

THERAPEUTIC POTENTIAL OF *AEGLE MARMELLOS* (L.) CORREA LEAVES AS AN ANTIOXIDANT AND ANTI-DIABETIC AGENT: A REVIEW

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ABSTRACT

With growing burden of diseases, the use of natural plant products is increasing due to its minimal side-effects and economical aspects. The *Aegle marmelos*, (Bael), is indigenous to India and its leaves, bark, roots and fruit have been used for over 5000 years in the Indian traditional system of medicine, the Ayurveda and in various folk medicine to treat various diseases. Even though all the parts of the plants are useful, the leaves and fruits are mostly used as important drug in the ancient system of medicine to cure almost all the common ailments of the human being. Extensive experimental and clinical studies prove that *Aegle marmelos* possesses antidiarrhoeal, anti-diabetic, antimicrobial, antiviral, radio protective, anticancer, chemo preventive, antipyretic, ulcer healing, antigenotoxic, diuretic, antifertility and anti-inflammatory properties, which help it to be useful in prevention and treatment of many diseases. *Aegle marmelos* has been used to control diabetes in traditional medicinal system. Many in vivo scientific studies have been conducted in animal models to evaluate the anti-diabetic activity of different organic extracts of *Aegle marmelos*. Compounds isolated from *Aegle Marmelos* have been proven to be biologically effective against several major diseases including cancer, diabetes and cardiovascular diseases. This review attempts to highlight the antioxidant and antidiabetic (hypoglycemic) property of *Aegle marmelos*.

Key words: *Aegle Marmelos*, antioxidant, anti-diabetic activity, pharmacological activity

INTRODUCTION

Over the last few years the importance of plant based substances have increased greatly for the treatment of various diseases¹. Natural products owing to their multiple medicinal properties attract lot of attention from indigenous communities of India. This system of medicine is pollution free, less toxic and without side effects. Out of the 6000 plants mentioned in the traditional systems of medicine, only 350 species are under use most of which are herbs.

Plants being important sources of natural antioxidants, their importance for use as food additives or nutritional supplements has already been established². The search for safe and effective naturally occurring antioxidants is now focused on edible plants especially spices and herbs³. The literature is replete with reports of extracts from natural sources like spices, herbs and hulls that have demonstrated strong antioxidant activity⁴. However scientific information on antioxidant properties of various plants particularly those that are less widely used in culinary and medicine, is still rather scarce³. The antioxidant activity of some medicinal plants in food and biological systems is poorly investigated. In the present review, an attempt has been made to gather information on the phytochemical and pharmacological activities of an important medicinal plant *Aegle marmelos*.

METHODS AND MATERIALS

Desk reviews were collected from personal visits to Gujarat Agricultural Universities namely: 1) Junagadh Agricultural University (JAU) 2) Sardar Patel Agricultural University 3) Anand Aromatic Plant Research Centre and 4) Jamnagar Ayurved College Jamnagar 5) Bael Vejalpur Research Station CSIR Panchmahals Godhra; Pub Med and other web sources and libraries across the state.

RESULTS

Aegle marmelos in Indian mythology

Aegle marmelos, is one such plant described in the ancient medical treatise in Sanskrit, Charak Samhita. It is popular medicinal plant in Ayurvedic and Siddha systems of medicine and folk medicines used to treat a wide variety of ailments. *Aegle Marmelos* commonly known as bael belongs to family Rutaceae. In Ayurveda Bael is termed tridosh har- remedy for three disturbances- bile, wind and phlegm⁵. *Aegle marmelos* (Bilva) is considered as an embodiment of Lord Shiva himself and it is one of the sacred trees in Hinduism having

spiritual powers. Bilva tree is said to have manifested from Goddess Sri Maha Lakshmi and Sri Sooktham eulogize Goddess Lakshmi as...

"Aadithya varnae tapassodhi jaatho

Vanaspathi stava vrukshotha *bilvaha*

Tasya phalani tapasaanudantu

Mayaantha raayaashcha baahya alakshmeehi"

The translation of this stotra is given below.

"Oh Lakshmi, your complexion is like that of a morning Sun, a vanaspathi (trees bearing fruits without blossoming) called by name *Bilva* was brought forth by your devout austerity. Through your favour may the fruits of the tree drive away my misfortunes and poverty both internal (ignorance) and external. It is believed and said that one who does penance under the *Bilva* tree and meditate on Goddess Sri Maha Lakshmi will be bestowed with fulfilment of all desires"⁶.

