

## Review

# Medicinal plants with potential antidiabetic activity - A review of ten years of herbal medicine research (1990-2000)

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### Abstract

Medical plants play an important role in the management of diabetes mellitus especially in developing countries where resources are meager. This review presents the profiles of plants with hypoglycaemic properties, reported in the literature from 1990 to 2000. The profiles presented include information about the scientific name, family, methodology used, the degree of hypoglycaemic activity and the active agents. The large number of plants described in this review (176 species belonging to 84 families) clearly demonstrated the importance of herbal plants in the treatment of diabetes. It also shows the effort to isolate new potential antidiabetic agents. The plant families, including the species (sp), most studied for their confirmed hypoglycaemic effects include: Leguminosae (11 sp), Lamiaceae (7 sp), Liliaceae (8 sp), Cucurbitaceae (7 sp), Asteraceae (6 sp), Moraceae (6 sp), Rosaceae (6 sp), Euphorbiaceae (5 sp) and Araliaceae (5 sp). The most studied species are: *Citrullus colocynthis* (*Opuntia streptacantha* Lem. (Cactaceae), *Trigonella foenum graecum* L. (Leguminosae), *Momordica charantia* L. (Cucurbitaceae), *Ficus bengalensis* L. (Moraceae), *Polygala senega* L. (Polygalaceae), and *Gymnema sylvestre* R. (Asclepiadaceae). Many studies have confirmed the benefits of medicinal plants with hypoglycaemic effects in the management of diabetes mellitus. The effects of these plants may delay the development of diabetic complications and correct the metabolic abnormalities. Moreover, during the past few years some of the new bioactive drugs isolated from hypoglycaemic plants showed antidiabetic activity with more efficacy than oral hypoglycaemic agents used in clinical therapy. (Int J Diabetes Metab 14: 1-25, 2006)

**Keywords:** Hypoglycaemic, antidiabetic, medicinal plants, diabetes mellitus, pharmacognosy

### Introduction

The aim of this review is to collate all available data on plants with hypoglycaemic effects reported in the Medline (PubMed) during the 1990-2000 period. This review and those of Ivorra *et al.*<sup>1</sup> and Atta-Ur-Rahman<sup>2</sup> show the importance and the interest placed on medicinal plants in the drive to demonstrate their antidiabetic effects and to isolate the bioactive agents.

Many ethnobotanical surveys on medicinal plants used by the local population have been performed in different parts of the world including Morocco, Saudi Arabia, Taiwan, and Trinidad and Tobago.<sup>2-5,8-9</sup> Several plant species have been described as hypoglycaemic. These include *Opuntia streptacantha* Lem, *Trigonella foenum graecum* L, *Momordica charantia* L, *Ficus bengalensis* L, *Polygala senega* L., *Gymnema sylvestre* R., *Allium sativum*, *Citrullus colocynthis*, myrrh, black seeds, helteet, fenugreek, aloe and *Artemisia*.<sup>2-5</sup> Other species are less well known.

In the present review, interest is focused on experimental studies performed on hypoglycaemic plants and their bioactive components. Studies which did not use

experimental procedures, such as casual surveys or folk medicine<sup>4,-6-9</sup> are not reported. Moreover, studies based on preparations of mixtures of plants with unknown origin were not considered in the present review.

Several medicinal plants have been used as dietary adjunct and in the treatment of numerous diseases without proper knowledge of their function. Although phytotherapy continues to be used in several countries, few plants have received scientific or medical scrutiny. Moreover, a large number of medicinal plants possess some degree of toxicity. For example, it was reported that about one third of medicinal plants used in the treatment of diabetes are considered to be toxic.<sup>11</sup>

We believe that the list of medicinal plants presented in this review is useful to researchers, as well as practitioners. This list is best used only as a preliminary screening of potential antidiabetic plants, not as a definitive or complete list of hypoglycaemic plants.

The list of potential hypoglycaemic plants is presented in the following paragraphs. The scientific name of the plant, the family and the name of the country in which they are available are indicated. The description of methods used in the experiments, model animals, and the degree of hypoglycaemia, doses, toxicity and active ingredients are also included. Plants which did not show any significant hypoglycaemic effect were not included.

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### **Acanthaceae**

Oral administration of the extract of *Asteracantha longifolia* Nees. (20 g/kg of starting material) can significantly improve glucose tolerance in healthy human subjects and diabetic patients.<sup>12</sup>

### **Amaranthaceae**

Oral administration of 2, 3, and 4 g/kg of *Achyranthes aspera* L produced a significant dose-related hypoglycaemic effect in normoglycaemic and alloxan-induced diabetic rabbits. In these animals, water and methanol extracts also decreased blood sugar levels. The plant may act by providing certain necessary elements like calcium, zinc, magnesium, manganese and copper to the beta-cells.<sup>13</sup>

### **Anacardiaceae**

The antidiabetic activity of *Mangifera indica* L(Mango) was seen when an extract of the leaves of *M indica* was given to rats 60 min before the glucose. The hypoglycaemic effect of the aqueous extract was compared with that of an oral dose of chlorpropamide (200 mg/kg). The hypoglycaemic action of this plant may be due to a reduction in the intestinal absorption of glucose.<sup>14</sup>

### **Apiaceae**

Male Swiss mice were orally loaded with glucose after the extracts of *Daucus carota* L.had been given by oral loading. The extract of *Daucus carota* L.was prepared by boiling the dried material with water or macerating it with 80 % ethanol. It was shown that the extract improved the glucose tolerance.<sup>15</sup>

Seeds of *Coriandrum sativum* L(Coriander)., when supplied in the diet (6.25 % by weight) and infusion (1 g/400 ml) in place of drinking, reduced the hyperglycaemia during the development of streptozotocin-induced diabetes in mice.<sup>16</sup>

The antihyperglycaemic effect *Cuminum cyminum* L.was studied in healthy rabbits subjected to weekly subcutaneous glucose tolerance tests after gastric administration of water, tolbutamide or a traditional preparation of the plant. The results showed that the *C. Cyminum* significantly decreased the area under glucose tolerance curve and the hyperglycaemic peak.<sup>17</sup>

Oral administration of the flavonoids content (8%) of the seeds of *Cuminum nigrum* caused a significant blood glucose lowering at a dose range of 0.5 to 1.5 g/kg, both in normoglycaemic and alloxan-induced diabetic rabbits. The maximum of decrease in glycaemia was obtained within 4-8 h; the normal level of glycaemia was reached within 24 h of drug administration. In contrast, the alkaloids isolated from *C. nigrum* (0.01%) had no significant hypoglycaemic effect in either normoglycaemic or diabetic rabbits. A high dose of 5g/kg did not produce any adverse effects in a 7-day acute toxicity study in rabbits.<sup>18</sup>

### **Apocynaceae**

Oral administration of the aqueous fraction of an alcoholic extract of leaves of *Vinca rosea* L. *Catharanthus roseus* Don leads to marked lowering of glycaemia in normal and streptozotocin-induced diabetic rats. This effect was

comparable with that of tolbutamide<sup>19</sup>. Three suspension cultures of *C. rosea* were obtained from three different cell lines (CWS, CW-A and CWS-G). In the production medium, the first cell line produced 0.1 % ajmalicine and the cell extract caused a 71 % decrease in glycaemia in diabetic rats. In contrast, in the growth medium, CWS produced trace amounts of alkaloids and the extract did not show any anti-diabetic activity. The CWA cell line synthesized 0.036 % ajmalicine. The extract had no hypoglycaemic effect while in the growth medium the cells produced trace amounts of alkaloids and the extract induced an 86 % decrease in blood sugar. The CWS-G cell line did not produce significant levels of alkaloids and had no hypoglycaemic effect.<sup>20</sup>

The extract of *Rhazya stricta* Decne at oral doses of 0.5, 2.0 and 4.0 g/kg reduced glycaemia 1 h (2 and 4 g/kg) and 2 h (4 g/kg) after administration to streptozotocin-diabetic rats. The insulin concentration increased 1, 2 and 4 h after administration of the extract at 2 and 4 g/kg. Treatment of control animals with the extract did not affect glycaemia, insulin or glucagon levels for up to 4 h after the administration of the extract. Simultaneous treatment of healthy and diabetic rats with the extract (0.5, 2.0 and 5.0 g/kg) and glibenclamide (5.0 mg/kg) exacerbated the effects on glucose, insulin and glucagon. At doses of 0.5, 2.0 and 4.0 g/kg/day for 6 consecutive days the glycaemia was reduced by approximately 6, 8 and 30 %, respectively.<sup>21</sup>

### **Araliaceae**

Ginseng polypeptides (GPP) isolated from the root of *Panax ginseng* Mey. (Asiatic ginseng)decreased the level of blood sugar and liver glycogen when injected i.v. to rats at doses of 50-200 mg/kg without affecting total blood lipid concentrations. When mice were injected subcutaneously with daily doses of 50 and 100 mg/kg for 7 successive days, GPP was also found to decrease blood glucose and liver glycogen and stimulated the release of insulin. In addition, GPP was found to decrease hyperglycaemia induced experimentally by injection of adrenaline, glucose and alloxan.<sup>22-23</sup> The oral administration of the water extract of *Ginseng Radix* (GR) to normal and adrenaline-induced hyperglycaemic mice caused a significant decrease in blood glucose level 4 h after its administration. The hepatic content of the facilitative glucose transporter isoform 2, liver type glucose transporter (GLUT 2) protein significantly increased in the orally GR-treated healthy and adrenaline-induced hyperglycaemic mice compared to that in the controls.<sup>24</sup> Recently, ginseng, which is among five crude drugs included in the traditional Chinese prescription, Byakko-ka-ninjin-to, was investigated using genetically obese diabetic KK-CA(y) mice and alloxan-diabetic mice. The water extract of ginseng, when individually tested, markedly lowered blood glucose level in diabetic animals.<sup>25</sup>

On 4 separate occasions, 10 non-diabetic subjects and 9 subjects with type 2 diabetes mellitus received 3 *Panax quinquefolius* L.(american ginseng)or placebo capsule,

either 40 minutes before or together with a 25 g oral glucose challenge (gc). Significant reduction in glycaemia was observed only when ginseng was taken 40 min before gc in non-diabetic subjects and the same result was seen in diabetic subjects.<sup>26</sup>

Saponin isolated from the leaves of *Acanthopanax senticosus* injected to mice (100, 200 mg/kg, i.p.) decreased experimental hyperglycaemia induced by injection of adrenaline, glucose and alloxan, without affecting the levels of blood sugar in untreated mice.<sup>27</sup>

Elatosides E was isolated from the root cortex of *Aralia elata* Seem. (Japanese Angelica) Seem. It was shown to affect the elevation of plasma glucose levels in an oral sugar tolerance test in rats. The structures of elatosides E and F have been elucidated. Moreover, the hypoglycaemic activity of oleanolic acid and nine oleanolic acid glycosides isolated from the root cortex of this plant were tested.<sup>28</sup> Five new saponins named elatosides G, H, I, J, and K were isolated from a garnish foodstuff "Taranome" which is the young root shoot of *A. elata* Seem. Elatosides G, H, and I were found to exhibit potent hypoglycaemic activity in the oral glucose tolerance test in rats.<sup>29</sup> Nine oleanolic acid oligoglycosides were isolated from the cortex of *A. elata*.<sup>30</sup>

In order to identify the antidiabetic agent from the stem bark of *Kalopanax pictus* Nakai, seven kinds of chemical constituents including hederagenin glycosides and phenolic glycosides were isolated. The antidiabetic evaluation of these isolates in streptozotocin-induced diabetic rats showed that kalopanax saponin A has a potent antidiabetic activity in contrast to a mild activity of hederagenin.<sup>31</sup> To investigate the relationship between the intestinal bacterial metabolism of kalopanaxsaponin B and H from *K. pictus*, and their antidiabetic effect, kalopanaxsaponin B and H were metabolized by human intestinal microflora and the antidiabetic activity of their metabolites was measured. The main metabolites of kalopanaxsaponin B were kalopanaxsaponin A and hederagenin. The main metabolites of kalopanax H were kalopanaxsaponin I and hederagenin. Among kalopanaxsaponin B, H and their metabolites, kalopanaxsaponin A showed the most potent antidiabetic activity, followed by hederagenin.<sup>32</sup>

#### Arecaceae

The hypoglycaemic effect of neutral detergent fiber from *Cocos nucifera* L. (*coconut*) was tested in rats fed 5%, 15% and 30% glucose. Increase in fiber intake caused a significant lowering in glycaemia and serum insulin. Moreover, it increases the fecal excretion of Cu, Cr, Mn, Mg, Zn and Ca. The results suggest the beneficial effect of inclusion of coconut fiber in the diet.<sup>33</sup>

#### Asclepiadaceae

Oral administration of an extract from *Pergularia tomentosa* Span. to normoglycaemic rats produced an hypoglycaemic effect comparable to Daonil.<sup>34</sup>

