



Tremendous Pharmacological Values of *Aegle marmelos*

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ABSTRACT

Aegle marmelos (L.) Correa is a sacred medicinal and neutraceutical tree of India. The leaves, bark, roots, fruits and seeds are used extensively in the Indian traditional system of medicine, the Ayurveda. *A. marmelos* is mainly used for the treatment of diabetes mellitus. This review critically assesses the phytochemical and pharmacological properties like free radical scavenging, antioxidant, inhibition of lipid peroxidation, antibacterial, antidiabetic, hepatoprotective, antiviral, anticancer & cardioprotective effects. This review also encompasses on the potential application of the above plant in the pharmaceutical field because of its wide pharmacological activities.

Keywords: Diabetes mellitus, *Aegle marmelos*, Pharmacological properties, Medicinal values.

INTRODUCTION

Diabetes mellitus was firstly reported in Egyptian manuscript about 3000 years ago. It is known as one of the oldest diseases known to man¹. Non-insulin dependent diabetes mellitus (Type 2 DM) was first described as a component of metabolic syndrome in 1988². Type 2 DM is the commonest form of DM symptomized by hyperglycemia, insulin resistance and relative insulin deficiency³. Type 1 Diabetes usually starts in people younger than 30 and is therefore also termed juvenile-diabetes, even though it can occur at any age. It is chronic disorder that precipitates in genetically susceptible individuals by environmental factors⁴.

Epidemiology

As of 2014, an estimated 387 million people have diabetes worldwide with type 2 diabetes making up about 90% of the cases. This represents 8.3% of the adult population with equal rates in both men & women. From 2012 to 2014, diabetes is estimated to have resulted in 1.5 to 4.9 million deaths each year. Diabetes at least doubles a person's risk of death. The number of people with diabetes is expected to rise to 592 million by 2035. The global economic cost of diabetes in 2014 was estimated to be 612 billion⁵.

Lifestyle & Genetics

Diabetes mellitus occurs due to lifestyle factors and genetics⁶. Some important lifestyle factors are physical inactivity, sedentary lifestyle, cigarette smoking and generous consumption of alcohol⁷. Obesity is also known as one of the major risk factor of diabetes⁸.

There is a strong inheritable genetic connection in type 2 DM. Now a day's specific genes include CDKAL1, SLC30A8, PPARG, FTO, KCNJ11, NOTCH2, TCF7L2, HHEX and JAZF1 discovered to be significantly associated with developing type 2 DM⁹.

Medical conditions include obesity, hypertension, elevated cholesterol, termed metabolic syndrome also known as syndrome X, Reaven's syndrome¹⁰.

Pathophysiology

Diabetes mellitus is characterized by insulin insensitivity as a result of insulin resistance, due to pancreatic beta-cell failure¹¹. Hyperglycemia occurs when inadequate levels of insulin given and increased insulin resistance. GLP-I analogues with increased half-lives and DPP-IV inhibitors, which prevent the breakdown of endogenous GLP-I as well as GIP¹².

Management

Due to lifestyle and diet modification, eating high fiber and unsaturated fat and diet low in saturated and trans-fats and glycemic index, regular exercise, abstinence from smoking and moderate consumption of alcohol¹³.

Herbal Treatment of Diabetes

There are a number of literature reviews by different authors about anti-diabetic herbal agents. The most informative is the review by Atta-ar-Rahman who has investigated more than 300 plant species accepted for their hypoglycemic properties¹⁴. One such plant is *Aegle marmelos*, whose fruit is known as Bael.

Bael is commonly known as wooden apple. *Aegle marmelos* [L.] Correa belongs to the Rutaceae family, widely used in Indian medicines because of its various medicinal properties¹⁵.

Bael is known in India from prehistoric time for its ayurvedic medicinal properties¹⁶. Bael is the single member of the monotypic genus *Aegle*. It also has a great mythological significance. It is utilized in our daily life in various forms. The products of Bael are highly nutritive and therapeutic and getting popularized in India as well as in international market¹⁷.



Bael plant acts as a sink for chemical pollutants because of it absorbs poisonous gases and harmful components from atmosphere and make them neutral.