Leaves are offered in prayers to *Shiva* and *Parvathi* since ancient time⁷. Bael having useful medicinal properties especially as a cooling agent, is a deciduous sacred tree, associated with Gods. This tree is popular in Shiva and Vishnu temples also popularly known as temple garden plant and it can be grown in every house. Its leaves are trifoliate symbolizing the Thrimurthies- Brahma, Vishnu, Shiva with spear shaped leaflets resembling trisoolam the weapon of Lord Shiva. The tree is also sacred to the Jains. The 23rd Tirthankara, Bhagwan Parasnathji attained enlightenment under a Bael tree⁵. The leaflets are given to devotees as prasadam in Shiva temples and as Tulsi in Vishnu temples. The leaves and fruits of *Aegle Marmelos* plant can be seen in Figure 1 and 2.



Fig:1 Aegle marmelos fruits



Fig:2 Aegle marmelos triplet leaf

Plant profile

- Botanical Name: *Aegle Marmelos*
- Sanskrit Name: Bilva
- English Name: Bael Tree
- Family: Rutaceae
- Parts of Plant used: Fruit, leaf, root, bark

Scientific classification⁸

- Kingdom: Plantae
- (unranked): Angiosperms
- (unranked): Eudicots
- (unranked): Rosids
- Order: Sapindales
- Family: Rutaceae
- Subfamily: Aurantioideae
- Tribe: Clauseneae
- Genus: *Aegle* Corrêa
- Species: *A. marmelos*

Binomial name: *Aegle marmelos* (L.) Corr. Serr.

The names of *Aegle marmelos* in different languages are given in table 1⁹

TABLE 1 SHOWING NAMES OF *AEGLE MARMELLOS* IN DIFFERENT LANGUAGES

Name	Language
<i>Aegle marmelos</i>	Latin
Wood/stone apple, Bengal Quince	English
Mbau Nau, Trai Mam	Vietnamese
Bel, Gudu	Nepali
Toum	Lao (Sino-Tibetan)
Bnau	Khmer
Modjo	Javanese
Oranger du Malabar	French
Ohshit, opesheet	Burmese
Mojo tree	Indonesian
Pokok Maja Batu	Malay
Mapin, Matum, Tum	Thai
Shreephal, Bilva, Bilwa	Sanskrit
Sir Phal	Old Hindi
Bel, Shreefal	Bengali
Kaveeth	Marathi
Vilva Maram, Vilva Pazham	Tamil
Maredu	Telugu
Bel	Urdu
Billi	Gujarati
Belo	Orissa

Botanical Description

Bael is the only member of the monotypic genus *Aegle*¹⁰. *Aegle marmelos* is a slow-growing, medium sized tree, 25 to 30 feet tall. The stem is short, thick, soft, flaking bark, and spreading, sometimes spiny branches, the lower ones drooping. 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 leaflets 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. In India flowering occurs in April and May soon after the new leaves appear and fruits ripens in 10 to 11 months from bloom March to June of the following year¹¹. Flowers occurs in clusters of 4 to 7 along the young branches, have 4 recurved, fleshy petals. The flowers are greenish white in color with a peculiar fragrant. 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. The seeds are small (nearly 1 cm in length) embedded in the pulp. hard, flattened-oblong, bearing woolly hairs and each enclosed in a sac of adhesive¹².

Soil Type

Aegle marmelos is said to do best on rich well drained soil, but it has grown well and fruited on the oolitic limestone of southern Florida. It also grows well in swampy, alkaline or stony soils having pH range from 5-8. In India it has a reputation of thriving where other fruit trees cannot survive¹³.

Tree Management

The tree has no exacting cultural requirements, doing well with minimum of fertilizer and irrigation. The spacing in orchards is 6-9 m between trees. Seedlings begin to bear in 6-7 years vegetative propagated trees in 5 years. Full production is reached in 15 years. Normally the fruit is harvested when yellowish-green and kept for 8 days while it loses its green tint. Then the stem readily separates from the fruit. A tree may yield as many as 800 fruits in a season¹².

