

## Review

# Beneficial effect and mechanism of action of *Momordica charantia* in the treatment of diabetes mellitus: a mini review

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### Abstract

Diabetes mellitus (DM) is the most common of the endocrine disorders and represents a global health problem. DM is characterized by chronic hyperglycaemia due to relative or absolute lack of insulin or the actions of insulin. Insulin is the main treatment for patients with type 1 DM and it is also important in type 2 DM when blood glucose levels cannot be controlled by diet, weight loss, exercise and oral medications alone. Prior to the availability of insulin, dietary measures, including the traditional medicines derived from plants, were the major form of treatment. A multitude of plants have been used for the treatment of diabetes throughout the world. One such plant is *Momordica charantia* (Linn Family: Cucurbitaceae), whose fruit is known as Karela or bittergourd. For a long time, several workers have studied the effects of this plant in DM. Treatment with *M. charantia* fruit juice reduced blood glucose levels, improved body weight and glucose tolerance. *M. charantia* fruit juice can also inhibit glucose uptake by the gut and stimulate glucose uptake by skeletal muscle cells. Moreover, the juice of this plant preserves islet  $\beta$  cells and  $\beta$  cell functions, normalises the systolic blood pressure, and modulates xenobiotic metabolism and oxidative stress. *M. charantia* also has anti-carcinogenic properties. In conclusion, *M. charantia* has tremendous beneficial values in the treatment of DM.

**Key words:** *Diabetes mellitus, Momordica charantia, hypoglycaemia, insulin,  $\beta$  cells, hypertension, xenobiotic metabolism, oxidative stress, anti carcinogenic, myelinated fibres, glucose transport*

### Introduction

Diabetes Mellitus (DM) is a major metabolic disorder characterized by chronic hyperglycaemia as a result of a relative or absolute lack of insulin or the actions of insulin.<sup>1</sup> The condition affects the metabolism of carbohydrates, protein, fat, water and electrolytes leading to structural changes in a range of cells especially those of the vascular system, subsequently leading to long-term complications of diabetes. Diabetes is the most common of the endocrine disorders. It is estimated that in the year 2010 more than 200 million people world wide will have DM and 300 million people will subsequently have the disease in 2025.<sup>2-4</sup> Most of these cases will be type 2 diabetes, which is strongly associated with a sedentary lifestyle and high calorie-nutrition and obesity.<sup>5-6</sup>

On the basis of the aetiology, type 1 may be due to immunological destruction of pancreatic  $\beta$  cells resulting in insulin deficiency. Its pathogenesis involves environmental triggers that may activate autoimmune mechanisms in genetically susceptible individuals, leading to progressive loss of pancreatic islet  $\beta$  cells.<sup>7</sup> Many of the acute affects of this disease can be controlled by insulin replacement therapy, but there are long-term adverse effects on blood vessels, nerves and other organ systems. Type 2 DM is associated with both impaired insulin secretion and insulin

resistance. Type 2 DM is more prevalent form of the disease and common in individuals over 40 years of age. It is often associated with obesity and hereditary disposition.<sup>8</sup> Despite enormous research efforts, the nature of the defect has been difficult to determine. In some patients, the insulin receptor is abnormal, in others some aspects of insulin signaling is defective, and in others no defect has been identified. Significantly, the disease is usually controlled through dietary therapy, exercise and hypoglycaemic agents.<sup>6, 9-10</sup>

### Symptoms

Although the symptoms are similar in both types of diabetes they vary in their intensity. The presentation is most typical and the symptoms develop most rapidly in patients with type 1 DM. These symptoms include polyuria, polydipsia, polyphagia, weight loss, fatigue, cramps, constipation, blurred vision, and candidiasis.<sup>1</sup> Long-standing type 1 DM patients are susceptible to microvascular complications, (nephropathy, neuropathy, retinopathy); and macrovascular disease (coronary artery, heart, and peripheral vascular diseases).<sup>1</sup>

Symptoms in patients with type 2 DM are similar but insidious in their onset. Many cases are diagnosed incidentally or because of the presence of diabetic complications. Type 2 DM carries a high risk of large vessel atherosclerosis; commonly associated with hypertension, hyperlipidaemia, and obesity. Myocardial infarction is also common and accounts for about 60% of the deaths in diabetic patients. Moreover, human studies have shown that

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diabetes mellitus can be associated with altered cardiac function<sup>11</sup> and this can occur independently of cardiovascular complications.<sup>12</sup>

### Complications of diabetes mellitus

There are several complications of DM. These are generally classified into acute, sub-acute and chronic complications.<sup>1</sup> Acute complications occur within 2-4 weeks and they include hypoglycaemia, diabetic ketoacidosis and hyperosmolar hyperglycaemic non-ketotic syndrome.<sup>13</sup> The usual sub-acute complications are thirst, polyuria and weight loss; other symptoms such as lack of energy and visual blurriness are also manifested.<sup>1</sup> The chronic complications of DM are hypertension, neuropathy, nephropathy, retinopathy and diabetic foot ulcers. Other complications of diabetes mellitus include aggravated atherosclerotic disease of the heart, myocardial infarction, heart failure, and a predisposition to infection, limited joint mobility, hardening of the skin and cataract formation.