In humans: GS4 (400 mg/day) extracted from leaves of

*Gymnema sylvestre* R. Br., was administered to type II diabetic patients for 18-20 months as a supplement to the conventional oral drugs. During GS4 supplementation, 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 drugs and maintain their blood glucose homeostasis with GS4 alone. These data suggested that pancreatic beta cells may be regenerated and/or repaired in type II diabetic patients on GS4 supplementation. This is supported by the appearance of raised insulin levels in the serum of patients after GS4 supplementation.<sup>35</sup> Furthermore, GS4 was administered (400 mg/day) to 27 patients with insulin-dependent diabetes mellitus (type I). GS4 therapy appears to enhance endogenous insulin release, possibly by regeneration/revitalisation of the residual beta cells.<sup>36</sup>

Investigation of the hypoglycaemic activity of saponin constituents from gymnemic acid, a crude saponin fraction of *G. sylvestre*, identified not only two new saponins, gymnemosides a and b, but also gymnemic acid V as the active principle.<sup>37</sup> Recently, effects of the water soluble fraction of an alcoholic extract of *G. sylvestre* leaves on glycogen content of isolated rat hemidiaphragm was studied in normal and glucose fed hyperglycaemic rats. In glucose fed rats, the leaf extract lowered the glycogen content of the tissue and this effect was amplified by insulin.<sup>38</sup>

Cryptolepine is a natural product isolated from *Cryptolepis sanguinolenta*. A series of substituted and heterosubstituted cryptolepine analogues have been synthesised. Antihyperglycaemic activity was measured *in vitro* and in a NIDDM mouse model to generate the first structure-bioactivity study of the cryptolepine nucleus.<sup>39</sup> It was shown that cryptolepine, an indoloquinolone alkaloid isolated from *C. sanguinolenta*, significantly lowers glucose when given orally to diabetic mice. The antihyperglycaemic effect of cryptolepine leads to a significant decline in blood glucose concentration, associated with evidence of an enhancement in insulin-mediated glucose disposal. Finally, cryptolepine increased glucose uptake by 3T3-L1 cells.<sup>40</sup>

#### Asteraceae

*In vivo* bioguided fractionation of the aqueous alcohol extract of the aerial part of *Bidens pilosa* Sch. Bip. Var. *radiata* using a model of type 2 diabetes (C57 BL/Ks-db/db mice) produced two known polyacetylenic glucosides. They were identified as 2-beta-D-glucopyranosyloxyl-1-hydroxy-6(E)-tidecene-7, 9, 11-triynone (1) and 3-beta-D-glucopyranosyloxyl-1-hydroxy-6(E)-tetradecene-8, 10, 12-triynone (2). A 3:2 mixture of glucosides 1 and 2 produced a significant decrease in blood glucose.<sup>41</sup>

Intraperitoneal administration of 300 mg/kg of the hexane extract from *Brickellia veronicaefolia* A. Gray to diabetic mice decreased blood glucose levels by 72 %. This extract administered to normal mice reduced blood glucose levels by 40 %. The hypoglycaemic effect of this plant extract confirmed its use in traditional medicine for the treatment of diabetes.<sup>42</sup>

Furthermore, hypoglycaemic activity-guided fractionation together with chemical analysis led to the isolation of one flavone (5, 7, 3'-trihydroxy-3, 6, 4'-trimethoxyflavone) from the chloroform extract of the leaves of *B. veronicaefolia*. This flavone produced a significant hyperglycaemic action when tested in normoglycaemic and alloxan-induced diabetic mice (CD 1 mice). The doses tested were 10, 20 and 50 mg/kg. The glycaemia was measured 1.5, 3, 4.5 and 24 hours after drug administration.<sup>43</sup>

A study was performed using healthy rabbits with intragastric administration of water, tolbutamide or decoction of the tested plant before the induction of hyperglycaemia by subcutaneous injection of 50 % dextrose solution (4 ml/kg) at the beginning of the experiment and after 60 min. Tolbutamide and *Calea zacatechichi* Schlecht significantly decreased the hyperglycaemia as compared with the control.<sup>44</sup>

An ethanolic extract of the leaves of *Gynura procumbens* Merr., at single doses of 50, 150 and 300 mg/kg given orally, significantly reduced glycaemia in streptozotocin-induced diabetic rats. The optimum hypoglycaemic dose was 150 mg/kg. In normoglycaemic rats, the extract did not show any hypoglycaemic effect. The plant may have biguanide-like activity.<sup>45</sup>

*Psacalium peltatum* Cass. significantly decreased the area under glucose tolerance curve in healthy rabbits subjected weekly to oral glucose tolerance tests compared to control (27.9 %), or tolbutamide-treated (14.3 %) animals.<sup>44</sup> Moreover, traditional preparation of *P. peltatum* had a hypoglycaemic effect similar to that of tolbutamide in healthy and mildly diabetic rabbits but had no effect in severely diabetic rabbits. These results suggested that some pancreatic function or the presence of insulin is required for the hypoglycaemic activity of these plants.<sup>46</sup>

The root decoction of *Psacalium decompositum* reduced the glycaemia of normal mice after i. p. administration and lowered the hyperglycaemic peak (17.1 %) in rabbits with temporal hyperglycaemia.<sup>47</sup> The water extract obtained from the root of *P. decompositum* significantly lowered blood glucose in a dose-dependent manner in healthy mice after intraperitoneal administration. Moreover, the precipitate obtained from the water extract macerated with methanol produced a decrease in glycaemia in normoglycaemic mice and in mildly diabetic mice. Two polysaccharides components isolated from this precipitate have hypoglycaemic effects in healthy mice.<sup>48</sup>

#### **Bignoniaceae**

Intraperitoneal administration of 300 mg/kg of chloroform extract from Bignoniaceae *Parmentiera edulis* DC to diabetic mice decreased the blood glucose levels by 43.75 %. This extract administered to normal mice reduced glycaemia by 29.61 %.<sup>42</sup>

A stem bark decoction from *Spathodea campanulata* Buch-Harm caused a decrease in plasma levels of glucose in mice. Polar fractions of stem bark exerted prominent effects in different biological models.<sup>49</sup>

A study was performed in rabbits subjected to weekly glucose tolerance tests after gastric administration of water, tolbutamide or a preparation of the plant. The results showed that *Tecoma stans* significantly decreased the area under glucose tolerance curve, compared to control (17.5 %), or tolbutamide (14.3 %).<sup>50</sup>

#### **Bombacaceae**

In Sprague-Dawley rats, a dose of 500 mg/kg of Shamimin (a C-flavonol glucoside from *Bombax ceiba*) produced a significant reduction in glycaemia.<sup>51</sup>

#### **Boraginaceae**

*Tournefortia hirsutissima* Linn. decreased the hyperglycaemic peak and the area under the glucose tolerance curve in hyperglycaemic rabbits.<sup>52</sup>

#### **Brassicaceae**

Daily oral administration of oil of *Eruka sativa* seeds 2 weeks before or after the induction of diabetes by single injection of alloxan (100 mg/kg) ameliorated hyperglycaemia, improved lipid profile, blunted the increase in malondialdehyde and 4-hydroxynonenal and stimulated glutathione content and superoxide dismutase activity in the liver.<sup>53</sup>

This study demonstrated the effect of *Brassica juncea* Coss (Leaf Mustard) on carbohydrate metabolism in rats. It showed significant hypoglycaemic action. There was increased activity of glycogen synthetase, and a decrease in glycogenolysis and gluconeogenesis demonstrated by a decreased activity of glycogen phosphorylase and gluconeogenic enzymes.<sup>54</sup>

Oral administration of an extract obtained from *Matthiola livida* DC to healthy rats produced a persistent hypoglycaemic effect. Moreover, in alloxanised diabetic rats, this extract showed a more potent hypoglycaemic effect than that of Daonil.<sup>34</sup>

#### **Bromeliaceae**

Four bioactive compounds were isolated from the water-soluble fraction of *Tillandsia usneoides* L. (Spanish Moss) Among these compounds, 3 hydroxy-3-methylglutaric acid (HMG) was shown to be hypoglycaemic in fasting healthy mice.<sup>55</sup>

#### **Buddleaceae**

A study was performed using healthy rabbits with intragastric administration of water, tolbutamide or a decoction of the tested plant before the induction of hyperglycaemia by subcutaneous injection of 50 % dextrose solution (4 ml/kg) at the beginning of the experiment and after 60 min. Tolbutamide and *Buddleia americana* Linn. significantly decreased the hyperglycaemia versus control.<sup>44</sup>

#### **Cactaceae**

Oral intake of 500 g of *Opuntia streptacantha* Lem. (*Nopal*) before infusion with 500 ml of 20 % dextrose during 2 hours in seven healthy volunteers produced a significant lowering of glucose level at 90 and 120 min. 500 g of nopal stems were given orally to 14 healthy volunteers and to 14 patients with type II diabetes. Serum glucose and insulin levels were measured at 0, 60, 120 and

180 min after nopal ingestion. A control test was performed with the intake of 400 ml of water. The intake of nopal by the type II group was followed by a significant reduction in serum glucose and insulin concentration reaching 40.8 mg/dl and 7.8  $\mu$ U/ml less than basal values at 180 min. Acute hypoglycaemic effect of nopal was observed in patients with type II diabetes but not in healthy subjects. Thus, the mechanism of this effect differs from that of current hypoglycaemic agents.<sup>57</sup> To find out if a second dose of *O. streptacantha* may enhance its hypoglycaemic effect, three tests were performed under fasting condition on 8 type II diabetic subjects and 6 healthy individuals. The tests were as follows: A). 500 g of broiled stems of the plant were given orally initially at 0 and 120 min. B) only the initial dose was given. C). control test with water. Serum glucose and C peptide were measured every 2 h from 0 to 6 h. In diabetic patients a significant decrease of serum glucose levels reaching from 41 to 46 % was observed in tests A and B, without differences between them. C peptide did not change. In healthy subjects, serum glucose and C peptide concentrations did not significantly differ between tests. A second dose of *O. streptacantha* given 2h after the first did not improve its hypoglycaemic activity.<sup>58</sup>

In animals: *O. streptacantha* significantly decreased the area under glucose tolerance curve compared with control (21.4 %), or tolbutamide (14.3 %) in rabbits under OGTT.<sup>44</sup>

In humans: Oral intake of 500 g of entire broiled, blend broiled, blend crude or blended crude and heated (at 60° C) *Opuntia ficus indica* Mill. (Indian fig) stems by eight patients with type II diabetes significantly decreased glycaemia after 120 and 180 min in each group. The major hypoglycaemic effect shown ranged from 23.3  $\pm$  4.4 to 25.4  $\pm$  14.3 mg/dl below the glucose levels at 0 min. No differences in the hypoglycaemic effects were observed between diverse preparations.<sup>56</sup>

#### Capparidaceae

The plant extract of *Cleome droserifolia* Delile significantly suppressed the rise in peripheral glycaemia, both in the basal (fasting) state and after glucose intake (rats rendered glucose intolerant by tetracycline-induced fatty liver). Suppression of basal blood glucose output indicated a lowering effect of the plant extract on hepatic glucose output. The postprandial hypoglycaemic effect of the plant extract in the absence of increased insulin secretion was explained by a) potentiation of peripheral and hepatic insulin sensitivity, b) diminished intestinal glucose absorption that was evident from blunted plasma glucose levels throughout the oral glucose challenge.<sup>59</sup>

#### Caryophyllaceae

In normoglycaemic rats, a water extract (WE) of *Spergularia purpurea* produced a significant lowering of glycaemia 4 h after single oral administration, and 1 week after repeated oral administration. In streptozotocin-induced diabetic rats, the WE caused a strong decrease in glycaemia. Moreover, 2 weeks after repeated oral administration of the WE, glycaemia was normalized in diabetic rats.<sup>60</sup>

#### Compositae

*Chamaemelum nobile* = *Anthemis mobilis* Linn. is a 3-hydroxy-3-methylglutaric acid (HMG) containing flavonoids, glucoside chamaemeloside which has been shown to have *in vivo* hypoglycaemic activity comparable to that of free HMG.<sup>61</sup>

In humans: This plant is among twelve herbs most commonly used to treat diabetes in Saudi Arabia.<sup>5</sup> Feeding diabetic rats and rabbits with the aqueous extract of the aerial parts of *A. herba-alba* (0.39 g/kg body weight) for 2-4 weeks showed a significant reduction in glycaemia, prevention of elevated glycosylated haemoglobin levels and a hypoliposis effect, in addition to protection against body weight loss.<sup>62</sup> In alloxan-treated rabbits and mice, it has been shown that the aqueous extract of the plant produced an initial hyperglycaemia which was followed by hypoglycaemia.<sup>63</sup> Moreover, only the aqueous extract of leaves or barks produced a significant reduction in glycaemia. In contrast, the aqueous extract of roots and the methanolic extract of the aerial parts of the plant that produced almost no reduction in blood glucose level.<sup>64</sup>

Oral administration of an extract of the aerial parts of *Artemisia pallens* Wall. produced a dose-dependent reduction in glycaemia in alloxan-induced diabetic rats. In fasted healthy rats, the extract caused moderate hypoglycaemia at a higher dose. Only the methanol extract was active whereas the water extract was inactive.<sup>65</sup>

