Aegle marmelos (L.) Correa as a potential candidate for treatment of diabetes mellitus: A review

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A R T I C L E  I N F O

Article Type: Review

Article History:
Received: 10 April 2017
Accepted: 20 August 2017

Keywords:
Aegle marmelos
Diabetes mellitus
Clinical
Toxicity

A B S T R A C T

Introduction: Aegle marmelos (L.) Correa is an important medicinal plant, commonly known as Bael which is belonged to family Rutaceae. It is widely distributed in Asian countries. According to the literature, various chemical constituents and pharmacological effects have been reported for this plant. In Ayurvedic and traditional medicinal systems, different parts of A. marmelos are used for diabetes mellitus. In the present review, an attempt was made to summarize the in vivo and in vitro studies and clinical trials conducted to evaluate or validate the anti-diabetic activity and toxicity of A. marmelos.

Methods: PubMed, Science Direct, Google Scholar, Directory of open access journals (DOAJ), EMBASE, and Web of Science were searched using the keywords Aegle marmelos and diabetes.

Results: Anti-diabetic potential, clinical applications of different parts of A. marmelos and possible toxic effects have been revealed in A. marmelos extract.

Conclusion: Aegle marmelos can be used as a potential candidate for diabetes mellitus.

Implication for health policy/practice/research/medical education:
Different parts of A. marmelos are used to control diabetes mellitus. Therefore, isolation of active compounds which exhibit anti-diabetic activity may lead to development of new anti-diabetic drugs.


Introduction

Diabetes mellitus has been recognized as one of the emerging health problems worldwide because of its high prevalence, adverse clinical outcomes, marked reduction in the quality of life of patients and high healthcare costs (1-3). It is characterized by abnormalities in carbohydrate, lipid and lipoprotein metabolism. The disease not only leads to hyperglycemia but also causes many complications such as hyperlipidemia, hyperinsulinemia, hypertension and atherosclerosis (4,5). Global projections suggest that more than 350 million people will have diabetes by 2030 and the cost of treating diabetes and its complications could reach more than trillion dollars annually. Accordingly, it has become an adverse public health crisis in most of the South Asian countries including Sri Lanka with a prevalence of 8.5% in the general population (6,7). Before the discovery of insulin in 1922, the only treatment options for diabetes were those based on the traditional practices. Ethno-botanical knowledge has played a particularly important role in historical diabetes therapies, with over 1200 species of medicinal plants recognized throughout the world for their ability to treat diabetic indications (8,9). Aegle marmelos (L.) Correa (Figure 1) is one of the medicinal plants used in Asian countries to treat diabetes mellitus. This article aimed to review (a) chemical composition (b) the anti-diabetic properties (in vivo, in vitro experiments and clinical trials) and (c) toxicities of different parts of A. marmelos.

Taxonomy of Aegle marmelos L.

Kingdom: Plantae
Order: Sapindales
Family: Rutaceae
Sub family: Aurantioideae

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Genus: *Aegle*
Species: *A. marmelos*

**Morphology**
*Aegle marmelos* tree is a slow-growing of medium size up to 25 or 30 feet tall with short trunk, thick, soft, flaking bark, and spreading, sometimes spiny branches, the lower ones drooping. Young suckers bear many stiff, straight spines. There are sharp, axial one inch long spikes on this tree. The leaflets are oval or lancet shaped 4-10 cm long, 2-5 cm wide. Leaves composed of 3 to 5 leaflet in it. The lateral leaflets are without petiole and the terminal one has a long one. The petiole is 1 to 2.5 inch long. Mature leaves emit a peculiar fragrance when bruised. Flowers occur in clusters of 4 to 7 along the young branchlets, have 4 recurved, fleshy petals. The flowers are greenish white in color with a peculiar fragrant. Flowering occurs during the month of May and June (10). Fruit is spherical or oval in shape with a diameter of 2 to 4 inch. Shell is thin, hard and woody in nature. It is greenish when unripe and upon ripening it turns into yellowish color. The pulp of the fruit has 8 to 15 segments. The pulp is yellow, soft, pasty, sweet, resinous and fragrant. Fruition occurs in the month of May and June. The seeds are embedded in the pulp. The seeds are small (nearly 1 cm in length), hard, flattened-oblong, bearing woolly hairs and each enclosed in a sac of adhesive (10,11).