### Treatment

The care of diabetes is based on self management by the patient, with the help of the specialist. Diabetes management should be set individually, based on the patient's clinical status and his/her ability to participate in self-care. Insulin replacement therapy is the mainstay for patients with type 1 DM and is also important in type 2 DM when blood glucose levels cannot be controlled by diet, weight loss, exercise and oral medications. Oral hypoglycaemic agents are also useful in the treatment of type 2 diabetic patients. The main objective of these drugs is to correct the underlying metabolic disorder, such as insulin resistance and inadequate insulin secretion. They should be prescribed in combination with an appropriate diet and attempts must be made to modify the patient's life style. Oral hypoglycaemic agents include sulphonylureas, biguanides, alpha glucosidase inhibitors and thiazolidenediones.<sup>1</sup> Although the administration of insulin, oral hypoglycaemic drugs or a combination of them is important in the management of DM, diet plays a major role in the management of this disease. Dietary measures include the use of traditional medicines mainly derived from plants.

### Use of herbal plants in diabetes mellitus

A multitude of plants have been used for the treatment of diabetes throughout the world. In fact, in many parts of the world especially in poor countries, this may be the only form of therapy available for treating diabetic patients. There are several literature reviews by different authors about anti-diabetic herbal agents, but of the most informative is the one on anti-diabetic plants by Atta-ar-Rahaman et al.<sup>14</sup> This review documented more than 300 plant species accepted for their hypoglycaemic properties and classified according to their botanical name, country of origin, parts used and nature of active agents. One such plant is *Momordica charantia* (Linn Family: Cucurbitaceae) whose fruit is known as Karela/corilla, or bittergourd. Although the country of origin is uncertain, the plant is commonly cultivated for its fruit in tropical regions of India, China, East Africa and Central and South America. Several studies have examined the antidiabetic potential of bitter gourd, both in humans as well as in experimental animals.



**Fig 1:** *Momordica charantia* fruit

Various parts of *M. charantia* such as the seed, fruit and even the whole plant were used in these studies.<sup>15</sup> This plant has been reported to have anti-leukaemia and antiviral activities<sup>16</sup>.

### Historical perspective

The first clinical study into the influence of the fresh juice of bittergourd on the management of DM was by Akhtar<sup>17</sup>. This suggested the intervention would effectively treat all symptoms of diabetes including polyuria, polydipsia, and polyphagia. Urinary excretion of sugar was also reduced, and insulin injections were stopped. Karunanayake et al.<sup>18</sup> later established a method of preparing the fruit juice of *M. charantia*. Although the initial results established that *M. charantia* juice possesses important anti-diabetic properties, the principal aim was to isolate the active components of the juice. For this purpose chloroform was used to partially extract and isolate various components of *M. charantia* fruit juice<sup>19</sup> and they succeeded in producing water-soluble extracts in adequate quantities for further study.

Studies on experimental animals have yielded contradictory results on the use of *M. charantia* in the treatment of DM. For example, Rao et al.<sup>20</sup> observed that in non-diabetic animals, at 100, 200 and 500-mg/kg body weight (bw), the bittergourd did not have any hypoglycaemic effect. A few recent studies on diabetic animals have also shown that bittergourd did not have any beneficial hypoglycaemic effect. The results of Chandrasekhar et al.<sup>21</sup> have shown that while the aerial part of the plant and the fruit did not have any hypoglycaemic effect (250 mg/kg bw orally), extract of the whole plant brought about a significant lowering of blood glucose levels with the same doses. Karunanayake et al.<sup>22</sup> noting that glucose tolerance did not improve when a dose of 10 ml/kg bw of *M. charantia* was given daily to streptozotocin (STZ)-induced diabetic rats, concluded that viable  $\beta$  cells, capable of secreting insulin upon stimulation, are probably required for bittergourd to exhibit its hypoglycaemic potential. Karunanayake et al.<sup>22</sup> found that oral administration of the juice (10 ml/kg for 30 days) did not show a significant effect, either acutely or cumulatively, on the ability to tolerate an external glucose load. The glycosylated haemoglobin concentrations were found to be significantly elevated in both juice-treated and untreated diabetic rats and there was no significant difference between the two groups.