The tree is also considered under the category of "fragrant" species, whose flowers and volatile vapours neutralize bad smell of petrified organic matter and save human life from bacterial attack by making them inert¹⁸.

Origin & Distribution

The *Aegle* is a small genus of three species distributed in tropical Asia and Africa.

Bael tree originates from Eastern Ghats and central India. Bael is found mainly in foothills of Himalayas, Uttar Pradesh, Madhya Pradesh, Rajasthan, Chhattisgarh, Bihar, The Deccan plateau and along the East coast¹⁹.

Huien Tsiang, the chinese Buddhist pilgrim who came to India in 1629 A.D. noticed the presence of this tree in this region²⁰.

Bael in Mythology

Hindus hold the tree in great veneration. The leaves are ternate²¹.

It is offered to Lord Shiva, whose worship cannot be completed without the leaves of this tree. It is also known as Shivadurme, the tree of Shiva²². The mentioned plant has also been found in ancient Indian scriptures like Yajurveda and Mahabharata.

Various Names of Bael

Table 1: Different Vernacular Names of *Aegle marmelos*

Language	Vernacular different names
Hindi	Bael, Bel, Belgiri
Sanskrit	Bilva, Shivdurma, Shivpala
English	Bengal Quince
Urdu	Belk, Belk ham
Gujarati	Bilvaphala
Malayalam	Marredy
Tamil	Vivla Marum Vivama

Description

Aegle marmelos is about 12-15m. tall with short trunk, medium sized tree, soft, thick, flaking bark and sometimes spiny branches²³.

Classification of *A. marmelos*

Kingdom: Plantae
 Order : Spindales
 Family : Rutaceae
 Subfamily: Aurantioideae
 Genus : *Aegle*
 Species : *A. marmelos*



Figure 1: *Aegle marmelos* Plant

The deciduous leaves originates singly or in 2's or 3's are composed of 3-5 oval leaflets, 4-10 cm. long, 2-5cm. wide, pointed and the terminal one with a long petiole.



Figure 2: Leaves of *Aegle marmelos*

Flowers are greenish white in color and have bisexual, actinomorphic, hypogynous. The calyx is gamosepalous, light green, five lobed pubescent and corolla with five petals and pale yellow color²⁴.



Figure 3: Flowers of *Aegle marmelos*

The Fruits are yellowish green, with small dots and the pulp of dried fruits retains it yellow. There are numerous seeds, embedded in the pulp and cotton-like hairs on their outer surface²⁴.



Figure 4: Fruits and seeds of *Aegle marmelos*

Table 2: Various phytoconstituents of *Aegle marmelos*

1	Leaf	Skimmianine, Aegeline, Lupeol, Cineol, Citral, Citronella, Cuminaldehyde, Eugenol, Marmesinine
2	Bark	Skimmianine, Fagarine, Marmin
3	Fruit	Marmelosin, Luvangetin, Auraptin, Psoralen, Marmelide, Tannin

Phytochemical Constituents & Their Biological Activities of *Aegle marmelos*

Major phytoconstituents have been isolated from the various parts of *Aegle marmelos*, which may be classified as²⁵.

Bael leaves contained *Aegeline*, lupeol, rutin, marmesinine, β -sitosterol, flavone, glycoside, oisopentenyl halfordiol and phenylethyl cinnamamides²⁶. Some isolated compounds are classified as:

Alkaloids

The alkaloids are secondary plant substances. The main four alkaloids of *A. marmelos* leaves are N-2-[4-(3', 3'-dimethylallyloxy) phenyl] ethylcinnamide, N-2-hydroxy-2-(4-hydroxyphenyl) ethylcinnamide, Marceline and *Angeline*²⁷.

Shahidine, an alkaloid having oxazoline core has been isolated as a major constituent from the fresh leaves of *Aegle marmelos* and it showed activity against a few Gram-positive bacteria²⁸.

Terpenoids

The essential oil of *A. marmelos* [L.] *Correa* leaves was studied very much extensively in India. α -phellandrene and p-cymene were extracted from its leaves oil²⁹.