Origin and Distribution

The *Aegle Marmelos* tree has its origin from Eastern Ghats and Central India. It is native to India and is found growing wild in Sub-Himalayan tracts from Jhelum eastwards to West Bengal, in central and south India. Bael

is found growing along foothills of Himalayas, Bihar, Chhattisgarh, Uttaranchal, Jharkhand, Gujarat and Madhya Pradesh. It is also grown in some Egyptian gardens in Surinam and Trinidad¹⁴.

Documented species distribution¹⁵

Native range: India

Exotic range: Bangladesh, Egypt, Malaysia, Myanmar, Pakistan, Sri Lanka, Thailand

Chemical compounds isolated from plant

Leaf- Skimmianine, Aeglin, Rutin, Y-sit sterol, β -sitosterol, Flavone, Lupeol, Eugenol, Cineol, citral, Glycoside, O-isopentenyl, Halfordiol, Marmeline, Citronellal, Cuminaldehyde phenylethyl cinnamamides, Eugenol, Marmesinin

Fruit- Marmelosin, Luvangetin, Aurapten, Psoralen, Marmelide, Tannin

Bark- Fagarine, Marmin.

Seed- Essential oil: D-limonene, A-D-phellandrene, Cineol, Citronellal, Citral, P-cyrene, Cumin aldehyde.

Nutritional value:

The fruit is eaten fresh or dried. The leaves and small shoots are eaten as salad greens in many Asian countries. The young shoots and leaf are used as vegetable in Thailand and used as seasonal food in Indonesia. These are used to reduce appetite¹⁶.

Various studies have been done to know the proximate composition of the leaves, pulp of fruit and seed powder of *Aegle Marmelos*. A study was conducted to analyze values for proximate composition of *Aegle Marmelos* leaf, pulp and seed powder using standard methods found that bael leaf, pulp and seed powder are good source of protein, fat, minerals, crude fiber and energy, rich source of available carbohydrates, dietary fiber and also contain antinutrient content which help in controlling blood sugar¹⁷. Another study reported that *Aegle Marmelos* leaf powder has 10.3g ash, 0.14 μ g zinc, 2.67 μ g iron and 1.73 μ g of chromium in leaf powder¹⁸.

The proximate composition of wild variety of *Aegle marmelos* leaves (Gir forest) and cultivated variety (*Gomayasi* from Vejalpur Research Station, Panchmahals, Godhra, Gujarat, India) was studied and it was found that both the varieties had good nutritional components however, the wild variety was superior to the cultivated variety in nutrients like carbohydrates, protein, fiber, moisture, ash content and many of the trace elements like Cu, Fe, Mn, Zn, Ca, Vanadium, Gold etc. Also heavy metals like lead, arsenic, mercury and cadmium were not detected in either of the variety proving it to be nontoxic¹⁹. The details are given in Table 2 below.

TABLE 2 PROXIMATE COMPOSTION OF AEGLE MARMELOS LEAF¹⁹

Parameter	A M Leaf (wild) (%)	A M Leaf (cultivated) (%)
Moisture	54.0	52.4
Crude Protein	7.6	2.22
Crude Fat	8.18	12.7
Crude Fiber	30.14	25.1
Ash	6.5	6.0
Carbohydrate	10.3	5.4
Zinc (ppm)	0.067	0.026
Chromium (ppm)	49	38
Iron (ppm)	181	169

Phytochemicals and their Biological Activities in *Aegle marmelos*:

Broadly, *Aegle marmelos* leaves contained γ -sitosterol, aegelin, lupeol, rutin, marmesinin, β - sitosterol, flavone, glycoside, Oisopentenyl halfordiol, marmeline and phenylethyl cinnamamides²⁰. The detailed investigations on isolated compound classes are as under:

1. Alkaloids:

The alkaloids comprise the largest single class of secondary plant substances. Four alkaloids were reported from dry leaves of *A. marmelos* *N*-2-[4-(3',3'-dimethylallyloxy)phenyl]ethylcinnamide, *N*-2-hydroxy-2-[4-(3',3'-dimethylallyloxy)phenyl] ethylcinnamide or marmeline, *N*-4- methoxystyryl cinnamide and *N*-2-hydroxy-2-(4-hydroxyphenyl) ethylcinnamide and aegeline^{21,22}. Aegeline was initially believed to be a sterol but after a critical study it was found to be a neutral nitrogenous compound.