#### Chenopodiaceae

Administration of extracts obtained from *Beta vulgaris* var. *Cicla* L. (Leaf beet); (Sugar beet) inhibited the increase in the nonenzymatic glycosylation of skin proteins and blood glucose. These results demonstrated the ability of this plant in preventing or at least retarding the development of some diabetic complications.<sup>66</sup> Betavulgarosides I, II, III, IV oleanolic acid oligoglycosides were isolated together with betavulgarosides VI, VII, VIII from the roots of *B. vulgaris*. Betavulgarosides II, III and IV produced hypoglycaemic effects that were demonstrated by an oral glucose tolerance test in rats.<sup>67</sup>

In a study of 31 desert plants collected from different Egyptian localities, oral administration of an extract of *Haloxylon salicoricum* Bunge to normoglycaemic rats exhibited persistent hypoglycaemic effects compared with Daonil.<sup>34</sup>

Oral administration of an extract obtained from *Arthrocnemum glaucum* Delile to normoglycaemic rats produced a persistent hypoglycaemic effect. Moreover, in alloxanised diabetic rats, this extract showed an hypoglycaemic effect that was more potent than that of Daonil.<sup>34</sup>

A methanolic extract of the Japanese fruit *Kochia scoparia* L. (*Tonburi*) (*Summer cypress*) was shown to inhibit the increase in serum glucose in glucose-loaded rats. The active principles shown to inhibit glucose and ethanol absorption in rats are: momordin Ic and its 2'-O-beta-D-glucopyranoside together with three saponins named

scoparianosides A, B and C.<sup>68</sup>

### Convolvulaceae

Oral administration of an extract obtained from *Convolvulus althaeoides* Linn. to normoglycaemic rats produced a persistent hypoglycaemic effect compared with Daonil.<sup>34</sup>

Oral administration of *Ipomea batatas* L. (*white skinned sweet potato*) produced a reduction in hyperinsulinemia in Zucker fatty rats by 23%, 26%, 60% and 50%, 3, 4, 6 and 8 weeks after treatment respectively. These results were comparable to that of troglitazone, an insulin sensitizer. After 7 weeks of treatment, increase in glycaemia after glucose load was inhibited by the administration of *I. batatas*. Moreover, it normalized lipid metabolism and produced a regranulation of pancreatic islet B-cells after 8 weeks of treatment.<sup>69</sup>

The boiled whole extract of *Ipomea aquatica* produced a significant decrease in glycaemia after glucose loading in healthy Wistar rats with both single (33%) and multiple (25%) doses. The optimum dose was 3.4 g/kg while the optimum activity was observed 2 h after the administration of the extract.<sup>70</sup>

### Crassulaceae

*Rhodiola sachalinensis* (Cf *Sedum*) polysaccharides (RSP) isolated from the root of the plant produced a decrease in glycaemia, liver glycogen and total blood lipid when injected intraperitoneally into mice at 50, 100 and 200 mg/kg once daily for 7 successive days. RSP also reduced hyperglycaemia induced by injection of adrenaline, glucose and alloxan in mice.<sup>71</sup> When RSP A and B were intraperitoneally injected to mice at dosages of 50 mg/kg and 100 mg/kg, data showed that RSP B was the effective hypoglycaemic ingredient of *R. sachalinensis*. In mice, it was shown that RSP B did not exert significant hypoglycaemic effects through intestinal absorption. However, RSP B possessed significant hypoglycaemic actions when administered subcutaneously, intramuscularly, intraperitoneally or intravenously.<sup>72</sup>

### Cucurbitaceae

The administration of trihydroxyoctadecadienoic acids obtained from the roots of the native Armenian plant *Bryonia alba* (0.05 mg/kg/day for 15 days i. m.) restores the disordered lipid metabolism of alloxan-diabetic rats and reduced thromboxane B2 generation with a corresponding increase in prostaglandin E2 release.<sup>73</sup>

This study showed the insulinotropic effect of *Citrullus colocynthis* Schrad. fruits. Different extracts were obtained from the seeds of this plant: RN II (crude extract), RN VI (aqueous alcoholic extract), RN X (purified extract) and RN XVII (beta-pyrazol-1-ylalanine, the major free amino acid derivative present in the seeds). All tested extracts, when perfused for 20 min at 0.1 mg/ml, immediately and significantly induced insulin secretion *in vitro* in the isolated rat pancreas and isolated rat islets in the presence of 8.3 mM glucose.<sup>74</sup> In normoglycaemic rabbits, oral administration of the aqueous extract (300 mg/kg) caused a significant reduction in glycaemia after 1 h and a highly significant reduction after 2, 3, and 6 h. Oral administration

of components isolated from the rind of *C. colocynthis* (tertiary and quaternary alkaloids, glycosides and saponins) were tested in normoglycaemic rabbits at a dose of 50 mg/kg. The alkaloids did not show any hypoglycaemic effect. In contrast, the glycosidic component significantly decreased glycaemia after 2 and 3 h and even more significantly after 6 h. The saponin component reduced glycaemia after 1, 2, 3 and 6h. Oral administration of graded doses of saponin extract (10, 15 and 20 mg/kg) caused a marked hypoglycaemic effect in alloxan-induced diabetic rabbits. The authors suggested that the saponin glycosides components could be responsible for the hypoglycaemic effect of the rind of *C. colocynthis*.<sup>75</sup>

The leaves of *Coccinia indica* Wight & Am. (*Ivy Gourd*) were extracted with 95 % ethanol. The residue obtained after evaporation of the solvents was suspended in distilled water. Oral administration of this extract produced a decrease in glycaemia in normal-fed (21 %) and 48 h fasted rats (24 %). This effect was due in part to the inhibition of the key gluconeogenic enzyme glucose-6-phosphatase.<sup>76</sup> Furthermore, the oral administration of the pectin isolated from the fruit of the *C. indica* at a dose of 200 mg/100 g BW/day produced a reduction in glycaemia and an increase in liver glycogen. Glycogen synthetase activity was significantly increased. Incorporation of labeled glucose into hepatic glycogen was also found to be higher. A significant reduction in phosphorylase activity was noted in the pectin-administered groups.<sup>77</sup>

*Cucurbita ficifolia* Bouché (*Fig leaf*); (*Molabard Gourd*) decreased the area under glucose tolerance curve, compared to control (26.4 %), or tolbutamide-treated (14.3 %) healthy rabbits subjected to a weekly oral glucose tolerance test.<sup>44</sup> Moreover, traditional preparations of *C. ficifolia* had a hypoglycaemic effect similar to that of tolbutamide in healthy and mildly diabetic rabbits but had no effect in severely diabetic rabbits. The authors suggested that some pancreatic function or the presence of insulin is required for the hypoglycaemic activity of this plant.<sup>46</sup>

In healthy mice, an aqueous extract obtained from *Momordica charantia* L. (*Karela*); (*Balsam Pear*) attenuated the glycaemic response to both oral and intraperitoneal glucose, without altering the insulin response. This aqueous extract and the residue after alkaline chloroform extraction reduced hyperglycaemia in diabetic mice after 1 h. It was concluded that the hypoglycaemia activity of orally administered Karela extracts was independent of intestinal glucose absorption and involved an extrapancreatic effect.<sup>10</sup> A 50 % methanolic extract (30 mg/kg) caused a decrease in blood glucose level (BGL) 3 h after oral administration to streptozotocin-induced diabetic rats. Other fractions, such as the n-butanol soluble fraction from *M. charantia* extract, were most effective in lowering BGL. In the oral glucose tolerance test, the n-butanol fractions of the two plants inhibited the initial increase BGL to the same degree. The n-butanol fraction of *M. charantia* inhibited the increase of BGL prominently after intraperitoneal glucose load. Like the action of sulfonylureas,<sup>78</sup> the *M. charantia* extract

seems to act like insulin or via insulin secretion from the pancreas. The aqueous fruit extract decreased the fasting glucose level in normoglycaemic and cyproheptadine-induced hyperglycaemic mice. This effect did not improve the tolerance to glucose in treated mice.<sup>79</sup> Oral administration of fruit juice and seed extract increased concentrations of certain key hepatic enzymes (serum gamma-glutamyl transferase, alkaline phosphatase) and so may contain hepatotoxins capable of causing cellular damage at the molecular level.<sup>80</sup> The alcoholic extract of the pulp (500 mg/kg), administered to healthy glucose-primed rats depressed plasma glucose levels at 1 h. Tolbutamide (100 mg/kg), under similar conditions, produced the same effect. This reduction in plasma glucose levels was not accompanied by increased insulin secretion. In streptozotocin-induced diabetic rats, it improved the oral glucose tolerance causing significant reduction in plasma glucose. The *M. charantia* extract caused a 4-5 fold increase in the rate of glycogen synthesis from U-14C glucose in the livers of normally fed rats. These data suggest that the mechanism of action of this plant could partly be attributed to increased glucose utilization by the liver rather than an insulin secretion effect.<sup>81</sup> Another study showed the effects of oral feeding of *M. charantia* fruit juice on the hepatic cytochrome P450 and glutathione S-transferase drug-metabolizing enzymes in streptozotocin-induced diabetic rats. The results obtained suggest that the changes in hepatic phase I and phase II drug-metabolizing enzyme activities in the diabetic animals may be associated with altered expression of different cytochrome P450 and glutathione S-transferase isozymes. In addition, *M. charantia* did not always reverse the effects on drug-metabolizing enzymes in streptozotocin-induced diabetes.<sup>82</sup> The activity of the juice of *M. charantia* fruit was tested on streptozotocin (STZ)-treated RIN cells and isolated islets *in vitro*. Feeding the juice of *M. charantia* fruit produced a reduction in hyperglycaemia in STZ-induced diabetic mice. It strongly reduced the STZ-induced lipid peroxidation in the pancreas of mice, RIN and islet cells. Moreover, it reduced the STZ-induced apoptosis in RIN cells.<sup>83</sup> In a separate experiment, rats were fed diets containing bitter melon freeze-dried powder at the level of 0.5, 1, and 3% without an added dietary cholesterol (experiment 1) and containing bitter melon at the level of 1% with or without 0.5% cholesterol and 0.15% bile acid (experiment 2) for 14 days. Dietary bitter melon resulted in a consistent decrease in glycaemia in rats fed cholesterol-free diets but not in those fed cholesterol-enriched diets.<sup>84</sup>

Treatment over 15 days with *Momordica cymbalaria* Hook fruit powder produced a significant blood glucose lowering effect in alloxan-induced diabetic rats, but not in normoglycaemic rats. Moreover, the fruit powder reduced the level of cholesterol and triglycerides in diabetic rats.<sup>85</sup>

*Cucumis sativus* L. (*Cucumber*) significantly decreased the area under glucose tolerance curve and the hyperglycaemic peak in healthy rabbits subjected to a weekly oral glucose tolerance test.<sup>19</sup>

#### Cupressaceae

Dried berries of *Juniperus communis* Linn. (Berries,

Juniper) supplied in the diet (6.25 % by weight) and decoction (1g/400 ml) reduced the level of hyperglycaemia in streptozotocin-induced diabetes.<sup>16</sup> Furthermore, administration of the decoction decreased glycaemia at a dose of 250 mg/kg. Administration of the decoction (125 mg/kg of total juniper/kg) to streptozotocin-induced diabetic rats during 24 days also produced blood glucose lowering effects.<sup>86</sup>

#### Discoreaceae

The aqueous fraction of a methanolic extract of *Discorea dumetorum* Linn. has an hypoglycaemic effect in healthy and alloxan diabetic rabbits when administered i. p. (20 mg/kg). In contrast, the chloroform fraction raised blood glucose level in healthy rabbits.<sup>87-88</sup>

#### Equisetaceae

A single oral administration of a water extract of *Equisetum myriochaetum* at dose of 7 and 13 mg/kg and a butanol extract at a dose of 8 and 16 mg/kg reduced the glycaemia in streptozotocin-induced diabetic rats 3 h after its administration. Glibenclamide (3 mg/kg) showed a similar effect. The effective components that were isolated from the plant were three kaempferol glucosides and one caffeoyl glucoside.<sup>89</sup>

#### Euphorbiaceae

Trans-dehydrocrotonin (t-DCTN), a 19-nor-clerodane diterpene isolated from the bark of *Croton cajucara* Benth. showed a significant hypoglycaemic activity in alloxan-induced diabetic rats but not in healthy rats at oral doses of 25 and 50 mg/kg body weight.<sup>90</sup>

An experimental study showed that *Euphorbia prostrata* J. Grah. decreased the hyperglycaemic peak and the area under the glucose tolerance curve in hyperglycaemic rabbits.<sup>52</sup>

Ten human subjects were treated with a preparation of the whole plant, *Phyllanthus amarus* Shum. & Thon., for ten days (9 subjects were hypertensive and four were diabetic). Glycaemia was reduced in the treated group.<sup>91</sup>

A decrease in blood glucose level (BGL) was observed 3 h after oral administration of a 50 % methanolic extract (30 mg/kg) of *Phyllanthus urinaria* Linn. in streptozotocin-induced diabetic rats. The n-butanol soluble fraction extract was most effective. In the oral glucose tolerance test, the n-butanol fraction of the two plants inhibited the initial increase of BGL. The n-butanol fraction of *P. urinaria* did not inhibit the increase of BGL prominently after intraperitoneal glucose load. *P. urinaria* extract may act via the facilitation of glucose metabolism and/or the inhibition of glucose absorption in the gut like the action of biguanides.<sup>78</sup>