Contrary to these negative findings, a number of studies

have reported the beneficial effects of bittergourd in diabetic animal models. Studies by Sarkar et al.<sup>23</sup> and Miura et al.<sup>24</sup> have shown significant reductions in blood sugar level after the administration of *M. Charantia*. The results of Leatherdale et al.<sup>25</sup> indicated that the fresh bitter-gourd juice caused a significant reduction in plasma glucose concentration, and an improvement in the response to an oral glucose load. Akhtar et al.<sup>26</sup> administered the dried fruit of bitter gourd to alloxan diabetic rabbits at doses of 0.25, 0.5, 1.0 and 1.5 g/kg bw, orally and found that only doses of 1.0 and 1.5 g/kg brought about a significant dose-dependent decrease in blood glucose levels. In normal mice, intraperitoneal administration of Cerasee, a wild variety of *M. charantia* improved glucose tolerance after 8 h, and in STZ diabetic mice the level of hyperglycaemia was reduced by 50% after 5 h. Chronic oral administration of Cerasee to normal mice for 13 days improved glucose tolerance. The Cerasee extracts did not significantly alter plasma insulin concentrations, suggesting that Cerasee may exert an extrapancreatic effect to promote glucose disposal.<sup>27</sup>

Kedar et al.<sup>28</sup> found that the seed also possesses a hypoglycaemic potential. They fed the finely powdered seed along with a casein diet to STZ diabetic rabbits at doses of 1, 2 and 3 g/kg bw. The 2 and 3 g/kg doses increased liver glycogen concentration. Glucose tolerance was only slightly improved by 1 g/kg of the seeds, and approached normal with 2 g/kg. Interestingly, the 3 g/kg dose controlled hyperglycaemia in a manner similar to that of glibenclamide, a hypoglycaemic drug. The hypoglycaemic effect was simultaneously accompanied by hypolipidaemia, determined by the levels of serum cholesterol, FFA (Free Fatty Acid) and triglycerides that were brought back to normal by the seed treatment. Blood urea and serum creatinine levels significantly rose with the seed treatment and were on par with values seen in uncontrolled diabetes. This showed that the seeds of bittergourd failed to control kidney damage in DM. In summary aqueous extract of bittergourd was found to have a significant hypoglycaemic effect in diabetic patients.<sup>29</sup> Indeed, significant hypoglycaemic effect of this vegetable has been reported by a large group of workers.<sup>15</sup> The effect of bittergourd seems to be more acute and transient rather than cumulative. Fresh aqueous extract of the whole fruit appears to be more effective than dried powder, or dietary consumption as a vegetable. The seed portion was also found to have a hypoglycaemic effect in a limited numbers of studies.

### Mechanism of action

The fruit juice significantly increased the number of beta cells in *M. charantia*-treated animals when compared with untreated diabetics. However, the number was still significantly less than that obtained in normal rats. The number of alpha cells did not change significantly in *M. charantia*-treated rats when compared with untreated diabetic rats.<sup>30</sup>

In another study,<sup>31</sup> feeding of 0.02, 0.1 and 0.5% w/w diet containing *M. charantia* for 8 weeks did not affect either blood sugar, food intake, growth, organ weights or haematological parameters of normal adult rats. However, 0.5% diet caused a significant hypocholesterolaemic effect.

STZ-diabetic rats fed with 0.5% diet containing *M. charantia* for 6 weeks did not show any beneficial hypoglycaemic effect and did not prevent diabetes-related abnormalities in the levels of urea and creatinine.<sup>32</sup>

*M. Charantia* markedly reduced the STZ-induced lipid peroxidation in the pancreas of mice, RIN cells (rat insulinoma cell line) and islets. Furthermore, it also reduced STZ-induced apoptosis in RIN cells indicating the mode of protection of bittergourd fruit juice on RIN cells, islets and pancreatic beta cells<sup>33</sup>. Oral supplementation (0.5, 1 and 3%) with freeze-dried powder of *M. charantia* for 14 days with and without 0.5% (w/w) cholesterol and 0.15% (w/w) bile acid in the diet resulted in a consistent decrease in serum glucose levels in normal rats only. The plant also exerted anti-atherogenic effect.<sup>34</sup>