Limonene was reported as an important constituent from *A. marmelos* leaves and it was shown that limonene as marker for identification of Bael soil samples³⁰. γ -sitosterol was separated from the leaves³¹.

Tannins

Approximately 9% tannin is reported in the pulp of Bael fruits. Tannin is also present in leaves in the form of skimmianine and named as 4,7,8-trimethoxyfuroquinoline³².

Seed oil

Seed oil is bitter in taste and contains 15.6% palmitic acid, 8.3% stearic acid and 28.7% linoleic acid³³.

Flavonoids

Rutin flavon, flavon glycosides and flavon-3-ols are the major flavonoids of *A. marmelos* leaves. The GC-MS analysis revealed the presence of many phytoconstituents like flavonoids, alcohols, aldehydes, aromatic compounds, terpenoids, phenolics, and steroids, that can be investigated for their antibacterial activities³⁴.

Phenylpropanoids

The phenylpropanoids included hydroxycoumarins, phenylpropenes and lignans. Coumarin is the parent compound which occurs in over twenty seven plant families. *Aegeline*, was initially claimed to be a new compound, was found to be identical to half ordinal, the basic constituent of halfordia scleroxyla³⁵.

Miscellaneous compounds

Researchers investigated Valencic acid, betukinic acid, trans-cinnamic acid, praealtin D, 4-methoxybenzoic acid, montanine, rutaretin, N-P-cis- & transcoumaroyltyramine from the leaves of methanolic extract of *Aegle marmelos*.

Various Proved Therapeutic Values of *Aegle marmelos*

Hepatoprotective activity

In 2008, Ramnik S. investigated that the aqueous extract of bael seeds and pulp of fruit are effective in the treatment and prevention of CCl₄ administered hepatic toxicity³⁶. The hepatoprotective effect of the leaves of *A. marmelos* was reported in Albino rats for 40 days. Then the rats were fed leaves for 21 days and the extreme effect was seen³⁷.

Antimicrobial activity

Bael has been traditionally used for the treatment of various infectious diseases and been reported to inhibit the broad range of pathogenic microorganisms. Many *in vitro* studies investigated the antimicrobial potential of *A. marmelos* extracts towards the pathogenic microorganisms including bacteria and fungi. In 2009, Maheshwari investigated on the ethanolic extract of dried fruit pulp of *Aegle marmelos* and found that pulp contains several phytochemicals including phenols, Tannins and flavonoids. These were effective against shigella boydi, S. sonnei & S. flexneri³⁸.

Analgesic activity

In 2007, Shankharananth V. evaluated the methanol extract of leaves of *Aegle marmelos* (L.) at a dose level of

200 and 300 mg/kg and observed significant analgesic activity on acetic acid induced writhing and tail flick test in mice³⁹.

Anti-inflammatory activity

In 2008, Ghangale G.R. studied aqueous extract of *Aegle marmelos* with the help of rat paw oedema model and assured that *A. marmelos* have anti-inflammatory activity⁴⁰. The various extracts of the leaves of Bael were evaluated for anti-inflammatory activity.

Anti-ulcer activity

Bael has a prominent gastro protective effect due to the presence of Luvangetin. Luvangetin lowers oxidative stress in the gastro duodenal mucosa because oxidative stress usually leads to gastric ulcer. In 2007, Dhuley J.N studied the unripe Bael fruit extract and observed that it produce a significant inhibition of ethanol induced gastric mucosal damage⁴¹.

Anti-cancer activity

Research shows that extracts from *Aegle marmelos* are able to inhibit the *in vitro* proliferation of human tumor cells, erythroleukemic HEL, melanoma colo38, MDAMB-231 and breast cancer MCF7 cell lines. In 2005, Gagetia G.C. investigated the anticancer activity of hydro alcoholic extract of leaves of Bael in the animal model of ascites carcinoma and suggested that induction of apoptosis because of Skimmianine, present in leaf extract⁴².

Anti-spermatogenic activity

In 2009, Sharma R.C studied the ethanol extract of leaves of *A. marmelos* on sperm motility and was reported that the extracts had a valuable effect on the locomotory activity of sperm. It was also reported that the increased concentration of extracts decrease the motility of sperms⁴³.