Recently, series of phenylethyl cinnamides, which included new compounds named anhydromarmeline, aegelinosides A and B were isolated from *Aegle marmelos* leaves as α -glucosidase inhibitors²³. The present result also supports ethno pharmacological use of *Aegle marmelos* as a remedy for diabetes mellitus²⁴.

A rare alkaloid, shahidine, having an unstable oxazoline core has been isolated as a major constituent from the fresh leaves of *Aegle marmelos*. It is moisture-sensitive, and found to be the parent compound of aegeline and other amides; however, it is stable in dimethyl sulfoxide. Its structure was established by spectroscopic analysis. Biogenetically, oxazolines may be considered as the precursor of hydroxyl amides and oxazoles found in plants. Shahidine showed activity against a few Gram-positive bacteria²⁵.

2. Phenylpropanoids:

These are naturally occurring phenolic compounds, which have an aromatic ring to which three-carbon side chain is attached. Among the phenylpropanoids are included hydroxycoumarins, phenylpropenes and lignans. The most widespread plant coumarin is the parent compound, coumarin itself, which occurs in over twenty-seven plant families. Marmesin was established as a new compound from leaves, which is also a constituent of heartwood and root²⁶. Aegelenine, a minor base of the leaves, which was initially claimed to be a new compound, was found to be identical to halfordinol, the basic constituent of *Halfordia scleroxyla*^{27, 28}.

Aegeline (N-[2-hydroxy-2(4-methoxyphenyl) ethyl]-3-phenyl-2-propenamamide) is a known constituent of the bael leaf and consumed as a dietary supplement for a variety of purposes^{29,30,24}. Fresh leaves on distillation yield yellowish-green oil with a peculiar aromatic odour marmelosin, marmesinine, β - sitosterol- β -D-glucoside and rutin in the leaves. Marmenol, a new 7-geranyloxy coumarin [7-(2,6-dihydroxy-7- methoxy-7-methyl-3-octaenyloxy)coumarin] was isolated from the leaves of methanolic extract of *A. marmelos*³¹.

3. Terpenoids:

The essential oil of *A. marmelos* (L.) Correa leaves was studied very much extensively in India by various workers since 1950. α -Phellandrene was found to be the common constituent of the essential oil from leaves, twigs and fruits^{32,33}. α -Phellandrene (56%) and p-cymene (17%) were reported from leaf oil³⁴. Later, similar report was published on leaf essential oil by many workers. p-Menth-1-en-3,5-diol was isolated and characterized from *A. marmelos* leaves³⁵. Limonene (82.4%) was reported as the main constituent from *A. marmelos* leaves and it was shown that limonene is characteristic marker for identification of *A. marmelos* oil samples³⁶. γ -Sitosterol was identified from the leaves³⁷.

4. Tannins:

There is as much as 9% tannin in the pulp of wild fruits, less in cultivated type. Tannin is also present in leaves as skimmianine. It is also named as 4, 7, 8-trimethoxyfuro-quinoline³⁸.

5. Flavonoids:

Mainly includes Rutin, flavone, flavan-3-ols, flavone glycosides³⁹.

In a study important medicinal plants were investigated on the phytochemical composition including *Aegle marmelos* and reported highest alkaloids (1.08%), tannins (15.26%), Flavonoid (0.98%) and saponins (2.62%) in *Aegle marmelos* leaves when compared with other plants⁴⁰. A study conducted qualitative and quantitative phytochemical evaluation, antimicrobial activity and determined bio-active components was conducted from 18 varieties/accessions of the leaves of *Aegle marmelos* from all over India and it was found that the crude extracts of *A. marmelos* revealed the presence of several biologically active phytochemicals with the highest quantity of alkaloids, flavonoids, and phenols in Pant Aparna variety. The GC-MS analysis revealed the presence of many bioactive compounds such as flavonoids, alcohols, aldehydes, aromatic compounds, fatty acid methyl esters, terpenoids, phenolics, and steroids that can be postulated for antibacterial activity⁴¹.

6. *Seed oil*: Seed oil is bitter and contains 15.6% palmitic acid, 8.3% stearic acid, 28.7% linoleic acid and 7.6% linolenic acid while seed residue contains about 70% proteins³⁹.