Oral administration of an ethanolic extract of *Maprounea africana* Muel.in showed glucose-lowering properties in the db/db mouse.<sup>92</sup>

#### Fabaceae

A new cardenolide (-)-14-methoxyhyrcanoside was isolated from an aqueous extract of the seeds of *Securigera securidacea* L together with five new dihydrobenzofuran

derivatives (securigran I to V). Kaempferol and astragalol were also isolated from the aqueous extract of the flowers of the plant. The total aqueous extract of these seeds was hypoglycaemic.<sup>93</sup>

Single doses of unroasted seeds of *Cajanus cajan* Millsp. (*Pigeon pea*) (60 % and 80 %) caused a significant reduction in serum glucose levels 1-3 h after oral administration to healthy and alloxanized mice. In contrast, roasted seeds caused a significant increase in serum glucose levels during the 3 h experimental period. The authors concluded that roasting of seeds at high temperature for 30 min resulted in the total loss of the hypoglycaemic component but not the hyperglycaemic principle present in the seeds.<sup>94</sup>

Oral administration of bakuchiol, a compound isolated from an extract of *Otholobium pubescens* reduced glycaemia in db/db mice in a dose-dependent fashion. In a new model of type 2 diabetes (fat-fed, streptozotocin-treated rats) an oral dose of 150 mg/kg produced a strong reduction in blood glucose and triglycerides levels.<sup>95</sup>

#### Geraniaceae

A single oral dose of 500 mg/kg *G. core-core* extract significantly reduced glycaemia in normal rats under glucose tolerance test condition. Moreover, after 7 days of oral treatment with 250 mg extract/kg body weight, *Geranium core-core* Steud. (Core-core) induced hypoglycaemia in normal rats. In alloxan-induced diabetic rats, a single oral dose of 500 mg/kg and chronic treatment at 250 mg/kg extract significantly lowered glycaemia in glucose tolerance test conditions.<sup>96</sup>

#### Gnetaceae

In a study of desert plants collected from some Egyptian localities, oral administration of an extract obtained from *Ephedra elata* DC to normoglycaemic rats produced a persistent hypoglycaemic effect when compared to Daonil.<sup>34</sup>

#### Gramineae

In humans: The postprandial glycaemic response of *Hordeum vulgare* L. (Barley) was studied in a pool of 18 healthy volunteers and 14 patients having non-insulin-dependent diabetes mellitus (type II). The glycaemic response to barley was significantly lower than that to white bread in both groups of subjects. However, the insulinemic response to barley was significantly lower than that to white bread in healthy subjects only. In type II diabetic subjects, there was a tendency for the response to barley to be higher than that to white bread 0.5 h after ingestion. Barley, with a low glycaemic index (105.2), seems to mobilize insulin in NIDDM subjects. This makes it an especially suitable cereal for diabetic patients.<sup>97</sup>

The water extract of *Bambusa vulgaris* Schrad (Feathery Bamboo) significantly lowered the fasting glycaemia and markedly improved glucose tolerance in Sprague-Dawley rats. Moreover, a maximum hypoglycaemic activity was observed after 3 h. The hypoglycaemic effect of this plant was superior to tolbutamide. The magnitude of the hypoglycaemic effects varied with the dosage used and the time of storage.<sup>98</sup>

A study was performed using healthy rabbits with intragastric administration of water, tolbutamide or decoction of the plant before the induction of hyperglycaemia by subcutaneous injection of 50 % dextrose solution (4 ml/kg) at 0 and 60 min. Tolbutamide and *Coix lachryma* Jobi L. or *Cynodon dactylon* L. (Pers.) significantly decreased hyperglycaemia compared to control.<sup>74</sup>

#### Gentianaceae

A xanthone was isolated from the hexane fraction of *Swertia chirayita* Bush-Ham. and identified as 1,8-dihydroxy-3,5-dimethoxyxanthone (swerchirin). It has a very significant blood sugar lowering effect in fasted, fed, glucose loaded, and tolbutamide pre-treated albino rats. The ED50 for 40 % glycaemia lowering in CF male albino rats is 23.1 mg/kg when orally administered<sup>99</sup>. The effect of swerchirin isolated from hexane fraction of *S. chirayita* on blood sugar levels of healthy and streptozotocin-treated rats was studied. Swerchirin (50 mg/kg, p.o.) suspended in gum acacia was fed through cannula to healthy and diabetic rats. Blood glucose levels measured at 0, 1, 3 and 7 h after treatment showed a very significant glucose lowering effect of this plant in healthy and mildly diabetic rats.<sup>100</sup> Single oral administration of the crude/impure swerchirin (SWI) isolated from the hexane fraction of *S. chirayita* (50 mg/kg) to fed CF rats induced an approximately 60 % fall in blood glucose by 7 h post-treatment. This was associated with marked depletion of aldehyde-fuch stained beta-granules and immunostained insulin in the pancreatic islets. *In vitro*, glucose uptake and glycogen synthesis by muscle (diaphragm) was enhanced by the serum of SWI-treated rats. At 100, 10 and 1  $\mu$ M final concentrations, SWI greatly enhanced glucose (16.7 mM)-stimulated insulin release from isolated islets. It is therefore concluded that SWI lowers glycaemia by stimulating insulin release from the islets of Langerhans.<sup>101</sup>

Hypoglycaemic activity-guided fractionation led to the isolation of five known xanthenes and two triterpenoids from the ethyl acetate soluble fraction of *Swertia japonica* (*javanica*) Blum Bijdr. One of the triterpenes, thysanolactone, was first isolated from this plant. Among the xanthenes, bellidifolin showed a potent and dose-dependent hypoglycaemic activity in streptozotocin-induced diabetic rats both in i.p. and p.o. administration<sup>102</sup>. Bellidifolin, by both oral and intraperitoneal administration, significantly lowered glucose concentrations in normal and streptozotocin-induced diabetic rats. Bellidifolin also lowered blood triglyceride levels. It also stimulated glucose uptake activity in rat 1-fibroblasts expressing human insulin receptors.<sup>103</sup>

#### Ginkgoaceae

In humans: An oral glucose tolerance test (OGTT) was undertaken (75g) before and after ingestion of *Ginkgo biloba* extract (120 mg/day at bedtime) for three months in 20 individuals (14 females and 6 males, ages 21-57). Fasting plasma insulin and C-peptide areas under the curve during the OGTT changed from 136 $\pm$ 55 to 162 $\pm$ 94 micro U/ml/h ( $p = 0.1232$ ) and 9.67 $\pm$ 5.34 to 16.88  $\pm$ 5.20 ng/ml/h ( $p < 0.001$ ), respectively. It seems that *G.*



*biloba* may increase insulin release.<sup>104</sup>

### **Globulariaceae**

Oral and intraperitoneal administration of the plant (0.7 g/kg) caused a significant reduction in glycaemia in normoglycaemic and hyperglycaemic rats. It produced a significant increase in insulinemia in healthy rats.<sup>105</sup>

### **Guttifere**

Kolaviron, a mixture of C-3/C-8 linked biflavonoids obtained from *Garcinia kola Heckel* produced significant hypoglycaemic effects when administered intraperitoneally to healthy and alloxan diabetic rabbits at a dose of 100 mg/kg. The fasting blood glucose in normoglycaemic rabbits was reduced from 115 mg/100 ml to 65 mg/100 ml after 4 h. In alloxan-diabetic rabbits the blood sugar was lowered at 12 h. Kolaviron inhibited rat lens aldose reductase activity with an IC 50 value of  $5.4 \times 10^{-6}$  M.<sup>107</sup>

### **Hippocastanaceae**

Five triterpene oligoglycosides named escins-Ia, Ib, IIa, IIb and IIIa were isolated from the seeds of *Aesculus hippocastanum L. (Common Horse-Chestnut)* plant. These compounds showed hypoglycaemic activity. Greater hypoglycaemic activities were obtained with escins IIa and IIb.<sup>108-109</sup>

### **Hippocrateaceae**

From the petroleum ether extract of the root bark of *Salacia oblonga Wall.*, two biologically active fractions have been isolated. The chloroform eluted fraction of the petroleum ether extract and a fluorescent compound separated from it by thin layer chromatography demonstrated about 60 % and 76 % of the hypoglycaemic potency of an equal dose of tolbutamide (250 mg/kg) in albino rats.<sup>110</sup>

Diabetic rats were given aqueous extract of *Salacia reticulata Wight* orally and the plasma glucose concentration was determined at regular intervals. An hypoglycaemic effect was obtained at all doses tested (0.5 g/kg, 1.0 g/kg and 5.0 g/kg). The maximum percentage decrease in plasma glucose was observed between 1-5 h following the administration of the extract<sup>111</sup>. A potent natural alpha-glucosidase inhibitor called kotalanol was isolated and found to show more potent inhibitory activity against sucrase than salacinol and acarbose.<sup>112</sup>

### **Juglandaceae**

Male swiss mice were orally loaded with glucose after the extracts of *Junglans regia L. (Persian walnut)* had been given orally. The extract of this plant was prepared by boiling the dried material with water or macerating it with 80 % ethanol. It was shown that the extract improved glucose tolerance.<sup>15</sup>

### **Labiatae**

*Lepechinia caulescens* significantly decreased the area under glucose tolerance curve when compared to control (26.0 %), or tolbutamide (14.3 %) in healthy rabbits subjected to weekly oral glucose tolerance tests.<sup>44</sup> *L. caulescens* had an hypoglycaemic effect similar to that of tolbutamide in healthy and mildly diabetic rabbits and had no effect in severely diabetic rabbits. These results

suggested that some pancreatic function or the presence of insulin is required for the hypoglycaemic activity of these plants.<sup>46</sup> More recently, a study demonstrated that *L. caulescens* significantly decreased the hyperglycaemic peak and the area under the glucose tolerance curve in hyperglycaemic rabbits.<sup>52</sup>

### **Lamiaceae**

Oral administration of an alcoholic extract of leaves of *Ocimum sanctum* Linn. (Tulasi) reduced glycaemia in normoglycaemic, glucose-fed hyperglycaemic and streptozotocin-induced diabetic rats. Furthermore, the extract potentiated the action of exogenous insulin in healthy rats. The activity of the extract was 91% and 70 % that of tolbutamide in healthy and diabetic rats, respectively.<sup>113</sup> Reduction in fasting blood glucose was obtained after one month of treatment of healthy and diabetic rats with *O. sanctum* leaf powder.<sup>114</sup>

*Teucrium cubense* significantly decreased the area under glucose tolerance curve, compared to control (19.4 %) or tolbutamide (14.3 %) in healthy rabbits given a weekly oral glucose tolerance test.<sup>44</sup>

Treatment with *Ocimum sanctum* and *Ocimum album* Roxb. (Holy basil) leaves showed a significant decrease in fasting and postprandial blood glucose levels compared to treatment with placebo leaves. Fasting blood glucose fell by 21.0 mg/dl, and postprandial blood glucose fell by 15.8 mg/dl. The lower values of glucose represented reductions of 17.6 % and 7.3 % in the levels of fasting and postprandial blood glucose, respectively. Urine glucose levels showed a similar trend.<sup>115</sup>

A study was performed using healthy rabbits with intragastric administration of water, tolbutamide or a decoction of the *Marrubium vulgare L.* before the induction of temporary hyperglycaemia by subcutaneous injection of 50 % dextrose solution (4 ml/kg of weight) at 0 and 60 min. Tolbutamide and *M. vulgare* significantly decreased the hyperglycaemia as compared to control (water) in healthy rabbits.<sup>44</sup>

The authors confirmed the hypoglycaemic effect of *Salvia lavandifolia Vahl.* reported previously and suggested that this hypoglycaemic effect may arise by several mechanisms: a). potentiation of insulin release induced by glucose; b) increased peripheral uptake of glucose; c) decreased intestinal absorption of glucose; d) hyperplasia of the pancreatic islet beta cells<sup>116</sup>. The antidiabetic activity of the extract of *S. lavandifolia* was investigated in streptozotocin-induced diabetic rats. The extract (10 mg dry residue/kg) induced an increase in the size and number of cells in the islets of Langerhans. There was also an increase in pancreatic insulin content. A significant decrease (>40 %) in blood glucose levels was obtained when the extract (10 mg/kg) and glibenclamide (1mg/kg) were both administered to streptozotocin-induced diabetic rats.<sup>117</sup>

Oral administration of an extract from *S. aegyptiaca* to normoglycaemic rats produced a persistent hypoglycaemic effect compared to Daonil. Moreover, in alloxanized rats,

the hypoglycaemic effect of the extract was more potent than that of Daonil. The hypoglycaemic effect of *Salvia aegyptiaca* L. in fasting rats has also been confirmed in alloxanised diabetic rats.<sup>34</sup>

