when compared to the individual extracts. It restored the glucose and lipid level near to normal level without gain in body weight which is the most commonly encountered side effect with the use of conventional antidiabetic agents.<sup>63</sup>

#### Clinical Studies

Human experience with Banaba is also based on combined preparation. Eighty adult subjects with impaired glucose tolerance were randomized to receive the combination 50-100 mg daily or placebo. After 12 weeks, the combination improved insulin resistance better than placebo as reflected by a reduced HOMA-IR. No serious hypoglycemia, edema, or cardiovascular-related adverse events were found in either groups. The authors concluded that the combination was well-tolerated, and promisingly efficacious in improving insulin sensitivity as well as preserving  $\beta$ -cell performance in subjects with impaired glucose tolerance.<sup>64</sup>

#### SUMMARY AND CONCLUSION

In summary, herbal preparation may have multiple beneficial effect for patients with diabetes. They decrease glucose absorption and gluconeogenesis, improve glucose utilization and insulin production. Unlike conventional anti-diabetics, herbal preparations also have favorable effect on lipid metabolism and as an anti-oxidant. Bitter melon seems to be the best herbal preparation (Table 2). But human studies of bitter melon showed it is inferior to conventional anti-diabetic drugs in terms of its anti-diabetic effect but better in terms of its effect on lipid metabolism and anti-oxidant properties. Turmeric, aloe vera and banaba have also been shown to have anti-diabetic effects. Combining these preparations to bitter melon can

produce complementation of the effects and may be a promising approach to the use of herbal supplementation as treatment standard among patients with diabetes.

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