The fruit juice increased glucose uptake by tissues without concomitant increase in tissue respiration.<sup>35</sup> Aqueous extract of immature fruits of *M. charantia* has also been shown to partially stimulate insulin release from isolated beta cell of obese-hyperglycaemic mice.<sup>36</sup>

Ethanollic extract of *M. charantia* (250 mg/kg dose orally) significantly lowered blood sugar in fasted as well as glucose loaded non-diabetic rats.<sup>21</sup> Oral administration of acetone extract of fruit powder of *M. charantia* for 15-30 days to alloxan-diabetic rats lowered the blood sugar and serum cholesterol levels to normal range and the blood sugar was found to be normal for up to 15 days after the end of the treatment<sup>37</sup>. Similar results were reported by Shibib et al.<sup>38</sup> in normal and diabetic rats. They observed that hepatic glucose-6-phosphatase and fructose-1,6-bisphosphatase activities were depressed by 32% and 30%, respectively in the STZ-diabetic rats, compared with 19% and 20% depression in the normal fed controls. Taken together, these results indicate that *M. charantia* extracts lowered blood glucose by depressing its synthesis, on the one hand through depression of the key gluconeogenic enzymes 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. Ali et al.<sup>39</sup> tested extracts of fruit pulp, seed and whole plant for their hypoglycaemic effects. The pulp juice was found to lower fasting blood glucose levels, and the saponin-free metabolic extract of the juice had more pronounced effect. Some efforts have been made to isolate the active hypoglycaemic agent from bittergourd. Parkash et al.<sup>40</sup> have isolated a non-nitrogenous neutral substance from the fruit of *M. charantia*, named "charantin", a peptide resembling insulin. This substance decreased blood sugar level on a temporary basis. Charantin lowered fasting blood sugar in rabbits gradually beginning from first and lasting until the fourth hour and slowly recovering to the initial level. Charantin (50 mg/kg bw) administered orally, lowered blood glucose by 42% at the fourth hour with a mean fall of 28% during the fifth hour.<sup>40</sup> Polypeptide-p, isolated from the fruit, seeds and tissue of *M. charantia* showed a potent hypoglycaemic effect when administered subcutaneously to gerbils and humans.<sup>41</sup>

Meir et al.<sup>42</sup> found that *M. charantia* contained two

compounds. One of the compounds has the potential to inhibit hexokinase activity and the other glucose uptake. Both showed the ability to reduce plasma glucose. A possible cause of reduction in the levels of glycaemia in diabetic rats could be due to a reduction in the intestinal absorption of glucose. Oral administration of different *M. charantia* extracts showed a varying pattern of anti-hyperglycaemic effect without altering the insulin response suggesting a mechanism of action, which is independent of intestinal glucose absorption and probably involves an extra-pancreatic effect<sup>43</sup>. Matsuda et al.<sup>44</sup> examined the structure-related activity of oleanolic acid glycosides with respect to their inhibitory effect on the increase in serum glucose in oral glucose-loaded rats and their mechanism of action using oleanolic acid 3-O-glucuronide and momordin Ic (an extract from *M. Charantia*). Both the 3-O-monodesmoside structures and 28-carboxyl group were confirmed to be essential for such activity, and the 3-O-glucuronide was more potent than 3-O-glucoside. On the other hand, the 28-ester glucoside moiety and 6'-methyl ester of the glucuronide moiety reduced such activity. Oleanolic acid 3-O-glucuronide and momordin Ic, both of which inhibited the increase in serum glucose in oral glucose-loaded rats, did not lower serum glucose in normal or intraperitoneal glucose-loaded rats, or alloxan-induced diabetic mice. These glycosides were found to suppress gastric emptying in rats, and also inhibit glucose uptake in the rat small intestine *in vitro*. These results indicate that oleanolic acid 3-O-glucuronide and momordin Ic, given orally, have neither insulin-like activity nor insulin releasing-activity. They probably exhibit their hypoglycaemic activity by suppressing the transfer of glucose from the stomach to the small intestine and by inhibiting glucose transport at the brush border of the small intestine. Oral feeding of *M. charantia* juice to normal rats prior to glucose loading increased hepatic and muscle glycogen content while triglyceride content was not affected. All these studies have resulted in several theories to explain the hypoglycaemic action of bittergourd. Some workers have suggested an extra-pancreatic effect. Recently, Shibib et al.<sup>38</sup> concluded that the hypoglycaemic effect of bittergourd is mediated through suppression of the key gluconeogenic enzymes and accelerated rate of glucose metabolism through the pentose phosphatase pathway by activating its key enzyme.