Oral administration of a leaf infusion *Salvia fruticosa* Mill. reduced the glycaemic level in alloxan-induced diabetic rabbits but not in normoglycaemic animals. The hypoglycaemic effect was not evoked in rabbits that received glucose load intravenously. This plant acts mainly by reducing intestinal absorption of glucose, without modifying plasma insulin levels.<sup>118</sup>

### Leguminosae

In healthy rats, both the aqueous and 50 % ethanolic extracts of *Caesalpinia bonducella* Fleming seeds exhibited hypoglycaemic activity as early as 4 h after administration at a lower dose of 100 mg/kg. The hypoglycaemia produced by the aqueous extract was of prolonged duration as compared to the ethanolic extract. In diabetic rats, both extracts produced marked antihyperglycaemic effects from day 5 onwards.<sup>119</sup>

Male Swiss mice were loaded orally with glucose after the extracts of *Galega officinalis* L. (Goats-Rue) had been given. The extract of this plant was prepared by boiling the dried material with water or macerating it with 80 % ethanol. It was shown that the extract improved glucose tolerance.<sup>15</sup>

A study was performed using healthy rabbits with intragastric administration of water, tolbutamide or decoction of the tested plant before the induction of hyperglycaemia by subcutaneous injection of 50 % dextrose solution (4 ml/kg) at 0 and 60 min. Tolbutamide and *Bauhinia divaricata* significantly decreased hyperglycaemia compared with control.<sup>44</sup>

The hypoglycaemic activity of a 20 % dried leaf infusion of *Bauhinia candicans* Benth. did not modify the glycaemia in healthy rats, but in alloxan-induced diabetic rats it produced a decrease in glycaemia (39 %).<sup>120</sup>

Oral administration of an extract from *Astragalus species* to normoglycaemic rats produced a persistent hypoglycaemic effect. Moreover, in alloxanised diabetic rats, this extract showed hypoglycaemic effects more potent than that of Daonil.<sup>34</sup>

*Phaseolus vulgaris* L. (Kidney Bean) significantly decreased the area under glucose tolerance curve, compared to control (18.5 %) or tolbutamide (14.3 %) in healthy rabbits.<sup>44</sup>

*Trigonella foenum graecum* L. (fenugreek) is among twelve herbs that is mostly used to treat diabetes in Saudi Arabia.<sup>5</sup> In insulin-dependent diabetic patients, the fenugreek diet significantly reduced fasting blood glucose and improved the glucose tolerance test. There was a 54% reduction in the 24 h urinary glucose excretion. The results showed the usefulness of fenugreek seeds in the management of diabetes.<sup>121</sup>

Oral administration of *T. foenum graecum* to healthy and alloxan induced diabetic rats (2 and 8 g/kg) produced a significant fall in blood glucose level (BGL) both in the

normal as well as in diabetic rats. The hypoglycaemic effect was dose related.<sup>122</sup> On the other hand, the aqueous extract of fenugreek leaf when given to both healthy and alloxan-diabetic rats, produced a significant reduction in BGL. However, an ethanolic extract of fenugreek leaf produced no reduction in BGL in healthy rats but i.p. administration of 0.8 g/kg of the ethanolic leaf extract to diabetic rats produced a significant reduction of BGC.<sup>123</sup> The Soluble Dietary Fibers (SDF) fraction of fenugreek seeds showed no effect on fasting blood glucose levels of non-diabetic or NIDDM (type II) rats. However, when fed simultaneously with glucose, it showed an hypoglycaemic effect in type II diabetic rats. The major constituent of the SDF is galactomannan.<sup>124</sup>

When steroid saponins extracted from the seed of fenugreek were administered chronically mixed with food (12.5 mg/day per 300 g body weight) to healthy and streptozotocin-induced diabetic rats, food intake and the motivation to eat in healthy rats were significantly increased and the food consumption in diabetic rats was also stabilized. In both healthy and diabetic rats, steroid saponins decreased total plasma cholesterol without any change in triglycerides.<sup>125</sup> More recently, it has been shown that the disrupted free radical metabolism in diabetic animals may be normalized by fenugreek seed supplementation in the diet.<sup>126</sup> Moreover, fenugreek significantly decreased the hyperglycaemic peak and the area under the glucose tolerance curve in hyperglycaemic rabbits.<sup>52</sup>

*Medicago sativa* L. (Lucerne, alfalfa) when supplied in the diet (6.25 % by weight) and infusion (1g/400 ml) reduced the level of hyperglycaemia in streptozotocin-induced diabetes.<sup>16</sup> An aqueous extract of the plant (1 mg/ml) stimulated 2-deoxy-glucose transport (1.8 fold), glucose oxidation (1.7 fold) and incorporation of glucose into glycogen (1.6 fold) in mouse abdominal muscle. In acute, 20 min tests, 0.25-1 mg/ml aqueous extract of lucerne evoked a stepwise 2.5-6.3 fold stimulation of insulin secretion from the BRIN-BD11 pancreatic beta cell line. This effect was abolished by 0.5 mM diazoxide, and prior exposure to the extract did not affect subsequent stimulation of insulin secretion by 10 mM L-alanine, thereby negating a detrimental effect on cell viability. The effect of the extract was potentiated by 16.7 mM glucose and by 1 mM 3-isobutyl-1-methylxanthine. L-alanine (10 mM) and a depolarising concentration of KCl (25 mM) did not increase the insulin-releasing activity of lucerne. Sequential extraction with solvents revealed insulin-releasing activity in both the methanol and water fractions indicating a cumulative effect of more than one constituent.<sup>127</sup>

A new tetrahydropyrane was isolated from a methanol extract of the roots of *Acrocomia mexicana*. The extract was hypoglycaemic in healthy and alloxan-induced diabetic mice (2.5 to 40 mg/kg i.p.).<sup>128</sup>

The hypoglycaemic effect was investigated after i. p. administration of marsupsin, pterosupin and pterostilbene (3 important phenolic constituents of heartwood of

*Pterocarpus marsupium* ). Marsupsin and pterostilbene significantly lowered the glycaemia of diabetic rats, and the effect was comparable to that of 1,1-dimethylbiguanide (metformin).<sup>129</sup>

The aqueous methanolic extract of the leaves and root of *Xanthocercis zambesiaca* and eight structurally related nitrogen-containing sugars, were evaluated for antihyperglycaemic effects in streptozotocin-induced diabetic mice. Glycaemia fell after i.p. injection of the extract (50 mg/kg). Four compounds (fagomine, 4-O-beta-D-glucopyranosylfagomine, 3-O-beta-D-glucopyranosylfagomine, and 3-epifagomine) reduced the blood glucose level after i.p. injection (150  $\mu$ mol/kg). Fagomine increased plasma insulin levels in diabetic mice and potentiated the 8.3-mM glucose-induced insulin release from the rat isolated-perfused pancreas. The fagomine-induced potentiation of insulin release may contribute in part to its antihyperglycaemic action.<sup>130</sup>

### Liliaceae

S-allyl cysteine sulphoxide (SACS), a sulphur-containing amino acid of *Allium sativum* L. (Garlic) that is the precursor of allicin and garlic oil, has been found to show significant antidiabetic effects in alloxan diabetic rats. Administration of a dose of 200 mg/kg significantly decreased the concentration of serum lipids, blood glucose and activities of serum enzymes like alkaline phosphatase, acid phosphatase and lactate dehydrogenase and liver glucose-6-phosphatase. It significantly increased liver and intestinal HMG CoA reductase activity and liver hexokinase activity.<sup>131</sup> Oral administration of SACS to alloxan diabetic rats for a month ameliorated the diabetic conditions of treated rats comparable with rats treated with glibenclamide and insulin<sup>132</sup>. Treatment of alloxan diabetic rats with SACS ameliorated the diabetic condition almost to the same extent as glibenclamide and insulin. In addition, SACS controlled lipid peroxidation better than the other two drugs. Furthermore, SACS significantly stimulated *in vitro* insulin secretion from beta cells isolated from healthy rats. Hence it can be surmised that the beneficial effects of SACS could be due to both its antioxidant and its secretagogue actions. The former effect is predominant and the latter is only secondary.<sup>133</sup>

Oral administration of *Allium cepa* L. (Onion) S-methyl cysteine sulphoxide (SMCS) daily at a dose of 200 mg/kg body weight for a period of 45 days to alloxan diabetic rats controlled the blood glucose and lipids in serum and tissues and altered the activities of liver hexokinase, glucose 6-phosphatase and HMG CoA reductase towards normal values. These effects of SMCS were comparable to those of glibenclamide and insulin.<sup>134</sup> Oral administration of onion SMCS to alloxan diabetic rats for a month, ameliorated the diabetic condition similar to rats treated with glibenclamide and insulin.<sup>135</sup> The effect of feeding a 15 mg % capsaicin diet or 3 % freeze-dried onion powder containing diet produced a significant reduction in the hyperglycaemic status of diabetic animals. This study revealed that onion feeding improves the metabolic status in diabetes probably because of its hypocholesterolemic as well as its hypoglycaemic effect.<sup>135</sup>

Acute oral administration of an exudate of *Aloe barbadensis* Mill. (Barbados) leaves (500 mg/kg) produced no reduction in blood glucose level whereas its bitter principle (5 mg/kg) administered intraperitoneally produced a significant hypoglycaemic effect that extended over a period of 24 h with maximum hypoglycaemia observed after 8h. In chronic studies, *A. barbadensis* and its bitter principle produced a maximum effect after 5 days. It seems that the hypoglycaemic effect of this plant and its bitter principle may be mediated through stimulating synthesis and/or release of insulin from the beta-cells of the islets of Langerhans.<sup>136</sup> Moreover, this plant slightly decreased the area under glucose tolerance curve compared to control (1.4 %) or tolbutamide (14.3 %) in healthy rabbits.<sup>44</sup>

A hot water extract of the rhizomes produced a lowering in glycaemia levels in alloxan-diabetic mice. Pseudoprotinosaponin AIII (glycoside) was isolated and compared with protinosaponins AIII. Both products affected glucose uptake and insulin release suggesting their hypoglycaemic effects are due to actions on hepatic gluconeogenesis and/or glycogenolysis.<sup>137</sup> The rhizome of *Anemarrhena asphodeloides* bunge was identified as an active plant of Seishin-kanro-to (SK) which is used in phytotherapy of diabetes. SK (1700 mg/kg) reduced the blood glucose of KK-Ay mice 7 h after a single oral administration.<sup>138</sup>

The n-butanol extract of rhizomes of *Ophiopogonis tuber* administered intraperitoneally (100 mg/kg) reduced the level of blood glucose in healthy mice 4 h after administration, and also significantly lowered the blood glucose of streptozotocin-induced diabetic mice under similar conditions. The extract also tended to suppress epinephrine-induced hyperglycaemia. The conclusion was that the hypoglycaemic effect of the extract does not alter the insulin concentration.<sup>139</sup>

The methanol extract of rhizomes of *Polygonatum officinale* (800 mg/kg) reduced the blood glucose level of healthy mice from  $170 \pm 3$  to  $136 \pm 5$  mg/100 ml 4 h after intraperitoneal administration, and also significantly lowered the blood glucose level of streptozotocin-induced diabetic mice from  $696 \pm 60$  to  $407 \pm 35$  mg/100 ml under similar conditions. *P. officinale* also suppressed epinephrine-induced hyperglycaemia in mice. In addition, the n-butanol fraction of the methanol extract elicited a significant decrease in the blood glucose level of streptozotocin-induced diabetic mice after 4 h.<sup>140</sup> Using the perfused rat liver *in vitro*, a significant decrease in the hepatic glucose content was produced by the infusion of *P. officinale* (250  $\mu$ g/ml). In addition, the hepatic content of GLUT2 mRNA and its protein content in the total membrane fraction from rat liver was significantly lower in the intraperitoneally-treated rats when compared with controls. Moreover, 500  $\mu$ g of the extract exhibited no apparent stimulatory effect on the insulin secretion from isolated rat pancreatic islets. The authors suggested that the hypoglycaemic effect of this plant is derived, at least in part, from the decrease in hepatic glucose output, due

presumably to the reduction of Glut2 mRNA expression in the liver.<sup>141</sup> The methanol extract of rhizomes of *P. officinale* (800 mg/kg) reduced the blood glucose of Wistar fatty rats 4 h after intraperitoneal administration. The hepatic content of GLUT2 mRNA from rat liver significantly decreased in the intraperitoneally-treated rats compared to controls.<sup>142</sup> In addition, Miura and Kato<sup>143</sup> investigated the difference between the hypoglycaemic effect of the rhizomes of *Polygonatum sibiricum* and *P. officinale* in KK-Ay mice. The methanol extract of the rhizomes of *P. sibiricum* and *P. officinale* (800 mg/kg) reduced the blood glucose in KK-Ay mice 4 h after intraperitoneal administration. *P. sibiricum* significantly decreased the blood glucose level, but did not change with *P. officinale*. The authors suggested that the hypoglycaemic effect of *P. officinale* arose from raised insulin sensitivity.