7. Miscellaneous compounds

Ali M.S. and Pervez M.K., (2004)³¹ reported praealtin D, *trans*-cinnamic acid, valencic acid, 4-methoxybenzoic acid, betulinic acid, *N*-*p*-*cis*-& *trans*coumaroyltyramine, montanine, and rutaretin from the leaves of methanolic extract of *Aegle marmelos*. Rutin, flavan-3-ols, anthocyanins, leucanthocyanins, flavone glycosides and tannins also have been reported from the leaves²⁴.

Antioxidant and Anti-diabetic activity of *Aegle marmelos* (animal studies):

Several studies have been conducted using various dosage of extract of leaves of *aegle marmelos* on various animal models and the hypoglycemic effect of the plant have been proven. A series of phenylethyl cinnamides were reported in a study where anhydroaegeline revealed the most potent inhibitory effect against α -glucosidase with IC50 value of 35.8 μ M²⁴.

Antioxidant effect of *Aegle marmelos* against experimental diabetes was examined in a study. *Aegle marmelos* extract effectively reduced the oxidative stress induced by alloxan and produced a reduction in blood sugar. There was a significant decrease in lipid peroxidation, conjugated diene and hydroperoxide levels in serum as well as in liver induced by alloxan. It was predicted from the results obtained that the methanolic leaf extract of *Aegle marmelos* have characteristics to be used as hypoglycemic and antioxidant agent⁴² Antioxidant

parameters like reduced glutathione, glutathione peroxidase, glutathione reductase, superoxide dismutase (SOD) and catalase have shown a dose related increase in their level/activity and a decrease in lipid peroxidation following the treatment with *Aegle marmelos* leaf extract⁴³.

In a study found the hypoglycaemic and antioxidant activity of aqueous extract of *Aegle marmelos* leaves by analyzing the glucose, urea & GST (glutathione-S-transferase) levels in plasma and GSH (glutathione) and MDA (malondialdehyde) levels in erythrocytes of alloxan induced diabetic rats⁴⁴.

Glutathione (GSH) is reduced in erythrocyte whereas plasma glutathione-S-transferase (GST) and melondeialdehyde (MDA) are increased in diabetic male albino rats which return to normal level with *aegle marmelos* leaf extract administration suggesting antioxidant potential of *aegle marmelos* leaves⁴⁵. Eugenol and marmesinin may be responsible for such an activity because these compounds have independently shown their activity against oxidative stress. Eugenol (C₁₀H₁₂O₂), present in AM leaf extract, has potent antioxidant property^{46,47}.

In vitro antioxidant activity of the methanolic extract of *Aegle Marmelos* leaf was studied using standard methods like DPPH scavenging activity, H₂O₂ scavenging activity and ferrous reducing power. In vitro activity of Methanolic extract of *Aegle marmelos* showed that it has good antioxidant activity with the IC50 value 23±0.08. It thus can be used as potential inhibitor of free radicals⁴⁸.

Aegle marmelos leaves were screened for phytochemicals, antioxidant (DPPH) and polyphenol content (Folin-ciocalteu assay) using a series of solvents. The methanol and water extract of *Aegle marmelos* was found to be rich in ascorbic acid, glutathione, flavonoids, saponins, reducing sugars, turpenoids and polyphenols (2.4g of Gallic acid per 100g of (dry wt.) of extract. Antioxidant activity of water extract was higher (92%) than BHT (81% standard antioxidant), It also exhibited significant radical scavenging activity due to higher content of tocopherol, glutathione and ascorbic acid in it⁴⁹.

A study carried out an efficient record of the comparative antioxidant activity and phenol content in methanolic extract of the selected parts (leaves, root and stem bark) of *Aegle marmelos*. The total phenolic contents varied from 9.8367 ± 0.0235 to 1.7281 ± 0.049 mg g⁻¹. Total flavonoid contents were between 8.248 ± 0.029 to 1.087 ± 0.002 mg g⁻¹. The highest free radical scavenging effect (using DPPH) was observed in leaves with IC50 = 2.096µg/ ml which was about 10 times greater than reference antioxidant butylated hydroxy toluene (BHT). The greater amount of phenolic compounds leads to more powerful radical scavenging effect as shown by methanolic extract of *Aegle marmelos* leaves⁵⁰.

A study reported that pre-treatment with *Aegle marmelos* leaf extract at doses of 100mg/kg and 200mg/kg body weight for 35 days showed a significant effect on the activities of marker enzymes, lipid peroxides, lipids, lipoproteins and antioxidant enzymes in isoproterenol treated rats. The effect of extract 200mg/kg was found to be equal to the effect of alpha-tocopherol 60mg/kg⁵¹.