Contrary to these theories, an insulin secretagogue effect has also been attributed to bittergourd because it exerts an indirect effect on blood glucose levels by stimulating the secretion of insulin. The work of Karunanayake et al.<sup>22</sup> and Kedar et al.<sup>28</sup> support these findings.

All of these contradictory findings show that we know little about the mechanism of action of bittergourd. Regardless of the mechanism of action, bittergourd could safely be prescribed to diabetic patients, since bitter gourd is a natural plant substance with no known harmful side effects.

## The beneficial effects of *M.charantia*.

### 1. Hypoglycaemic effect

It is unanimously agreed that *M.charantia* fruit juice administration reduces blood glucose levels. This effect

may be due to two reasons: firstly its effect over the gluconeogenic enzymes, and second it may exert its action on the transporters of glucose.

### The depression of key gluconeogenic enzymes

Initial data showed that the treatment of diabetic rats with karela fruit juice resulted in significant reduction in blood glucose levels as compared to untreated diabetic rats. At present, the mechanisms involved in the hypoglycaemic effects of *M.charantia* are not established. However, it has been suggested that the depression of key gluconeogenic enzymes such as glucose-6-phosphatase and fructose-biphosphatase may be partly involved in the hypoglycaemic effects of this fruit juice.<sup>38</sup>

### Increase in the levels of intestinal Na<sup>+</sup> /glucose co-transporters

*M. charantia* may cause hypoglycaemia via an increase in glucose oxidation through the activation of glucose metabolism and/or the inhibition of glucose absorption in the gut.<sup>45-46</sup> It was shown by Dyer et al.<sup>47</sup> that there is an increase in the levels of intestinal Na<sup>+</sup>/glucose co-transporters (SGLT1) in STZ-induced diabetes resulting in increased glucose uptake in the gut of these animals. The increase of Na<sup>+</sup>- and K<sup>+</sup>-dependent glucose uptake by small intestine BBM (brush border membrane) vesicles in STZ-induced diabetes has been demonstrated recently. Oral feeding of *M. charantia* to STZ-diabetic rats brought the glucose uptake level in the gut close to control values. The inhibition of glucose uptake in the gut may be one of the mechanisms by which this plant exerts its hypoglycaemic effect<sup>45</sup>. Recently, momordin Ic has been reported to suppress gastric emptying and inhibit glucose transport at the brush border of small intestine.<sup>48</sup> There is about 80% reduction in the glucose uptake in *M. charantia*-treated diabetic rats; however, the blood glucose levels are only marginally reduced. This discrepancy may be because there are several compensatory mechanisms to preserve glucose levels *in vivo* (peripheral uptake, gluconeogenesis in the liver, hormones and catecholamines) which can alter blood glucose levels irrespective of how glucose transport is regulated at the gut level.

### 2. Preservation of the pancreatic islet β cells

It has been reported that viable β cells are required for the expression of oral hypoglycaemic activity of *M. charantia* suggesting that the oral hypoglycaemic activity of *M. charantia* is at least partly mediated by increased insulin secretion<sup>49</sup>. The action of this plant may be mediated in part by the preservation of the islet β cells and β cell functions since basal insulin levels were higher in *M. charantia* treated compared to untreated STZ-diabetic animals and glucose administration caused a significant rise in plasma insulin levels.<sup>46</sup> The increase in insulin secretory activity by *M. charantia* has also been shown *in vitro*.<sup>36</sup> In this study the tropical plant *M. charantia* was found to be a potent stimulator of insulin release from beta-cell-rich pancreatic islets isolated from obese-hyperglycaemic mice. The stimulation of insulin release was partially reversible. It differed from that of D-glucose and other commonly employed insulin secretagogues in not being suppressed by L-epinephrine and in even being potentiated by the removal

of  $\text{Ca}^{2+}$ . This anomalous behaviour was not associated with general effects on the metabolism of the beta cells as indicated by an unaltered oxidation of D-glucose. Studies of  $\text{Ca}^{2+}$  fluxes suggest that the insulin-releasing action is the result of perturbations of membrane functions.<sup>45</sup> In support of the idea of a direct effect on membrane lipids, the action of the extract was found to mimic that of saponin in inhibiting the  $\text{Ca}^{2+}/\text{H}^+$  exchange mediated by the ionophore A23187 in isolated chromaffin granules and released  $\text{Ca}^{2+}$  from preloaded liposomes. Further studies are required to find a dose-response relationship of the active ingredient and or molecules involved and to establish the mechanism of action of *M. charantia*.