**Distribution**
*Aegle marmelos* is a subtropical plant growing well in the dry forests on hilly and plain regions. It is a widely distributed plant and found in India, China, Nepal, Sri Lanka, Myanmar, Vietnam, Laos, Cambodia, Pakistan, Bangladesh, Thailand, Indonesia, Java, Philippines, Malaysia, Tibet, and Fiji. In India it found in sub-Himalayan tracts from Jhelum eastwards to West Bengal, in central and south India (10-12). *A. marmelos* is known by different names in different parts of world, some of them are mentioned in Table 1 (13).

**Propagation**
Usually seeds are used for propagation. At first, ripe fruits are collected. Then seeds are squeezed out, washed thoroughly, dried in shade and stored in airtight containers. Seeds are pretreated by soaking in cold water for 24 hours and sown on sandy beds. The beds should be regularly watered. Germination commences on the ninth day onwards and completed within 20 days. The percentage of germination is around 90%. Four leaved seedlings are transplanted to containers. Sprouted root cuttings are also used for propagation. These are obtained by making incision on lateral roots and taking root cuttings with sprouted portions, usually 9-12 months after making incision (14).

**Phytochemical constituents**
Several research groups have isolated and identified various chemical constituents present in different parts of *A. marmelos* (Table 2).

**Anti-diabetic activity**

**In vivo experiments**
In vivo experiments on anti-diabetic activity of *A. marmelos* are summarized in Table 3.

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**Table 1. Names of *Aegle marmelos* L. in different languages**

<table>
<thead>
<tr>
<th>Name</th>
<th>Language</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Aegle marmelos</em></td>
<td>Latin</td>
</tr>
<tr>
<td>Wood/Stone apple,</td>
<td>English</td>
</tr>
<tr>
<td>Bengal Quince, Indian</td>
<td>Vietnamese</td>
</tr>
<tr>
<td>Quince</td>
<td></td>
</tr>
<tr>
<td>Bel, Gudu</td>
<td>Nepali</td>
</tr>
<tr>
<td>Toum</td>
<td>Lao (Sino-Tibetan)</td>
</tr>
<tr>
<td>Bnau</td>
<td>Khmer</td>
</tr>
<tr>
<td>Modjo</td>
<td>Javanese</td>
</tr>
<tr>
<td>Oranger du Malabar</td>
<td>French</td>
</tr>
<tr>
<td>Ohshit, opesheet</td>
<td>Burmese</td>
</tr>
<tr>
<td>Mojo tree</td>
<td>Indonesian</td>
</tr>
<tr>
<td>PokokMajaBatu</td>
<td>Malay</td>
</tr>
<tr>
<td>Mapin, Matum, Tum</td>
<td>Thai</td>
</tr>
<tr>
<td>Shreephal, Bilva, Bilwa</td>
<td>Sanskrit</td>
</tr>
<tr>
<td>Sir Phal</td>
<td>Old Hindi</td>
</tr>
<tr>
<td>Bel, Shreefal</td>
<td>Bengali</td>
</tr>
<tr>
<td>Kaveeth</td>
<td>Marathi</td>
</tr>
<tr>
<td>VilvaMaram, VilvaPazham</td>
<td>Tamil</td>
</tr>
<tr>
<td>Maredu</td>
<td>Telugu</td>
</tr>
<tr>
<td>Bel</td>
<td>Urdu</td>
</tr>
<tr>
<td>Belli</td>
<td>Sinhala</td>
</tr>
</tbody>
</table>
Table 2. Phytochemical constituents of different parts of Aegle marmelos L.