The hypoglycaemic effect of *Aegle marmelos* extract and *Hibiscus rosa sinensis* was studied in glucose induced hyperglycaemic rat for 7 consecutive days, at 250 mg/kg oral dose and it showed significant improvements in its ability to utilize the external glucose load. Average blood glucose lowering caused by *Aegle marmelos* was 67% and the efficacy of *Aegle marmelos* was 71% of glibenclamide⁵². The effect of the aqueous, alcoholic and petroleum ether extracts of *marmelos* for the hypoglycaemic and other pharmacological actions was studied and it was observed that the aqueous and alcoholic extracts at 500 mg/kg dose produce hypoglycaemia in normal fasted rabbits, but the petroleum ether extract did not⁵³. In a clinical trial, a branded formulation having leaves of *Aegle marmelos* as one of the constituents was found effective in mild to moderate diabetic patients, which included even the insulin dependent ones. The treatment, reportedly, tends to increase insulin secretion from pancreas⁵⁴.

The effect of leaf of *Aegle marmelos* on histological and ultra structural changes in tissues of streptozotocin induced diabetic rats was studied. The treatment of leaf extract on diabetic pancreas showed improved functional state of pancreatic beta cells. This study indicates the hypoglycaemic nature of the leaf extract, helping in regeneration of damaged pancreas⁵⁵.

The potential of the leaf extract of *Aegle marmelos* as an anti-diabetic agent on the liver of streptozotocin diabetic rats was investigated in a study. The leaf extract of *Aegle marmelos* was found to be as effective as insulin in restoring of blood glucose and body weight to normal levels.⁵⁶ It was reported that aqueous extract of leaves given in the dose equivalent to 1 gm powder/kg/day produced significant (p<0.01) anti-hyperglycaemic effect within three days in alloxan induced diabetic rabbits while similar treatment in normal rabbits produced decrease up to 35.3% in blood glucose level after 4 hours of administration. Moderate hypoglycaemic effect was recorded even after 12 hours⁵⁷.

In a study the potential antidiabetic effect of *Aegle marmelos* leaf extract in diabetic rats was explored. The diabetic animals were given insulin injection and another group *Aegle marmelos* leaf extract orally. This study indicated that the active principle in *Aegle marmelos* leaf extract has similar hypoglycaemic activity to insulin treatment⁵⁸.

Aegle marmelos is one of the most widely used medicinal and nutraceutical plant in the family Rutaceae. The leaf juice of *Aegle marmelos* used in diabetes and oedema⁵⁹. Ethno botanically this plant is reported for various medicinal properties.

In vitro antioxidant activity of the methanolic extract of *Aegle Marmelos* leaf was studied using standard methods like DPPH scavenging activity, H₂O₂ scavenging activity and ferrous reducing power and it showed good antioxidant activity with the IC₅₀ value 23±0.08. It thus can be used as potential inhibitor of free radicals⁵⁰.

Antioxidant and antiplasmodial Activities of *Curcuma Longa* and *Aegle Marmelos* on Malaria Infected Mice (*In Vitro and In Vivo*) were studied using DPPH (1, 1-diphenyl-2-picryl- hydrazyl) free radical scavenging activity. *Aegle marmelos* exhibited higher antioxidant activity and polyphenol content than *Curcuma Longa*⁶⁰. A study was conducted on the maximum percentage scavenging of DPPH for Ascorbic Acid, petroleum ether, chloroform, alcohol, and aqueous extracts (fresh Juice) of *Aegle marmelos* and it was found to be 94.56 %, 62.56 %, 86.81 %, 76.78 % and 72.74 % respectively at highest concentration. The more potent activity observed in chloroform extract (AMCL) compare to control group⁶¹.

In a study it was found that the ethanol extract of *Aegle marmelos* has higher antioxidant activity values of 46.08%, 50.56% and 54.32% at different concentration of 5, 10 and 15mg/ml respectively. The total phenolic compounds are major compounds responsible for antioxidant activity. Among the three solvents derivation of phenolic compounds was observed maximum by the ethanol solvent (1.921mg/g) and lowest by distilled water extract (1.510mg/g)⁶².