### 3. Normalisation of the hypertension

*M. charantia* fruit juice can produce a normalisation of the systolic blood pressure.<sup>46</sup> The incidence of hypertension is increased in individuals with DM. In these patients, high blood pressure is common at the time of diagnosis of diabetes, but the development of diabetes is often preceded by a period during which hyperinsulinaemia and insulin resistance is already present. Diabetes represents by itself a major risk of cardiovascular morbidity and mortality. This risk is considerably enhanced by the co-existence of hypertension.<sup>50-51-52</sup>

The result of Ahmed<sup>46</sup> has demonstrated clearly that the administration of *M. charantia* fruit juice to STZ-diabetic rats can result in normalisation of the systolic blood pressure. The systolic blood pressure in control rats ranged from 69.3 to 98.9 mm Hg ( $88.0 \pm 2.7$  mm), the mean systolic pressure for the untreated diabetic rats ranged from 87 to 148.3 mm Hg ( $122.8 \pm 7.1$  mm Hg) and was significantly higher than those of controls. The values for the *M. Charantia* treated group ranged from 67.6 to 114.5 mm Hg ( $92.2 \pm 4.6$  mm Hg). The mean systolic blood pressure was normalised in the *M. charantia* treated group as the values were significantly less than in untreated diabetics and were not different from those in controls.

### 4. Effects of *M. Charantia* on glucose uptake in muscle cells

Insulin can evoke increases of D-glucose uptake in L<sub>6</sub> muscle cells, but in contrast, Karela fruit juice extracts evoke a dose-dependent (50-200 ug/ml) decrease in glucose uptake by these cells. Combining the *M. Charantia* fruit juice extracts with insulin resulted in a significant increase in glucose uptake in contrast with insulin alone. The mechanism by which *M. Charantia* fruit extract improved insulin sensitivity is not known. One possibility is that *M. Charantia* fruit extract may modify the structure of insulin to make it more potent but it may be that the insulin receptors become more sensitive to insulin. Another possibility is that *M. charantia* fruit juice may exert its hypoglycaemic effect not by stimulating glucose uptake in muscle cells, but by inhibiting glucose uptake into the blood.<sup>46</sup> In a more recent study, it was shown that when physiological doses (1- 10 ug/ml) of *M. charantia* fruit extract were employed, they evoked a marked uptake of glucose into L6 skeletal muscle cells. The effect of 5 ug ml<sup>-1</sup>

was similar to that of 100 nM insulin. The effects of both insulin and *M. charantia* fruit juice extract were completely blocked by wortmannin, an inhibitor of the PI3-kinase. Taken together, these results indicate that the active ingredient of the juice is exerting its action through insulin to stimulate glucose uptake by skeletal muscles.<sup>53</sup>

### 5. Effects of *M. charantia* fruit juice on the morphology and function of the pancreas

After treatment with *M. charantia* fruit juice there is a significant change in the distribution of insulin, glucagon and somatostatin-positive cells in the islet of Langerhans. The number of insulin-positive cells decrease markedly in both the *M. charantia* treated and untreated diabetic rats when compared to control animals, but the decrease is much greater in the untreated rats. This interesting observation indicated that *M. charantia* plays an important role in increasing the number of insulin-positive cells in the pancreas. There are two explanations for this effect, first, *M. charantia* may exert its effect by either preventing the death of beta cells or it may permit the recovery of partially destroyed beta cells. *M. charantia* may have prevented further pancreatic beta cell death by decreasing the oxidative stress caused by STZ in diabetic rats.<sup>54</sup> Moreover, *M. charantia* is a fruit and will likely contain anti-oxidants (vitamin C), which have been shown to be beneficial in diabetes mellitus.<sup>55-56</sup> Antioxidants presumably help in preventing pancreatic beta cell death by neutralising the free radicals released by STZ during the induction of diabetes.

Possible regeneration of endocrine cells in islets of Langerhans by the oral administration of plant products has also been reported by several investigators.<sup>57-59</sup> Shanmugasundaran et al.<sup>57</sup> suggested on the basis of histological and morphometric observations that oral administration of *Gymnesia sylvestre* leaf extracts to STZ-diabetic rats resulted in repair/regeneration of endocrine pancreas. Similar observations were reported by Rao et al.<sup>59</sup> who used alloxan- induced diabetic rats in their studies and the treatment of the diabetic animals was done by a mixture of 10 plant products shown to possess hypoglycaemic activity termed as "Pancreas Tonic", their major component was *M. charantia*. Histological analysis of the pancreas showed a generalized reduction in size and number of islets in the diabetic group and regeneration of islet cells in the diet-treated group compared with the diabetic group. The diet-treated group contained a significantly increased number of cells compared with the diabetic group. These data suggest that "Pancreas Tonic" induced an antidiabetic effect through pancreatic islet cell regeneration in experimental rats.