The methanol extract of rhizomes of *Smilax glabra* ROXBURGH (SM, 100 mg/kg body weight) reduced the glycaemia of healthy mice and KK-Ay mice 4 h after intraperitoneal administration. However, SM did not affect the blood glucose level in streptozotocin-induced diabetic mice. SM also suppressed epinephrine-induced hyperglycaemia in mice. The authors concluded that the hypoglycaemic effect of SM arose from increased insulin sensitivity.<sup>144</sup>

#### Logoniaceae

Oral administration of an extract obtained from finely pulverized root of *Anthocleista voglii* (100, 400, and 800 mg/kg) produced a dose-related lowering of blood glucose in mice and rats. The dose of 800 mg/kg was hypoglycaemic at 8 h in normoglycaemic rabbits. The doses of 400 and 800 mg/kg were both hypoglycaemic in alloxan-induced diabetic animals. These data were compared to chlorpropamide.<sup>145</sup>

#### Lycopodiaceae

Intraperitoneal administration of *Selaginella tamariscina* Beauv. complex (25 g/kg) for 12 days produced a decrease in blood glucose and serum lipid peroxide, as well as an increase in the concentration of serum insulin. Histological observations showed that this plant could repair the structure of pancreatic islet beta cells injured by alloxan.<sup>146</sup>

#### Lythraceae

Among many medicinal plants tested, *Lagerstroemia speciosa* Pers. (*Queen Carpe-Myrtle*) (Banaba) was the most active on D-glucose uptake by Ehrlich ascites tumor cells. Two terpenoids were isolated: colosolic acid and maslinic acid. The first was shown to be a glucose transport activator.<sup>147</sup> The hypoglycaemic effects of *L. speciosa* were studied using hereditary diabetic mice (Type II, KK-Ay/Ta Jcl). A treatment of 5-week duration with different extracts from banaba leaves showed beneficial effects on the level of plasma glucose in non-insulin dependent diabetes mellitus.<sup>148</sup>

#### Malvacées

Seven polysaccharides and peptidoglycans obtained from the seeds of *Malva verticillata* were tested for hypoglycaemic activity. Neutral polysaccharide especially

showed remarkable hypoglycaemic activity, and the polysaccharide-rich fraction also exhibited significant activity.<sup>149</sup>

*Sida cordifolia* extracts of the aerial and root parts showed hypoglycaemic activity. Moreover, the methanol extract of root was found to possess significant hypoglycaemic activity.<sup>150</sup>

#### Melastomaceae

Oral administration of an alcoholic extract of the leaves of *Memecylon umbellatum* produced a significant decrease in the serum glucose level in normoglycaemic and alloxan-induced diabetic mice.<sup>151</sup>

The water extract of *Osbeckia octandra* significantly lowered the fasting blood glucose level and markedly improved glucose tolerance in Sprague-Dawley rats. Moreover, the maximum hypoglycaemic activity was observed after 3 h. The hypoglycaemic activity of this plant was comparable to that of tolbutamide.<sup>98</sup>

#### Meliaceae

An *Azadirachta indica* leaf extract was found to have no action on peripheral utilization of glucose or on hepatic glycogen in healthy and streptozotocin-induced diabetic rabbits. The reduction in peripheral utilization of glucose and glycogenolytic effect due to epinephrine was blocked by the *A. indica* leaf extract, almost completely in diabetic rabbits and to a certain extent in healthy animals.<sup>152</sup> More recently, it has been demonstrated that in an *in vitro* rat pancreas preparation, *A. indica* leaf extract significantly blocked the inhibitory effect of serotonin on insulin secretion mediated by glucose.<sup>153</sup> Furthermore, *A. indica* leaf extract was found to have the most potent blood sugar-lowering followed by *Catharantus roseus*, *Gymnema sylvestre* and *Ocimum sanctum*.<sup>154</sup>

#### Menispermaceae

A study showed that the antihyperglycaemic effect of *Tinospora crispa* was not due to interference with intestinal glucose uptake or uptake of the sugar into peripheral cells. Rather, the antihyperglycaemic effect of *T. crispa* is probably due to stimulation of insulin release via modulation of intracellular Ca<sup>2+</sup> concentration in pancreatic beta-cells.<sup>155</sup>

Oral administration of an aqueous extract of *Tinospora cordifolia* roots produced a significant decrease in glycaemia and brain lipids in alloxan-induced diabetic rats.<sup>156</sup>

#### Moraceae

The effect of a decoction of leaves of *Ficus carica* L. (Common Fig) as a supplement to breakfast, was studied in insulin-dependent diabetes mellitus (IDDM) patients. Post-prandial glycaemia was lower during supplementation with FC [156.6 ± 75.9 mg/dl vs commercial tea 293.7 ± 45.0 mg/dl (p<0.001)] without pre-prandial differences (145.0 ± 41.5 and 196.6 ± 43.2 mg/dl, respectively). It was concluded that the addition of FC to diet in IDDM could help to control postprandial glycaemia<sup>157</sup>. Moreover, from the aqueous decoction of fig leaves, after treatment with HCl, centrifuging, treatment with NaOH and extraction

with chloroform, the administration of the organic phase to diabetic rats produced a decrease in hyperglycaemia and a decline in the level of total cholesterol and reduction in the total cholesterol/HDL cholesterol ratio.<sup>158</sup>

The oral administration of the extract obtained from *Ficus bengalensis* L. (Banyan) resulted in enhancement of serum insulin levels in normoglycaemic and diabetic rats. The incubation of isolated islets of Langerhans from healthy as well as from diabetic animals with this plant extracts resulted in increased insulin secretion. This extract inhibited insulinase activity from liver and kidney.<sup>159</sup> The antidiabetic effect of a dimethoxy derivative of perlargonidin 3-O-alpha-L rhamnoside (250 mg/kg, single dose study and 100 mg/kg/day, long term study) isolated from the bark of *F. bengalensis* has been compared with that of glibenclamide (2 mg/kg and 0.5 mg/kg/day respectively) in moderately diabetic rats. The single dose glycoside treatment decreased fasting blood glucose by 19 % and improved glucose tolerance by 29 %. After one-month treatment with the plant, the fasting blood glucose level went down to almost half of the pre-treatment levels in both the groups and their glucose tolerance improved by 41 % in the glibenclamide group and by 15 % in the glycoside treated group. Urine sugar decreased to trace amounts in both groups. *In vitro* studies showed that insulin secretion by beta-cells was greater in the presence of the perlargonidin derivative than in the presence of a leucocyanidin derivative, reported to be a good antidiabetic agent.<sup>160</sup> Glycoside of leucopelargonidin isolated from the bark of *F. bengalensis* demonstrated significant hypoglycaemic, hypolipidemic and serum insulin raising effects in moderately diabetic rats with close similarities to the effects of a minimal dose of glibenclamide.<sup>161</sup> Dimethoxy ether of Leucopelargonidin-3-O-alpha-L rhamnoside isolated from the bark of *F. bengalensis* was used at a dose of 100 mg/kg on oral administration. The compound showed significant hypoglycaemic and serum insulin raising actions in healthy and alloxan induced-diabetic dogs during a period of 2h. This compound appears to stimulate insulin secretion.<sup>162</sup> A leucodelphinidin derivative isolated from the bark of *F. bengalensis* L. showed hypoglycaemic action at a dosage of 250 mg/kg when given to both healthy and alloxan diabetic rats. Its action was similar to that of an effective dose of glibenclamide (2 mg/kg) tested under the same conditions. However, after a glucose load, the plant product was only just significantly active and not as effective as the sulphonylureas. The efficacy of the plant product as an hypoglycaemic agent adds to the other therapeutic effects associated with this class of flavonoids.<sup>163</sup>

The water extract of *Artocarpus heterophyllus* Lam. (Jack Fruit) significantly lowered the fasting blood glucose level and markedly improved glucose tolerance in Sprague-Dawley rats. Moreover, the hypoglycaemic activity of this plant was greater than that of tolbutamide. The magnitude of the hypoglycaemic effects varied with the dosage used but did not change with storage, even up to 3 days.<sup>98</sup>

*Cecropia obtusifolia* Bertol. significantly decreased the area under glucose tolerance curve compared to control (18.9 %)

or tolbutamide (14.3 %) in healthy rabbits.<sup>44</sup>

Ethyl acetate and n-butanol-soluble portions of the leaves of *Morus insigni* showed hypoglycaemic activity in streptozotocin-diabetic rats. Two new compounds mulberrofuran U and moracin (M-3-O-β-D-glucopyranoside) were isolated together with 6 known compounds.<sup>164</sup>

The hypoglycaemic effects of hot water extracts (WE) from *Morus alba* L. (Folium mori, Mulberry leaves) or cortex Mori Radicis were tested in fasted and nonfasted streptozotocin-induced diabetic mice at a single dose of 200 mg/kg (i.p.). The WE of *M. alba* exhibited the most potent hypoglycaemic effects. The most potent fractions of *M. alba* and cortex Mori Radicis were ethanol-insoluble extracts (A2). These A2 fractions produced a decrease in glycaemia of  $24.6 \pm 6.0$  % and  $60.5 \pm 9.1$  % in nonfasted streptozotocin-mice, and  $81.4 \pm 7.9$  % and  $77.3 \pm 5.8$  % in fasted streptozotocin-mice, respectively. The authors concluded that the increased hypoglycaemic action of WE and A2 of *M. alba* was mediated by an increase in glucose uptake.<sup>165</sup>

#### Myrsinaceae

The methanol extract of leaves of *Embelia madagascariensis* (EL)(500 mg/kg) reduced the glycaemic level of healthy mice from  $206 \pm 9$  to  $137 \pm 10$  mg/100 ml 4 h after i.p. administration, and also significantly lowered the blood glucose level of streptozotocin-induced diabetic mice from  $570 \pm 29$  to  $401 \pm 59$  mg/100 ml under similar conditions. EL also suppressed epinephrine-induced hyperglycaemia in mice.<sup>166</sup>

#### Myrtaceae

The methanolic extract and ethyl acetate-soluble portions of the leaves of *Myrcia multiflora* DC showed an inhibitory activity on aldose reductase and alpha-glucosidase. The plant also inhibited the increase of serum glucose level in sucrose-loaded rats and in alloxan-induced diabetic mice. A new flavanone glucosides (myrciacitrins I and II) and new acetophenone glucosides (myrciaphenones A and B) were identified.<sup>167</sup>

Infusions of 3 g leaves/day of *Myrcia uniflora* were given to a group of healthy subjects and a group of type II diabetic patients. After ingestion of the infusions, no acute or chronic effects on plasma glucose levels or glycated haemoglobin were found in either group. However, plasma insulin levels in the diabetic group were lower after *M. uniflora* than after placebo. The conclusion is that infusions prepared from *M. uniflora* have no hypoglycaemic effect in healthy subjects or type II diabetic patients.<sup>168</sup> In contrast, the evolution of the diabetic state of streptozotocin-diabetic rats treated with aqueous leaf extracts of *M. uniflora* was positive. The rats were treated with 7.5 mg of lyophilized powder twice a day, by oral loading, for three weeks. Treatment of diabetic rats fed a balanced diet did not affect body weight gain but reduced the hyperglycaemia, polyphagia, polydipsia, urine volume and the urinary excretion of glucose and urea. *M. uniflora* administration for three weeks had no effect on the levels of pancreatic and

serum insulin. The intestinal absorption of glucose was markedly inhibited by this plant. The data showed that aqueous extracts of *M. uniflora* have a beneficial effect on the diabetic state, mainly by improving metabolic parameters of glucose homeostasis.<sup>169</sup>

*Eucalyptus globulus* Labill. (Tasmanian Blue Gum) when given to streptozotocin-diabetic mice reduced the level of hyperglycaemia.<sup>16</sup> In contrast, it has been found that the decrease in hyperglycaemia caused by *E. globulus* was not significant.<sup>41</sup> In another study, it was demonstrated that *E. globulus* possesses an antihyperglycaemic action due to pancreatic and extrapancreatic effects in diabetic mice.<sup>170</sup>

The hypoglycaemic activity of the extract of jamun pulp from the fruit of *Eugenia jambolana* Lam. (Gambol) = *Syzygium cumini* Skeels (Jamun) was seen after 30 min, while the seeds of the same fruit required 24 h to produce the same effect. These results were confirmed in streptozotocin-induced diabetic animals. The oral administration of the extract resulted in the enhancement of insulinemia in normoglycaemic and diabetic rats. The incubation of isolated pancreatic islet cells of normal and diabetic animals with this plant extracts resulted in increased insulin secretion. This extract inhibited insulinase activity from liver and kidney.<sup>159</sup> Oral administration of 2.5 and 5.0 g/kg body weight of the aqueous extract of the seeds of *S. cumini* for six weeks in alloxan-diabetic rats resulted in a significant reduction in blood glucose concentration and an increase in total haemoglobin, but in the case of 7.5 g/kg body weight, the effect was not significant. It also resulted in decreased free radical formation in tissues.<sup>171</sup>

#### Musaceae

Among the plants most used in the treatment of diabetes mellitus *Musa sapientum* Kuntze (Banana) significantly decreased the hyperglycaemic peak and the area under the glucose tolerance curve in hyperglycaemic rabbits.<sup>52</sup> Oral administration of 1.5, 0.2 and 0.25 g/kg body weight of the chloroform extract of the flowers of *M. sapientum* during a 30-day period caused a decrease in blood glucose and glycosylated haemoglobin levels and an increase in total haemoglobin. The extract showed antihyperglycaemic action and an antioxidant effect. Banana flower was more effective than glibenclamide.<sup>172</sup>