<table>
<thead>
<tr>
<th>Type of the part plant</th>
<th>Chemical constituents</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fruit</strong></td>
<td>Hexanal, isoamyl acetate, limonene, β-phellandrene, p-cymene, acetoin, (E)-2-octalene, (E,E)-2,4-heptadienal, dehydro-p-cymene, linalool, 3,5-octadiene-2-one, α-cubebeene, trans-p-mentha-2,8-dien, citronellal, cineole, p-cymeine, citronella, citral, cuminaldehyde, β-cubebeene, β-caryophylle-lene, hexadecane, pulegone, α-humulene, verbone, carvone, carvylacetate, dihydro-β-ionone, (E)-6,10-dimethyl-5,9-undecadien-2-one, β-ionone, carophyllene oxide, humulene oxide and hexadecanolic acid</td>
<td>(15)</td>
</tr>
<tr>
<td><strong>Fruit</strong></td>
<td>Courmarins like aegeline, aegelenine, marmelin, α-menthylhalfordinol, alloimperatorin, fuorrowumariains, psoralen, α-isopentenylhalfordinol, marmelosin, tartaric acid, linoleic acid, tannins, philobatamins, leucoanthocyanins, anthocyanins, flavonoid glycosides</td>
<td>(16-19)</td>
</tr>
<tr>
<td><strong>Fruit Pulp</strong></td>
<td>Carotenoids, phenolics, alkaloids, pectins, tannins, coumarins, flavonoids, terpenoids</td>
<td>(15,17-19)</td>
</tr>
<tr>
<td><strong>Bark</strong></td>
<td>Isomeric lignan-glucosides: glucoside, (-) – l-lyoniresinol 2α-O-β-D glucopyranoside, (–) 4 - epi-l-lyoniresinol, 3α-O-β-D-glucopyranoside, (+-) l-lyoniresinol. 3α-O-β-D-glucopyranoside, (–)-lyoniresinol 3α-O-β-D-β-D-glucopyranoside</td>
<td>(20)</td>
</tr>
<tr>
<td><strong>Stem Bark</strong></td>
<td>Marmesin – 1”-α -L – rhamnopyranoside, 1,5 -dihydroxy - 6 - methoxy -2 -methyl amthraquinone, lupeol, β-sitosterol</td>
<td>(21)</td>
</tr>
<tr>
<td><strong>Leaves</strong></td>
<td>Aegeline, lupeol, rutin, marmesinine, β-sitosterol, flavone, glycoside, oisopenteny halfordinol and phenylethyl cinnamamides, N-2-[4-(3’), 3’-dimethylallyloxy] phenyl ethylvinnamid, N-2-hydroxy-2-[4-hydroxyphenyl]</td>
<td>(22-24)</td>
</tr>
</tbody>
</table>

In vitro experiments
In an experiment lectin extract of A. marmelos increased the glucose uptake in yeast cell by 71.1% at the highest concentration (5 μg/mL) and 2.6% at the lowest concentration used (0.313 μg/mL) whereas the standard drug, metformin increased the glucose uptake in yeast cell by 4.6% at the highest concentration (5 μg/mL). This result indicates that lectin extract of A. marmelos has high efficiency in increasing the glucose uptake by yeast cells as compared to standard drug i.e. metformin. Two groups of researchers have carried out alpha amylase inhibition assay to evaluate in vitro anti-diabetic activity of A. marmelos. According to Saha and Verma (35), aqueous methanol extracts (50% and 100%) were prepared using leaves of A. marmelos. Both extracts obtained were subjected to an in vitro amylase inhibition assay using starch as a substrate and pancreatic amylase as the enzyme. The plant leaves methanol extract (50%) at doses of 50 to 500 μg/mL decreased amylase activity. However, the 100% methanol extract showed the least inhibitory activity. According to Soneji et al (36), petroleum ether and ethanol extracts were prepared using leaves of A. marmelos. Petroleum ether and ethanol extracts of A. marmelos revealed a significant inhibitory action of alpha amylase enzyme (36). As a concentration of 20 ug/mL of A. marmelos petroleum ether and ethanol extracts showed a 90.3% and 96.6% inhibition respectively and for 100 ug/mL extracts showed 94.5% and 99.3% inhibition respectively. In a non-enzymatic glycosylation of hemoglobin (Hb) assay the petroleum ether and ethanol extracts of A. marmelos showed higher inhibition of glycosylation for the concentrations of 20 ug/mL and 40 ug/mL as compared to the reference drug (36).

Clinical trials on anti-diabetic activity of different parts of Aegle marmelos L.
A study was conducted to evaluate the hypoglycemic effect of the A. marmelos flower extract in diabetic patients (37). In diabetic patients, daily administration of A. marmelos flower extract significantly reduced the fasting glucose levels and oral glucose tolerance test (OGTT) values, while the post glucose load plasma insulin levels were significantly increased by 62%. Serum levels of tested enzymes, creatinine and Glycated hemoglobin (HbA1c) were not significantly altered at the end of one month. The A. marmelos flower extract exerted a significant hypoglycemic effect and increased insulin secretion in type II diabetic patients with no adverse effects. In another study A. marmelos leaves were evaluated on non-insulin dependent diabetes mellitus patients. It caused significant changes in postprandial blood glucose level (PPBGL) of patients who were receiving A. marmelos leaves in comparison to patients who were on their standard oral hypoglycemic therapy (38).

Toxicity on different parts of Aegle marmelos L.
Herbal medicines are regarded by the public and some health care providers to be gentle and safe, but there is no scientific basis for this belief. The active components of plants have potential to cause serious adverse effects (39). The usefulness of drugs depends greatly on their lack of toxicities or adverse side effects. Therefore, many attempts have been taken by researches to assess any toxic effects of A. marmelos using different parts of the plant. A single dose of 500 mg/kg A. marmelos flower extract was used for 42 consecutive days to evaluate any toxic effects on the levels of blood aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), Hb, creatinine and gamma GT on rats (40).
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Table 3. In vivo experiments on anti-diabetic activity of different parts Aegle marmelos L.