Another interesting point is the significant increase in the number of somatostatin positive cells in diabetes.<sup>60</sup> It appears that somatostatin-producing cells rise in number to compensate for the relative reduction in insulin secreting cells. An increase in the number of glucagon producing alpha and somatostatin producing delta cells in diabetes has been reported by Pons et al.<sup>61</sup> and Wang et al.<sup>62</sup> The reason for the increase in number of somatostatin positive cells in

diabetic pancreas is not clear. It has been shown that neuropeptides and peptide increase in quantity and number in experimental diabetes.<sup>60</sup> The increase in the number of somatostatin positive cells and in plasma somatostatin level may play a role in the pathogenesis of acute and chronic complications associated with diabetes.

Physiological studies have shown that *M. charantia* can stimulate insulin secretion<sup>35</sup> and induce glucose uptake in liver.<sup>35</sup> It seems that the induction of an increase in the number of insulin producing cells may be one of the several pathways of action of this vegetable. It is also possible that *M. charantia* may have initiated cell proliferation, since it has been reported that pancreatic endocrine cells have the potential to proliferate after induction of diabetes with STZ<sup>62</sup>. The absolute values of insulin positive cells in the *M.charantia* treated rats are still lower than the controls. The reason for this discrepancy may be attributed to the fact that some  $\beta$  cells may have been completely destroyed with no possibility of recovery whereas the others were partially damaged. In this respect, *M.charantia* may act to prevent the destruction of the insulin positive cells by an unknown mechanism,<sup>46</sup> possibly acting as a growth factor.

#### **6. Modulation of xenobiotics metabolism and oxidative stress in STZ-induced diabetic rats fed with *M. charantia* fruit extract**

There are studies,<sup>63</sup> which have investigated the long-term effects of STZ-induced diabetes on tissue-specific cytochrome P450 (CYP) and glutathione-dependent (GSH-dependent) xenobiotic metabolism in rats. The antidiabetic effects of *M. charantia* fruit extract on the modulation of xenobiotic metabolism and oxidative stress in rats with diabetes have been demonstrated. The results have indicated an increase (35-50%) in CYP4A-dependent lauric acid hydroxylation in liver, kidney, and brain of diabetic rats. About a two-fold increase in CYP2E-dependent hepatic aniline hydroxylation and a 90-100% increase in CYP1A-dependent ethoxycoumarin-O-deethylase activities in kidney and brain were also observed. A significant increase (80%) in aminopyrene N-demethylase activity was observed only in rat kidney, and a decrease was observed in the liver and brain of diabetic rats. A significant increase (77%) in NADPH-dependent lipid peroxidation (LPO) in kidney of diabetic rats was also observed, while a decrease in hepatic LPO was seen during chronic diabetes. During diabetes an increased expression of CYP1A1, CYP2E1, and CYP4A1 isoenzymes was also seen using Western blot analysis. Karela juice modulates the enzyme expression and catalytic activities in a tissue- and isoenzyme-specific manner. A marked decrease (65%) in hepatic GSH content and glutathione S-transferase (GST) activity and an increase (about two-fold) in brain GSH and GST activity was observed in diabetic rats. On the other hand, renal GST was markedly reduced, and GSH content was moderately higher than that of control rats. Western blot analysis have confirmed the tissue-specific alterations in the expression of GST isoenzymes. Karela juice feeding, in general, reversed the effect of chronic diabetes on the modulation of both P450-dependent monooxygenase activities and GSH-dependent oxidative stress related LPO and GST activities.

These interesting results have suggested that the modulation of xenobiotic metabolism and oxidative stress in various tissues may be related to altered metabolism of endogenous substrates and hormonal status during diabetes.<sup>63</sup>

#### **7. Anticarcinogen activity of the *Momordica***

It has been shown that *M. charantia* fruit juice, peel, pulp, seed and whole fruit extract modulate detoxification pathways in diabetic rats, specifically altering P450 and GSH dependent metabolism.<sup>64-65</sup> Modulation of biotransformation system enzymes may be the cause of anti carcinogenic properties of *M. charantia*.<sup>65</sup>

The study by Kusamran *et al.*<sup>66</sup> determined the effects of *M. charantia* on the levels of phase I enzymes, which include cytochrome P450 (P450), aniline hydroxylase (ANH) and aminopyrene-N-demethylase (AMD) and to induce the phase II enzymes [i.e. glutathione S-transferase (GST)] in rat liver. It was demonstrated that bitter-gourd fruits contain phases I and II enzyme inducers and compounds capable of repressing some monooxygenases, especially those involved in the metabolic activation of chemical carcinogens.