#### Nyctaginaceae

*Salpianthus macrodonthus* decreased significantly the area under glucose tolerance curve, in relation to the water control (15.0 %) and tolbutamide (14.3 %) in healthy rabbits subjected to weekly oral glucose tolerance tests.<sup>44</sup>

#### Nymphaeaceae

A methanol extract of *Nelumbo nucifera* Gaertn (East Indian Lotus) obtained by Soxhlet extraction from finely pulverized rhizomes was used. The extract (300 mg/kg and 600 mg/kg, orally) caused a decrease in glycaemia in streptozotocin-induced diabetic rats by 53 % and 55 %, respectively at the end of 12 h.<sup>173</sup> Oral administration of the ethanolic extract of rhizomes of *N. nucifera* markedly reduced the glycaemia of healthy, glucose-fed hyperglycaemic and streptozotocin-induced diabetic rats compared to control. The extract improved glucose

tolerance and potentiated the action of exogenously injected insulin in normal rats. The extract exhibited activity of 73% and 67 % of that of tolbutamide in normal and diabetic rats, respectively.<sup>174</sup>

#### Oleaceae

Maximum hypoglycaemic activity of *Olea europea* L. olive leaf was obtained from samples collected in the winter months, especially in February. One of the compounds responsible for this activity was oleuropeoside, which showed activity at a dose of 16 mg/kg. This compound also demonstrated antidiabetic activity in animals with alloxan-induced diabetes. The hypoglycaemic activity of this compound may result from two mechanisms: (a) potentiation of glucose-induced insulin release, and (b) increased peripheral uptake of glucose.<sup>175</sup>

#### Oxalidaceae

Oral glucose tolerance test (OGTT) in both normoglycaemic and streptozotocin-induced diabetic rats showed an optimal hypoglycaemic effect at a dose of 125 mg/kg. Repeated administration (twice a day) of a dose of 125 mg/kg of ethanolic extract obtained from *Averrhoa bilimbi* L. (bilimbi) leaves reduced glycaemia in diabetic rats by 50% and blood triglyceride by 130% when compared with vehicle (water).<sup>176</sup>

Subdiabetic, mildly diabetic and severely diabetic male rabbits were induced by alloxan. Assessment of the activity of the extract from *Biophytum sensitivum* DC leaves was made by measuring the fall in fasting plasma glucose level and improvement in the OGTT, following single dose and prolonged administrations. Following a single dose administration, there was fall in 1 and 2.5 h glucose values by 26 % and 27 %, respectively in the subdiabetic rabbits, and by 37 % and 38 % in the mildly diabetic rabbits. Improved OGTT response was also shown in the subdiabetic as well as in the mildly diabetic rabbits. More significant improvements occurred following one week of the above treatment. It was concluded that the plant composites had an hypoglycaemic effect probably due to pancreatic  $\beta$ -cell stimulating action.<sup>177</sup>

#### Palmae

A new tetrahydropyran was isolated from the methanolic extract of roots from *Acrocomia mexicana* Karw. The extract was hypoglycaemic in healthy and alloxan-induced diabetic mice (2.5 to 40 mg/kg i. p.).<sup>128</sup>

#### Papilionaceae

The hypoglycaemic effect of *Lupin marmalades* flour was tested in seven non insulin dependent diabetic adult patients using the glucose tolerance test. Postprandial blood glucose concentrations were lower in individuals after a test meal of *L. marmalades* compared with fructose marmalade.<sup>178</sup>

The effect of dietary fiber from *White lupin bran* sweet hull (slh) was evaluated on metabolic control in 16 non insulin dependent diabetic patients (11 males, mean age: 52 years). Eleven patients received in addition oral hypoglycaemic drugs. Intake of crude dietary fiber initially resulted in an increase in blood glucose and later a decrease when compared to control.<sup>179</sup>

**Pandanaceae**

Administration of the extract obtained from the root of *Pandanus odoratus* (Toei-hom) at doses of 0.125-0.5g/kg p.o. did not significantly affect the plasma glucose level in healthy rats, whereas the extract significantly lowered the plasma glucose level at a dose of 0.5g/kg p.o. in streptozotocin-induced diabetic rats. In an oral glucose tolerance test, administration of the extract at doses of 0.5 and 1.0 g/kg p.o. significantly lowered the plasma glucose level in diabetic rats.<sup>180</sup> Hypoglycaemic activity-guided fractionation led to the isolation of the known compound, 4-hydroxybenzoic acid from this plant. This compound showed hypoglycaemic effects in healthy rats after the oral administration of 5 mg/kg. The compound increased serum insulin levels and liver glycogen content in healthy rats.<sup>181</sup> Moreover, oral administration of 4-hydroxybenzoic acid caused a dose-dependent decrease in plasma glucose levels in the streptozotocin-induced diabetic rats. The component did not affect serum insulin level and liver glycogen content in the diabetic model, but increased glucose consumption in healthy and diabetic rat diaphragms. These results suggested that 4-hydroxybenzoic acid produced a hypoglycaemic effect mediated by an increase in the peripheral glucose consumption.<sup>182</sup>

**Phytolacaceae**

Extracts from leaves and stem powder of *Petiveria alleaceae* L. (Anamu) produced a decrease in blood concentration of more than 60% 1 h after oral administration in male Balb/C mice.<sup>183</sup>

**Piperaceae**

A single oral administration of the water extract from the whole plant of *Piper sarmentosum* Roxb. (Chaplu) at doses of 0.125 and 0.25 g/kg significantly lowered the plasma glucose levels in healthy rats. In contrast, the repeated oral administration of the water extract at a dose of 0.125 g/kg for 7 days produced hypoglycaemic effect in the diabetic rats.<sup>184</sup>

**Plantaginaceae**

Administration of *Plantago psyllium* L. reduced the elevation of postprandial glucose by 14% at breakfast and 20 % at dinner relative to placebo. Postprandial serum insulin concentrations measured after breakfast were reduced by 12 % relative to placebo. Second-meal effects after lunch showed a 31% reduction in postprandial glucose elevation compared to placebo. The authors suggested that *P. psyllium* as a meal supplement reduced proximate and second-meal postprandial glucose level in NIDDM.<sup>185</sup> In NIDDM patients, treatment with *P. psyllium* significantly reduced the net area under the glucose curve (AUC). In healthy individuals, AUC-glucose did not significantly change with the treatments. *P. psyllium* decreased the glycaemic index of bread in NIDDM patients and diminished the insulin index in NIDDM and in healthy subjects. Authors suggested that adding *P. psyllium* to meals may reduce glycaemic index of carbohydrate foods and may help diabetic control.<sup>186</sup>

**Polygalaceae**

Senegin-II, the main component of *Polygala senega* (L.)

var. *Latifolia* Torrey & Gray. (*Senega radix*), when given at 2.5 mg/kg, reduced the level of blood glucose in healthy mice 4 h after intraperitoneal administration. It also significantly lowered the blood glucose level in KK-Ay mice under similar conditions.<sup>187</sup> The hypoglycaemic effect of the rhizomes of this plant was investigated in healthy and KK-Ay mice, one of the models type II diabetes. The n-butanol extract of *P. senega* rhizomes (SN) (5 mg/kg) reduced the blood glucose of normal mice from  $191 \pm 3$  to  $120 \pm 3$  mg/dl 4 h after intraperitoneal administration, and also showed a significant decrease in the glucose level of KK-Ay mice. However, streptozotocin-induced diabetic mice did not experience a change in the blood glucose after administration of SN. The authors proposed that the hypoglycaemic effect of SN occurs without altering the insulin concentration. Moreover, SN needs the presence of insulin in order to act. A triterpenoid glycoside named senegin II was identified as the active component of the hypoglycaemic effect of SN.<sup>188</sup> E-senegasaponins a, b and c were isolated from the root of *Senega radix*. Their Z-isomers were also isolated. They were named: Z-senegasaponins a, b, and c. The E and Z-senegasaponins a and b were found to be hypoglycaemic in the oral D-glucose tolerance test in rats.<sup>189</sup> Other bioactive saponins, named E-senegasaponin c and Z-senegasaponin c, were isolated from the roots of *P. senega* together with Z-senegins II, III and IV. The E and Z-senegasaponins c and E and Z-senegins II, III, and IV were also found to exhibit hypoglycaemic activity in the oral D-glucose tolerance test. E and Z-senegins II also showed an inhibitory effect on alcohol absorption in rats.<sup>190</sup> The effect of four triterpenoid glycosides isolated from the rhizomes of *P. senega*, senegins II-IV (1-3) and desmethoxysenegin II (4) were tested in healthy and KK-Ay mice. Compounds 1 and 2 reduced the blood glucose of healthy mice 4 h after intraperitoneal administration and also significantly lowered the glucose level of KK-Ay mice under similar conditions. Compounds 3 and 4, as well as senegose A (5), an oligosaccharide ester, were inactive when tested in healthy mice.<sup>191</sup>

**Polypodiaceae**

Male Swiss mice were orally loaded with glucose after oral administration of the extracts of *Adiantum capillus veneris* L. The extract of this plant was prepared by boiling the dried material with water or macerating with 80 % ethanol. It was shown that the extract improved glucose tolerance.<sup>15</sup>

**Primulaceae**

Water-soluble polysaccharide (FA) from fruiting bodies of *Auricularia auricula-juda* significantly lowered plasma glucose, urinary glucose, and food intake in genetically diabetic KK-Ay mice. Moreover, FA administration also increased the tolerance to intraperitoneal glucose loading and hepatic glycogen content.<sup>192</sup>

**Punicaceae**

Oral administration of the aqueous-ethanolic (50%, v/v) extract of the flowers of *Punica gratum* L. (*Gulnar farsi*) produced a significant decrease in glycaemia in normoglycaemic, glucose-fed hyperglycaemic and alloxan-

induced diabetic rats. The maximum effect was found at 400 mg/kg.<sup>193</sup>

#### Ranunculaceae

Paeoniflorin and 8-debenzoylpaeoniflorin, isolated from the dried root of *Paeonia lactiflora* Pall., produced a significant blood sugar lowering effect in streptozotocin-treated rats and had a maximum effect at 25 min after treatment. This hypoglycaemic action was also observed in normoglycaemic rats only at 1 mg/kg. Plasma insulin was not changed in paeoniflorin-treated normoglycaemic rats indicating an insulin-independent action. This glucoside reduced the elevation of blood sugar in glucose challenged rats. Increase in glucose utilization by paeoniflorin can thus be considered.<sup>194</sup>

#### Rhamnaceae

In healthy rats, treatment of one to four weeks duration with the butanol extract of *Zizyphus spina-christi* (Christ-Thoron) leaves as well as christinin-A, (its principal saponin glycoside) produced insignificant changes in all studied parameters. However, in streptozotocin-induced diabetic rats, both treatments significantly reduced serum glucose levels, liver phosphorylase and glucose-6-phosphatase activities, and significantly increased the serum pyruvate level and liver glycogen content after 4 weeks of treatment. There was also marked improvement in glucose utilization in diabetic rats in both cases. Serum insulin and pancreatic cAMP levels showed significant increases in diabetic rats treated for a period of 4 weeks with the butanol extract.<sup>195</sup>

#### Rhizophoraceae

*Rhizophora mangle* significantly decrease the hyperglycaemic peak and the area under the glucose tolerance curve in hyperglycaemic rabbits.<sup>52</sup>

#### Rosaceae

The hypoglycaemic activity of a 20% dried leaf infusion of *Rubus ulmifolius* Schott. used for diabetes in Chilean popular medicine did not modify glycaemia in healthy rats, but it showed hypoglycaemic activity in both alloxan and streptozotocin-induced diabetic rats (28 % and 29 %). Activity-guided fractionation of *R. ulmifolius* showed that petroleum ether extracts elicited a marked hypoglycaemic effect (35 %) in the streptozotocin-induced diabetes model.<sup>120</sup>

*Agrimony eupatoria* L. (Agrimony) reduced the level of hyperglycaemia in streptozotocin-induced diabetic rats.<sup>16</sup> Oral administration of dried leaves of *A. eupatoria*, (12 days of treatment) did not alter plasma glucose and insulin concentrations in healthy mice whereas treatment with *A. eupatoria*, reduced the level of hyperglycaemia in diabetic mice. Aqueous extract of agrimony (1 mg/ml) stimulated 2-deoxy-glucose transport (1.4-fold), glucose oxidation (1.4-fold) and incorporation of glucose into glycogen (2.0-fold) in mouse abdominal muscle comparable with 0.1  $\mu$ M insulin. In acute 20 min tests, 0.25-1 mg/ml aqueous extract of agrimony evoked a stepwise 1.9-3.8-fold stimulation of insulin secretion from the BRIN-BD11 pancreatic beta cell line. The effect of extract was glucose-independent and was not evident in BRIN-BD11 cells exposed to a depolarizing concentration of KCl. The authors concluded that

antihyperglycaemic, insulin-releasing and insulin-like activities were present in *A. eupatoria*.<sup>196</sup>