Anti-thyroid activity

In 2006, Panda S. and Kar A. separated Scopoletin from *A. marmelos* leaves and evaluated for its capacity to regulate hyperthyroidism mechanism and it decreased thyroid hormone level. It was also suggested that the scopoletin have more dominant therapeutic activity than propylthiouracil drug⁴⁴.

Toxicity Studies

In 2007, Veerappan A. studied on four different extracts of *A. marmelos* leaves in rats for their toxicity.

After then he found no histopathological changes and also concluded that the extracts have a high margin of drug safety.

This study was investigated to demonstrate the toxicity of the *Aegle marmelos* plant in rats.

The various extracts like methanolic, whole aqueous, total aqueous and total alcoholic of leaves of *A. marmelos* isolated and studied their toxic effects⁴⁵.

Antifungal activity

In 1997, Rana B.K. demonstrated antifungal activity of essential oils isolated from the leaves of Bael using spore germination technique. They concluded that essential oil from Bael leaves may interfere with the Ca²⁺ dipicolonic acid metabolism pathway and possibly control the spore formation⁴⁶.

Antiviral activity

Virus is the smallest pathogen. The ethanolic Bael fruit extract have shown antiviral activity against virus of Ranikhet disease. The Lc 50 of leaves having marmelide compound are 1000µg/ml, whereas the Lc50 of standard antiviral agent Ribavirin is 2000µg/ml for the same viruses for same period. Marmilide is the most effective viricidal agent of Bael fruit interfering with early events of replicating cycle⁴⁷.

Antibacterial activity

The minimum inhibitory concentration of methanolic extract is more potent than the aqueous extract of Bael fruit and have shown strong action against *Salmonella typhi* bacteria⁴⁸. The antibacterial activity of leaf extract identified due to the presence of cuminaldehyde and eugenol. Bael has antimicrobial activities may be by blocking protein synthesis either at transcription and translation level⁴⁹.

Cardioprotective effects

The cardio protective activity is due to the presence of auraptin as potent compound. The leaf extract of Bael has preventing effects in isoprenaline-induced myocardial infarction in rats⁵⁰. Further studies concluded that Bael can be used as cardiac depressant⁵¹.

Diarrhoea & Dysentery

Bael fruit is the most effective remedy for diarrhoea & dysentery without fever. The unripe fruit can also be baked with brown sugar⁵². After the use of the fruit powder, the blood and mucus gradually disappears and the stools resume a more feculent form⁵³.

Respiratory infections

Medicated oil prepared from *A. marmelos* leaves gives relief from cold and respiratory infections. In south India juice of leaves is used to bring relief from wheezing cough and respiratory spasm⁵⁴. The effect of the alcoholic extract of the leaves of Bael was concluded as this plant is used traditionally to treat asthma and related infections.

Radioprotective effect

Now these days radiotherapy is one of the most important therapies to cure those patients who are suffering from vital visceral malignancies. A large number of cancer patients are getting their treatment by this therapy. Various researches investigated that the treatment with extract of Bael reduces the severity of symptoms of radiation. The radioprotective action might



be due to arrest of lipid peroxidation and free-radical scavenging⁵⁵.

Constipation

The Bael fruit cleans the intestines because it has laxative property. It should be taken as sharbat for its best use. Its regular use for two to three months helps in evacuation of the old accumulated foecal matter from the bowels because it cleans and tones up the intestine. Milk and sugar can be add up to its pulp to make it more palatable⁵⁶.

Burn cases

It is also used in burn cases. The one part of dry fruit powder and two parts of mustard oil are mixed and are applied externally or superficially in burn patients⁵⁷.

Anti-diabetic, Antihyperlipidaemic & Anti-oxidant activity

In 2004, Kuttan & Sabu studied on leaf extract of *Aegle marmelos* on Alloxan induced diabetic rats and demonstrated that the extract was much capable to reduce oxidative stress and affect anti-oxidant levels, so that the elevated level of blood sugar become diminished⁵⁸.