In another study<sup>67</sup> carcinogen-induced lipid peroxidation in liver and DNA damage in lymphocytes were reduced following treatment with *M. charantia*. The fruit extract was found to significantly activate the liver enzymes glutathione-S-transferase, glutathione peroxidase and catalase, which showed a depression following exposure to the carcinogen. The results suggest a preventive role of water-soluble constituents of *M. charantia* fruit during carcinogenesis, which is mediated possibly by their modulatory effect on enzymes of the biotransformation and detoxification system of the host.

While the mechanism of the effects of this natural product remains to be clarified, there were no adverse effects of treatment with these agents as estimated from body weight, food and water intake and various plasma component levels as well as external appearance.

#### **8. The influence of *M.charantia* fruit juice on myelinated fibres**

Human diabetic neuropathy is a worrying complication of DM and may be a cause of severe disability<sup>68</sup>. It has been reported that in STZ-induced diabetic rats, the myelinated fibre size is reduced following the induction of diabetes.<sup>69</sup> Previous studies have revealed that conventional insulin treatment did not completely normalise myelinated fibre area and the axonal areas in the tibial nerve of experimental diabetic rats.<sup>70</sup> An excellent metabolic control of DM as judged by body weight, blood glucose levels and glycosylated haemoglobin levels has been shown by pancreatic islet transplantation over a longer period in experimental diabetic rats. This is associated with the normalisation of myelinated fibre size.<sup>71</sup>

It is known that myelinated fibre area is reduced in experimental diabetic rats and the metabolic effects of diabetes equally affect their axons and myelin cover. This has been observed in the tibial nerve of genetically diabetic

mutant mice.<sup>69</sup> These authors observed that myelinated fibre size was smaller in diabetic animals at all stages and affected cross-sectional axon area and myelin thickness equally without affecting un-myelinated axons.<sup>46</sup>

The administration of *M. charantia* slightly increased the myelinated fibre area. The mechanism for the beneficial effects of *M. charantia* administration on the structural abnormalities of peripheral nerves in experimental diabetes has yet to be established. There is evidence to suggest that antioxidant administration prevents the development of functional abnormalities in STZ-diabetic rats.<sup>56,72-74</sup> Antioxidants prevent the development of vascular mediated nerve dysfunctions such as reduced motor nerve conduction velocity, reduced blood flow and decreased endoneurial oxygen tension in diabetic rats<sup>75</sup>. *M. charantia* administration can normalise the myelinated fibre population in diabetic rats, probably due to the reduction of blood glucose levels. Assuming that the results of the animal studies could be extended to man, *M. charantia* administration may be useful as an adjunct therapy in order to reduce the dosage of insulin or oral hypoglycaemic agents in the management of DM and its complications.

### Conclusion

DM is a major global health problem, which is now becoming an epidemic. Diet and exercise are essential parts of the treatment of this disease. Previous to the use of insulin, dietary measures involving the use of traditional medicines, derived from plants, were the major form of treatment. In fact, the use of this kind of medicine still persists in many parts of the world, especially in Asia. *M. charantia* is extensively cultivated in many parts of the world including India, South East Asia, Africa, the Caribbean and South America. The fruit of this plant named Karela or bittergourd has been used as a herbal medicine for the treatment of diabetes in folk medicine. The hypoglycaemic action of *M. charantia* has been extensively studied. Its mechanism of action and its effects on the complications of diabetes are still poorly understood. It can be concluded, that administration of *M. charantia* to STZ-diabetic rats decreases blood glucose levels. This hypoglycaemic effect may be due to depression of key gluconeogenic enzymes or the increase in the levels of glucose transporters and stimulation of glucose uptake in skeletal muscle cells. Another effect of this plant is to preserve the islet  $\beta$  cell and  $\beta$  cells functions, which result in a significant increase in insulin secretory activity. In addition, the administration of *M. charantia* fruit juice is effective in reducing systolic blood pressure.

The plant extract can also reduce xenobiotic metabolism and oxidative stress and increase cytochrome P450 and a tissue specific alteration in GSH (Glutathione) expression and GST (Glutathione S transferase) activity.

Furthermore *M. charantia* can modulate the biotransformation system enzymes and have anti carcinogenic as well as antihypertensive effects. Finally, fruit juice can either delay or prevent diabetes-induced

neuropathy by acting like antioxidants preventing the development of functional abnormalities caused by diabetes.

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