A study was performed using rabbits with intragastric administration of water, tolbutamide or decoction of the plant before the induction of hyperglycaemia by subcutaneous injection of 50 % dextrose solution (4 ml/kg of weight) at 0 and 60 min. Tolbutamide and *Crataegus pubescens* Steud. decreased hyperglycaemia compared to control.<sup>44</sup>

*Eriobotrya japonica* Lindl. (Loquat) significantly decreased the area under the glucose tolerance curve compared to control (17.2 %), tolbutamide (14.3 %) in healthy rabbits.<sup>44</sup> The effects of the constituent sesquiterpene glycosides 1-3 and polyhydroxylated triterpenoids 5-6 isolated by methanol extraction of *E. japonica* were studied in genetically diabetic mice (C57BL/KS-db/db/Ola) and normoglycaemic rats. The sesquiterpene glycoside 3 and the polyhydroxylated triterpenoids 5 and 6 produced a marked inhibition of glycosuria. Furthermore, 5 and 6 were able to reduce blood glucose levels in normoglycaemic rats.<sup>197</sup>

Administration of 2.5 g *Prunus amygdalus* Batsch (Almond) seed and its proportionate fractions, namely 1.22 g defatted seed and 1.28 g oil, to three groups of albino rabbits, showed a definite hypoglycaemic action during a two-month study. The active factor appeared to be a non oil fraction which is only partly soluble in ethyl ether.<sup>198</sup>

Intraperitoneal administration of a methanolic extract of *Prunus davidiana* Franch stems and its main component, prunin (naringenin 7-O-beta-D-glucoside), produced a significant hypoglycaemic effect. The authors suggested that the methanolic extract contains one or more hypoglycaemic principles including the main flavone glycoside, prunin, which can significantly reduce the level of blood glucose and total lipids in streptozotocin-induced diabetic rats.<sup>199</sup>

#### Rubiaceae

Intraperitoneal administration of 300 mg/kg of chloroform extract of *Bouvardia ternifolia* Schlecht. to diabetic mice decreased glycaemia by 58.6 %. This extract reduced glycaemia level by 33.4% in healthy mice.<sup>42</sup>

Oral intragastric administration of an extract of *Hintonia latiflora* cortex or intragastric administration of the pure substance, coustareagin (neoflavonoid) produced a significant blood glucose lowering effect.<sup>200</sup>

Oral administration of the aqueous root extract of *Mprinda lucida* (140 mg/kg and 280 mg/kg) decreased blood glucose levels by  $32 \pm 1\%$  and  $52 \pm 2\%$ , respectively in normoglycaemic mice. In the alloxan-induced diabetic mice the extract produced hypoglycaemic activity 4 h after its administration. The dose of 140 mg/kg produced a decrease of  $51 \pm 1\%$  and the dose of 280 mg/kg produced a decrease of  $60 \pm 2\%$ .<sup>201</sup> More recently, the methanol extract of *M. lucida*, showed significant and dose-dependent hypoglycaemic activity within 4 h after oral administration in healthy rats. In hyperglycaemic rats, the extract produced a significant antidiabetic effect 3 days after oral administration. The authors concluded that the leaves of *M.*



*lucida* have strong hypoglycaemic activity in streptozotocin-induced diabetic rats.<sup>202</sup> The effect is comparable to that of glibenclamide.

#### Rutaceae

The leaf extract of *Aegle marmelose* (L.) Coreia ex Roxb. was found to be as effective as insulin in the restoration of blood glucose and body weight to normal levels. *A. marmelose* can be used as potential hypoglycaemic agent.<sup>203</sup> Alloxan-induced diabetic animals were given insulin injections while another group received *A. marmelose* leaf extract. The blood glucose levels in the extract-treated animals was near to that of controls. Blood urea and serum cholesterol increased significantly in alloxan diabetic rats. Treatment with the leaf extract decreased the blood urea and serum cholesterol compared to controls. A similar effect was seen with insulin treatment. Consequently, the active principle of *A. marmelose* extract had similar hypoglycaemic effect to that of insulin.<sup>204</sup>

This study demonstrated the hypoglycaemic activity of *Murraya koenigii* Spreng. There was increased activity of glycogen synthetase, and decrease in glycogenolysis and gluconeogenesis as shown by decreased activity of glycogen phosphorylase and gluconeogenic enzymes after treatment with *M. koenigii*.<sup>53</sup>

#### Salsolaceae

A study was performed in healthy rabbits subjected to weekly subcutaneous glucose tolerance tests after intragastric administration of water, tolbutamide or traditional preparation of the plant. The results showed that *Spinacea oleracea* L. (Spinach) significantly decreased the area under glucose tolerance curve and the hyperglycaemic peak.<sup>17</sup>

#### Sapotaceae

An unsaturated triterpene acid isolated from an ethanolic extract of *Bumelia sartorum* Mart. root bark produced an hypoglycaemic effect in alloxan-induced diabetic rats. It increased glucose uptake and glycogen synthesis in isolated rat diaphragm and plasma insulin levels. It appears that this effect was mediated by an insulin secretagogue effect in pancreatic  $\beta$  cells.<sup>205</sup>

#### Scrophularinaceae

In a study of desert plants collected from some Egyptian localities, oral administration of an extract from *Scrophularia deserti* to normoglycaemic rats produced a persistent hypoglycaemic effect compared to Daonil.<sup>34</sup>

#### Scrophulariaceae

Intraperitoneal administration of the fraction (ethanol precipitate fraction RG-WP) obtained from the hot water extract from the rhizome of *Rehmania glutinosa* Stend produced hypoglycaemic activity in healthy and streptozotocin-induced diabetic mice. Chemical modification and proteinase treatments of RG-WP suggested that the activity exists in the polysaccharide moiety. Moreover, administration of RG-WP to normoglycaemic mice increased the activities of hepatic glucokinase and glucose-6-phosphatase deshydrogenase, but decreased those of hepatic glucose-6-phosphatase and

phosphofruktokinase. RG-WP stimulated the secretion of insulin and reduced the glycogen content in the livers of healthy mice<sup>206</sup>. The radix of *R. glutinosa* Libosch was identified as an active plant of Seishin-kanro-to (SK) which is used in traditional medicine in the treatment of diabetes. SK (1700 mg/kg) reduced the blood glucose level of KK-Ay mice from  $557 \pm 17$  to  $383 \pm 36$  mg/100 ml 7 h after its oral administration.<sup>207</sup>

#### Simarubiaceae

Oral administration of the aqueous extract of mesocarps of the fruits of *Balanites aegyptiaca* Delile exhibited prominent antidiabetic activity in streptozotocin-induced diabetic mice. From one of the active fractions of this extract, two new steroidal saponins were isolated. The authors showed that the individual saponins did not exhibit antidiabetic activity while a combination of these saponins resulted in significant activity.<sup>208</sup>

#### Solanaceae

In a study of 31 desert plants collected from different Egyptian localities, oral administration of an extract obtained from *Lycium shawii* produced a persistent hypoglycaemic effect in healthy rats compared with Daonil.<sup>34</sup>

A study in rabbits showed that *Solanum verbascifolium* significantly decreased the area under glucose tolerance curve, compared to control (21.1%) and tolbutamide (14.3%).<sup>50</sup>

Six mild NIDDM subjects and six mild hypercholesterolemic subjects were treated with a powder of *Withania somnifera* (*ashvagandha*, *Dunal*, *winter cherry*) roots for 30 days. The treatment produced a decrease in blood glucose levels that was comparable of that of an oral hypoglycaemic drug. The authors concluded that *W. somnifera* could be a potential source of hypoglycaemic agents.<sup>209</sup>

#### Sterculiaceae

*Guazuma ulmifolia* Wall. significantly decreased the hyperglycaemic peak and the area under the glucose tolerance curve in hyperglycaemic rabbits.<sup>50</sup>

The root mucilages of *Glossostemon bruguieri* Desf. (Moghat) had remarkable hypoglycaemic activity decreasing the blood glucose levels in diabetic rats by 54.5% within 15 days.<sup>210</sup>

#### Theaceae

The hot water extract of *Camellia sinensis* L. (black tea) significantly reduced the blood glucose levels of streptozotocin-induced diabetic in rats. This extract was found to possess both preventive and curative effects on experimentally produced diabetes in rats. The study revealed that black tea, like green tea, also possesses antidiabetic activity.<sup>211</sup>

#### Turneracea

*Turnera diffusa* significantly decreased the hyperglycaemic peak and the area under the glucose tolerance curve in temporarily hyperglycaemic rabbits.<sup>52</sup>

### Verbenaceae

Once daily administration of the juice of *Lantana camara* L. leaves given at different dose levels (60, 300, 600 and 1500 mg/kg/day) for 14 days in rats resulted in alterations in various haemato- and biochemical parameters. A strong hypoglycaemic effect was seen with 1500 mg only.<sup>212</sup>

### Zygophyllaceae

Traditional preparations of *Guaiacum coulteri* produced a hypoglycaemic effect similar to tolbutamide in healthy and mildly diabetic rabbits but had no effect in severely diabetic rabbits. These results suggest that some pancreatic function or the presence of insulin is required for the hypoglycaemic activity of these plants.<sup>46</sup> Others studies also confirmed the hypoglycaemic effect of *G. coulteri*.<sup>4</sup>

Masoprocol (nordihydroguaiaretic acid, a lipoxygenase inhibitor) is a pure compound isolated from *Larrea tridentata* (Creosote bush). The oral administration of masoprocol produced a fall in the plasma glucose concentrations in two mouse models of type 2 diabetes; without any change in plasma insulin concentrations. In addition, oral glucose tolerance improved and the ability of insulin to lower plasma glucose concentrations was accentuated in masoprocol-treated db/db mice.<sup>213</sup>

Oral and intraperitoneal administration of the *Zygophyllum gaetulum* Emb. and Maire (0.7 g/kg) caused a significant reduction in glycaemia in healthy and diabetic rats. It produced a significant increase in insulin levels in healthy rats.<sup>105</sup> In another experiment, the aqueous extract of the aerial parts of *Z. gaetulum* was administered orally (1 g/kg b. w.) in alloxan-induced diabetic rats. The infusion was partitioned between water and butanol to yield a butanol fraction (B), and an aqueous fraction (W) which on reduction in volume gave a precipitate (WP) and supernatant (WS). Fractions B and WP produced a significant lowering in glycaemia. In contrast, WS caused no significant decrease of glycaemia.<sup>106</sup>

### Results and Discussion

Diabetes is a metabolic disorder which can be considered as a major cause of high economic loss which can in turn impede the development of nations.<sup>9</sup> Moreover, uncontrolled diabetes leads to many chronic complications such as blindness, heart failure, and renal failure. In order to prevent this alarming health problem, the development of research into new hypoglycaemic and potentially antidiabetic agents is of great interest.

The families of plants with the most potent hypoglycaemic effects include: Leguminosae (11 species), Lamiaceae (8 sp.), Liliaceae (8 sp.), Cucurbitaceae (7 sp.), Asteraceae (6 sp), Moraceae (6 sp.), Rosaceae (6 sp.), Euphorbiaceae (5 sp.) and Araliaceae (5 sp.). The most commonly studied species are: *Opuntia streptacantha* Lem, *Trigonella foenum graecum* L, *Momordica charantia* L, *Ficus bengalensis* L, *Polygala senega* L. and *Gymnema sylvestre* R.

The methods used in the experiments are diverse. Transient hyperglycaemia can be produced by an oral glucose

tolerance test (OGTT). However, the diabetic model that was most commonly used was the streptozotocin- and alloxan-induced diabetic mouse or rat to obtain type I diabetic models. Some authors have used hereditary diabetic mice e.g. KK Ay mice as a model of type II diabetes with hyperinsulinemia.

The majority of the experiments confirmed the benefits of medicinal plants with hypoglycaemic effects in the management of diabetes mellitus. Numerous mechanisms of actions have been proposed for these plant extracts. Some hypotheses relate to their effects on the activity of pancreatic  $\beta$  cells (synthesis, release, cell regeneration/revitalization) or the increase in the protective/inhibitory effect against insulinase and the increase of the insulin sensitivity or the insulin-like activity of the plant extracts. Other mechanisms may involve improved glucose homeostasis (increase of peripheral utilization of glucose, increase of synthesis of hepatic glycogen and/or decrease of glycogenolysis acting on enzymes, inhibition of intestinal glucose absorption, reduction of glycaemic index of carbohydrates, reduction of the effect of glutathione. All of these actions may be responsible for the reduction and or abolition of diabetic complications.

In conclusion, this paper has presented a list of anti-diabetic plants used in the treatment of diabetes mellitus. It showed that these plants have hypoglycaemic effects. Many new bioactive drugs isolated from plants having hypoglycaemic effects showed antidiabetic activity equal and sometimes even more potent than known oral hypoglycaemic agents such as daonil, tolbutamide and chlorpropamide. However, many other active agents obtained from plants have not been well characterized. More investigations must be carried out to evaluate the mechanism of action of medicinal plants with antidiabetic effect. The toxic effect of these plants should also be elucidated.

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