<table>
<thead>
<tr>
<th>Preparation of the extract</th>
<th>Experimental procedure</th>
<th>Results</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seeds were extracted with boiling water for 10 h and filtered. The filtrate was evaporated in a vacuum to give a residue.</td>
<td>The anti-diabetic property was evaluated in diabetic rats by following methods: (a) Evaluating the effect of different doses of A. marmelos seed extract on blood glucose levels in rat. (b) Evaluating by giving the most effective dose of the extract (250 mg/kg) once a day for 14 consecutive days and observing the changes in FBG level, body weight, urine sugar and lipid profile.</td>
<td>A significant (P ≤ 0.05) reduction in blood glucose level was observed after 6 h of administration. Highest hypoglycemic activity was observed with 250 mg/kg. The mid dose (250 mg/kg) of A. marmelos produced a maximum anti-diabetic activity after 2 h of glucose administration. The FBG levels of rats were decreased by 37.4% and 60.8% respectively, after 1 h and 2 weeks of treatment. Furthermore, decreased the levels of TC (by 25.4%), LDL (by 53.9%), TG (by 45.7%) and urine sugar levels (75%) while increased the levels of HDL (by 33.3%) and body weights after continuous treatment of 14 days.</td>
<td>(25)</td>
</tr>
<tr>
<td>Aqueous fruit extract (brown dry powder) was suspended in distilled water</td>
<td>Evaluating by giving 125, 250 mg/kg doses twice a day for 28 consecutive days to STZ-induced diabetic rats</td>
<td>A significant reductions in blood glucose, plasma thiobarbituric acid, hydroperoxides α-tocopherol and ceruloplasmin as well as an elevation in plasma glutathione and vitamin C in diabetic rats. At dose of 250 mg/kg was more effective than the reference drug, glibenclamide in restoring the values of these parameters.</td>
<td>(26)</td>
</tr>
<tr>
<td>Aqueous fruit extract was suspended in distilled water</td>
<td>Experimentation design was similar to the previous study (25). After 30 days of treatment blood was collected to determine FBG level and removed the heart and pancreas (to assess the antioxidant activities) after the rats were sacrificed.</td>
<td>A significant reduction blood glucose was observed in rats treated with extracts The lowered glutathione content in the heart and pancreas of diabetic rats was found to increase on treatment with extracts. The effect of 250 mg/kg dose was more than that of the reference drug, glibenclamide.</td>
<td>(27)</td>
</tr>
<tr>
<td>Aqueous fruit extract was suspended in distilled water</td>
<td>By evaluating anti-lipid peroxidative activity in hepatic and renal tissues in diabetic rats. Experimentation design was similar to the previous study (26).</td>
<td>A. marmelos fruit extracts prevented STZ-induced hyperglycaemia and hypoinsulinemia. A significant decrease in peroxidation products and hydroperoxides in diabetic rats. Antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase increased in the hepatic and renal tissues of diabetic animals treated with extracts. A. marmelos fruit extract at a dose of 250 mg/kg, was more effective than glibenclamide.</td>
<td>(28)</td>
</tr>
<tr>
<td>Aqueous fruit extract was suspended in distilled water</td>
<td>Positive effects on heart and pancreas antioxidants in STZ-induced diabetic rats. Experimentation design was similar to the previous study (25).</td>
<td>A significant reduction was observed in rats treated in the elevated levels of peroxidation products, viz. thiobarbituric acid reactive substances and hydroperoxides in the tissues of diabetic rats. The depressed activities of superoxide dismutase, catalase and glutathione peroxidase and lowered glutathione content in the heart and pancreas of diabetic rats increased. However, effect of 250 mg/kg dose of A. marmelos on tested parameters was found to be more than that of the reference drug, glibenclamide.</td>
<td>(27)</td>
</tr>
<tr>
<td>Aqueous fruit extract was suspended in distilled water</td>
<td>Effects in normal and STZ- induced diabetic rats and anti-lipid peroxidative activity was studied in hepatic and renal tissues in diabetic rats (26)</td>
<td>The fruit extracts prevented STZ-induced hyperglycaemia and hypoinsulinemia and produced significant decrease in peroxidation products and hydroperoxides in diabetic rats. The activity of antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase increased in the hepatic and renal tissues of diabetic animals treated with extracts. However, A. marmelos fruit extract at a dose of 250 mg/kg, was more effective than glibenclamide.</td>
<td>(28)</td>
</tr>
<tr>
<td>Aqueous fruit extract was suspended in distilled water</td>
<td>Effects in normal and STZ- induced diabetic rats and serum and tissue (e.g. Liver, kidney and heart) lipids such as total cholesterol, triglycerides, free fatty acids and phospholipids were evaluated</td>
<td>The fruit extract at doses of 125 and 250 mg/kg to diabetic rats twice daily for 1 month significantly lowered these lipids in diabetic rats. The fruit extract at a dose of 250 mg/kg had greater effect than that of glibenclamide (300 μg/kg). The results of this study demonstrate that an aqueous A. marmelos fruit extract exhibits an antihyperlipidemic effect in STZ-induced diabetic rats.</td>
<td>(29)</td>
</tr>
</tbody>
</table>
Aqueous fruit extract was suspended in distilled water. Effects in histopathological examinations of the pancreas of STZ-induced diabetic rats. A. marmelos fruit extract improved functional state of the pancreatic β-cells and partially reversed the damage caused by STZ to the pancreatic islets. (30)