In 2010, Gohil demonstrated that the treatment with extracts of *Eugenia jambolana* seed and *Aegle marmelos* leaf extracts prevents hyperglycemia and hyperlipidemia in alloxan induced diabetic rats. Due to the administration of plant extracts, there is higher reduction in hyperglycemia and hyperlipidemia and significant ($p < 0.001$) increment of serum insulin level in experimental rats⁵⁹.

In 2014, R. Bhavani studied the anti-hyperglycemic activity of alcoholic leaf extract of *Aegle marmelos* (Linn.) on Alloxan induced diabetic rats. Due to the continuous administration of the extract, reduction in blood sugar level could be seen. Blood sugar levels were found to be reduced by 54%. The level of body weight were back to near normal. After the administration of *A. marmelos* extract, the level of serum protein, insulin, urea,

triglycerides were reverted back to near normal level⁶⁰.

In 2012, Ram Prakash Prajapat studied the extraction and isolation of Marmelosin from *Aegle marmelos*, synthesis and evaluation of their derivative as antidiabetic agent. It was found that the Marmelosin possessed highest significant reduction in blood glucose level as compared to synthesized compounds against alloxan induced diabetic rats, after daily administration of extract for 14 days⁶¹.

In 2012, Bhatti studied the effect of *Aegle marmelos* leaf extract treatment on diabetic neuropathy in rats: a possible involvement of A_2 adrenoceptors. The leaf extract of *A. marmelos* was found to increase the paw licking and tail flicking latency ($p < 0.05$) as compared to the vehicle treated diabetic controls. The propranolol did not alter the effect of AME but the administration of yohimbine was found to attenuate the protective effect of AME⁶².

In 2014, Ferdous investigated the antihyperglycemic and antihyperlipidemic effects of the alcoholic extracts of *Aegle marmelos* L. leaves. This study shows that after administration of *A. marmelos* leaves extract at different doses, the blood glucose level, total cholesterol, triglycerides, LDL decreased and HDL level increased⁶³.

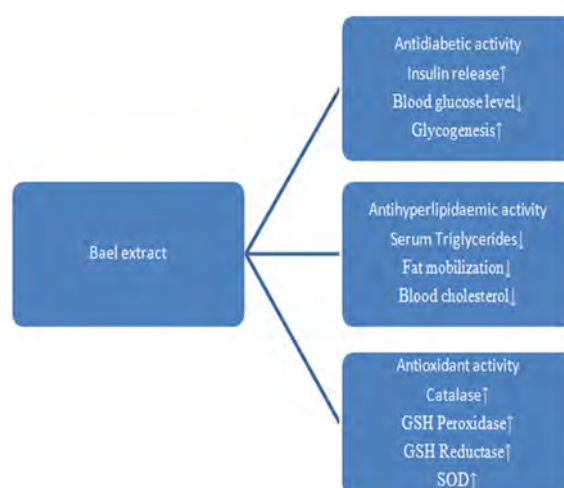


Table 3: Various Manufactured products of *Aegle marmelos*

S. No.	Marketed formulations	Company name	References
1.	Chawanprash	Himalaya	64
2.	<i>Aegle marmelos</i> capsules	La-Medicca (India) pvt. Ltd.	65
3.	Leucare capsules	Shrey Nutraceuticals & Herbals	66
4.	Entrostat Syrup	Ambika Medico	67
5.	Kof-Rid Syrup	Ambika Medico	68
6.	Pregeight	Sydler Remedies Pvt. Ltd.	69
7.	Ojamin	Tates Remedies	70
8.	Manasamithravatakram	Oushadhi	71
9.	Pushyanugam gulika	Oushadhi	72
10.	Vilwadi gulika	Oushadhi	72

CONCLUSION

The medicinal properties of *A. marmelos* have been described in the Ayurveda. This review presents the phytochemicals, antioxidant, antidiabetic, antihyperlipidaemic etc. properties of Bael. The most important pharmacological activity of the leaves of *A. marmelos* has been found to be its antidiabetic activity but the mechanism of hypoglycaemic action of leaves is not clear and may be the result of improvement in the functional status of beta cells. The evaluation needs to be carried out an *Aegle marmelos* in order to uses and formulation of the plant in their practical clinical therapies, which can be used for the welfare of human being.

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