Aegle marmelos is widely used in Indian Ayurvedic medicine for the treatment of diabetes mellitus⁶³ Oral as well as intraperitoneal administration of the aqueous extract of various parts of *aegle marmelos* exhibited hypoglycemic effect against streptozotocin-induced diabetic rats⁶⁴. Antidiabetic mode of action is of multidirectional as the extract can significantly lower the levels of blood glucose and glycosylated hemoglobin and increased the plasma insulin as well as liver glycogen in diabetic rats⁶⁵. The leaf extract at a dose of 250mg/kg exhibited to be more effective than glibenclamide, a well-known hypoglycemic drug. This antidiabetic effect is probably due to the presence of eugenol and marmesin in bael leaves extract suggesting antioxidant potential of the leaves which potentiate the insulin secretion from existing beta cells of the islets of Langerhans⁶⁶.

It was further proved that aqueous leaf extract of *Aegle marmelos* have anti hypoglycemic activity, as the aqueous extract of the *Aegle marmelos* leaves were found to inhibit primarily the uptake of glucose across rat inverted gut sacs⁶⁷.

In a study it was found that aqueous extract of the leaves of *Aegle marmelos* (single dose of 10mg/100g every day morning for one month) fed to alloxan-induced diabetic rats significantly (p<0.001) decreased blood glucose levels and significantly (p<0.01) increased body weight changes while in non-diabetic rats, bael leaves didnot cause any hypoglycemia effect and body weight changes indicating that *Aegle marmelos* leaves have anti-diabetic activity. No mortality was seen even with the 20 times high dose feed of the leaf extracts. This further indicates high margin of safety. The leaf extracts appears to be inhibiting glucose-6-phosphate dehydrogenase, hepatic glucose output and controlling the elevated blood glucose levels. *Aegle marmelos* leaf is an insulin sensitizer which can be used in the treatment of diabetes. It improves the glycemic control by enhancing the insulin sensitivity in liver and muscle⁶⁸.

Comparative evaluation of hypoglycemic activity of some 30 hypoglycemic Indian medicinal plants from indigenous folk medicines (Ayurvedic, Unani and Siddha systems of medicines) including *Aegle marmelos* was studied in alloxan induced diabetic rats. In all the herbal samples (vacuum dried 95% ethanolic extracts), definite blood glucose lowering effect close to normal at a dose of 250mg/kg within 2 weeks had been confirmed in alloxan diabetic albino rats. *Aegle marmelos* was one among 24 samples causing significant hypoglycemic activity⁶⁴.

It can thus be concluded that the methanolic, alcoholic and aqueous extract of bael leaves have antidiabetic action. These extracts significantly decreased the serum glucose levels, improve the ability to utilize the external glucose load and increased the plasma insulin levels in artificially induced diabetic animal models. The Table 3 highlights summary of the studies conducted on animal models and their results.

Clinical trials using *Aegle marmelos* leaves on diabetic subjects- Human studies

Very few studies have been done to explore the therapeutic effect of *Aegle marmelos* leaf with respect to human subjects however antidiabetic activity of *Aegle marmelos* leaf decoction was evaluated. The study was performed in 4 groups having ten NIDDM patients (5gm powder) given for a period of one month daily orally. Pre and postprandial blood glucose level (PPBGL) was estimated. and it was found that antidiabetic effect was more markedly observed when it was combined with the oral hypoglycemic therapy⁶⁹.

In another study 120 NIDDM subjects in 4 groups were supplemented with 2gms of (bael leaf powder - group II, bael pulp and bael seed powder- group III and group I treated as control) for 3 months and then along with supplementation, nutritional counseling for the next 3 months. The results indicated significant reduction in FBS level There was a significant reduction in total cholesterol and triglycerides and increase in HDL⁷⁰.

In a study done T2D subjects were given sulfonylurea drug plus *A. marmelos* leaves (2 g/twice a day) or sulfonylurea plus placebo. After 8 weeks, the combined therapy had more effects on the level of fasting blood glucose (FBG), PPBG and urinary glucose⁷¹.

The Table 3 given below highlights the summary of the studies conducted on animal models and their results.