Methanolic extract of the bark. Effects in hypoglycemic and β-cells regenerative effects of STZ-induced diabetic rats. At 200 and 400 mg/kg doses showed significant reduction in blood glucose level by 19.1% and 47.3%, respectively in diabetic rats. A. marmelos bark extract treatment significantly increased insulin level, and produced similar effects on other biochemical parameters. Histological studies showed the regenerative effect of A. marmelos bark extract on the β-cells of diabetic rats. The extract increased insulin immunoreactive β-cells. (31)

Hot aqueous flower extract. Effects in hypoglycemic effects of alloxan monohydrate-induced diabetic rats. 500 mg/kg for continuous 42 days increased hypoglycemic effect and decreased the HbA1c level in diabetic rats. (32)

Methanolic extract of the leaves. Hypoglycemic effects and antioxidant activity of alloxan monohydrate-induced diabetic rats. Reduce blood sugar in alloxan diabetic rats. Decrease the lipid peroxidation, conjugated diene and hydroperoxide levels in serum as well as in liver induced by alloxan. Catalase and glutathione peroxidase activities in blood and liver were found to be increased from 9th day onwards after drug administration. Superoxide dismutase and glutathione levels were found to be increased only on 12th day. (33)

Abbreviations: FBG, fasting blood glucose; HbA1c, glycated hemoglobin; Hb, hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; TC, total cholesterol; TG, triglyceride; STZ, streptozotocin.
There was no statistically significant ($P > 0.05$) difference between the values of above parameters of test group compared to the control group. The results of the present study showed that the water extract of dried flowers of A. marmelos does not exert any adverse effects as judged by the parameters studied (40).

Acute, sub acute toxicities and LD$_{50}$ values of total alcoholic, total aqueous and methanolic extracts prepared from leaves of A. marmelos were evaluated. There were no remarkable changes noticed in the histopathological studies after 50 mg/kg body weight of the extracts of A. marmelos when administered intraperitoneally for 14 days successively. Pathologically, neither gross abnormalities nor histopathological changes were observed. After calculation of LD$_{50}$ values using graphical methods, we found a broad therapeutic window and a high therapeutic index value for A. marmelos extracts. Intraperitoneal administration of different doses of the leaves extracts of the plant (50, 70, 90 and 100 mg/kg for 14 consecutive days) to male and female Wistar rats did not induce any short term toxicity (41).

**Conclusion**

Aegle marmelos has been evaluated for its anti-diabetic activity by using in vivo, in vitro and clinical researches. According to the promising anti-diabetic properties and non toxicity, A. marmelos can be used as a potential candidate for treatment of diabetes mellitus. Therefore, necessary researches should be undertaken for the development of functional foods, nutraceuticals and herbal medicine for better therapeutic utilization of the plant.

**Authors’ contributions**

All the authors contributed to data collection and preparation of the manuscript equally. All read the final version and confirmed for publication.

**Conflict of interests**

The authors declared no competing interests.

**Ethical considerations**

Ethical issues have been completely observed by the authors.

**Funding/Support**

None.

**References**

Aegle marmelos as a candidate for diabetes mellitus

37. Kumari KDKP, Suresh TS, Samarasinghe K, Handunnetti SM, Samarayake TSP. Evaluation of a traditional Sri Lankan herbal beverage (water extract of dried flowers of Aegle marmelos, Bael fruit) in type II diabetic patients. 4th World Congress on Diabetes Metabolism; Holiday Inn, USA; August 14-16, 2013.