TABLE 3 SUMMARY OF EFFECT OF VARIOUS DOSAGES OF *AEGLE MARMELLOS* LEAVES ON ANTIHYPERGLYCEMIC ACTIVITY IN VARIOUS ANIMALS MODELS

Parts of Plant used	Investigators and the year	Dosage used	Result
Leaf extract	Ponnachan <i>et al.</i> , 1993 ⁵⁸	250mg/Kg body weight	Anti-hyperglycemic activity in alloxan diabetic rats along with decreased cholesterol and blood urea.
Leaf extract	Paulose <i>et al.</i> , 1993 ⁷²	250mg/Kg body weight	Leaf exhibited insulin like activity in diabetic rats.
Aqueous leaf extract	Das <i>et al.</i> , 1996 ⁵⁵	50mg/100gm body weight	Improved state of pancreatic cells in streptozotocin induced diabetic rats.
Aqueous leaf extract	Sharma <i>et al.</i> , 1996 ⁷³	250 and 500mg/kg orally	Produced hypoglycemic effect and increased plasma insulin level. LD ₅₀ observed greater than 10g/kg at oral administration to rats.
Leaf extract	Sachdeva <i>et al.</i> , 2001 ⁵²	250mg/kg orally	Anti-hyperglycemic activity caused in glucose fed hyperglycemic rats.
Aqueous leaf extract	Upadhya <i>et al.</i> , 2004 ⁴⁴	For one month	Decrease in blood glucose, increase in erythrocyte GSH and plasma GST levels and decrease in MDA compared to their controls. Hence leaves indicated hypoglycemic and antioxidant properties.
Aqueous leaf extract	Murlidharan L. 2014 ⁶⁸	10mg/100g for 30 days	Significantly decreased blood glucose levels (P<0.01)

Anti-toxicity Activity

Generally, *A. marmelos* is considered safe and few studies have been carried out with respect to its toxicity. A study was designed to elucidate the toxicity of the widely used plant *Aegle marmelos* in rats. Total alcoholic, total aqueous, whole aqueous and methanolic extracts of leaves of *A. marmelos* were used for the toxicity studies by determining acute, sub acute and LD50 values in experimental rats. Following the chronic intraperitoneal administration of 50mg/kg *A. marmelos* for 14 days, the vital organs such as heart, liver, kidney, testis, spleen and brain were carefully evaluated by histopathological studies. Pathologically, neither gross abnormalities nor histopathological changes were observed. After calculation of LD50 values using graphical methods, researchers found a broad therapeutic window and a high therapeutic index value for *A.marmelos* extracts⁷⁴.

CONCLUSION

Aegle marmelos, commonly known as bael, is a spiny tree belonging to the family Rutaceae. The medicinal properties of this plant have been described in the Ayurveda also. In fact, as per Charaka (1500 B.C) no drug has been longer or better known or appreciated by the inhabitants of India than the *Aegle marmelos*. *Aegle* leaf extract has been reported to regenerate damaged pancreatic β -cells in diabetic rats. It is found to be as effective as insulin in the restoration of blood glucose and body weight to normal levels.

The detailed information presented in this review on the phytochemicals, antioxidant, anti-diabetic and anti-toxic properties of the plant extract might provide detailed evidence for the use of this plant as a remedy for diabetes. Various therapeutic effects of leaves of *A. marmelos* have been reported by different workers but 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, and by reversing the histologic and ultra structural changes in the pancreas

and liver of rats with streptozotocin-induced diabetes⁷⁵. So there is the urgent need of correlating the therapeutic activity with the chemical marker of the plant as well as studying the mode of action of that marker compound. Skimmianine and Anhydroaegeline can be used as markers to standardize the plant material with respect to its potential anti diabetic activity.

The leaves contain many bioactive compounds which are known to provide health benefits and work as nutraceutical. In addition, it can be used as a food additive because of its typical flavor and nutrient contents. The obtained compounds have potent antimicrobial and antioxidant properties along with other therapeutic potential and may play an important role in drug development, food storage, health supplement and spa. In view of this scientific screening of various phytoconstituents of this plant may be useful in the alleviation of damages due to aging and may thus increase life expectancy. The development of *Aegle marmelos* as a nutraceutical suggests further preclinical and clinical studies to explore its utility and efficacy in treatment of chronic diseases.

An attempt has been made to review different in vitro models for estimating antioxidant properties of bio active compounds from *Aegle marmelos*. There are large number of studies showing in vitro antioxidant activity but in vivo studies are still lacking.

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CONFLICT OF INTEREST

None

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