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Ethno-medicinal and Pharmacological activities of *Aegle marmelos* (Linn.) Corr: A review

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Abstract
Aegle marmelos is native to India. The monotypic genus *Aegle* belongs to family Rutaceae has several neutraceutical and medicinal properties which are being used in traditional medicinal systems to cure a variety of diseases. The plant has been extensively studied for its medicinal and pharmacological properties by advanced scientific techniques and a variety of bioactive compounds have been isolated from different parts of the plant. This review is summarized information concerning the morphology, distribution, pharmacological and ethno-medicinal uses and phytochemistry of *A. marmelos*.

Keywords: *Aegle marmelos*, traditional medicine, pharmacological activities, phytochemistry

Introduction
Aegle marmelos, a plant of Indian origin having tremendous therapeutic potential, belongs to family Rutaceae [1]. The fruits of *A. marmelos* are used to cure fever, mental diseases, diarrhea, dysentery and diabetes. It has several pharmacological uses i.e. hypoglycaemic, antifungal, antibacterial, analgesic, anti-inflammatory, antipyretic, antidyslipidemic, immunomodulatory, anti-proliferative, wound-healing, antifertility and insecticidal activities [2]. Every part of plant such as fruit, seed, bark, leaves and root is used as an ingredient of several traditional formulations. Due to its curative properties, it is one of the most useful medicinal plants of India. The product obtained from bael, being highly therapeutic and is getting popularized in India and international market [3]. It is a subtropical plant which grows in the dry forest of hilly and plain area and found in Bihar, Chhattisgarh, Uttar Pradesh, Uttarakhand, Jharkhand and Madhya Pradesh [4]. Bael is a scared tree of Hindus as its leaves are offered to Lord Shiva for fulfillment of wishes. The tree is symbol of fertility [5].
In bilvapatra Sattva component is present due to which it emits and absorbs Sattivaik frequencies. So it reduces raja-tama particles form environment. A person suffering from distress, negative energy when brought in contact of bilvapatra the black energy present within him is reduced [1]. In Ayurvedic medicine the fruit is used to cure Vata (air) and Kapha (cough) in the body. Mainly half ripen fruits are used in preparation of medicine than the fully ripened fruits [6].

Classification
Kingdom - Plantae
Order - Spaindales
Family - Rutaceae
Subfamily - Aurantioidea
Genus - *Aegle*
Species - *marmelos*

Vernacular Name
Bael, Bel, Belgiri (in Hindi), Bilva, Shivdurma, Shivpala (in Sanskrit), Bengal Quince (in English), Belk, Belk ham (in Urdu), Bilvaphala (in Gujarati), Marredy (in Malayalam) and Vivla MarumVivama (in Tamil).

Botanical description
A. marmelos is a slow-growing, medium sized tree, up to 12 to 15m tall. The stem is short, thick, soft, flaking bark, and spreading, sometimes spiny branches, the lower ones drooping. Young suckers bear many stiff, straight spines. There are sharp, axial 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 fruits are round, pyri form oval, or oblong, 5-20 cm in diameter, may have a thin, hard, woody shell or a more or less soft rind, grey green until the fruit is fully ripe, when it turns yellowish. Seeds are numerous, oblong, compressed, testa mucous.

Occurrence and Habitat

A. marmelos commonly known as bael, Bengal quince and wood apple is native to India. *A. marmelos* adapt wide range of habitat and can be cultivated worldwide. It is subtropical plant and can grow up to altitude of 1200 m from sea level. It is found mainly in dry forest of hilly and plain areas. It is native to India and has origin form Eastern Ghats and central India [7]. Bael is found growing along the foothills of Himalayas, Uttar Pradesh, Chhattisgarh, Uttarakhand, Jharkhand, Madhya Pradesh and along East coast [8]. The bael tree is also found in many South East Asian countries including Pakistan, Sri Lanka, Nepal, Myanmar, Bangladesh, Vietnam, Cambodia Thailand, Malaysia, Java, Philippines and Fiji. The trees are of great importance to the environment as they act as climatic purifier that is they release greater percentage of oxygen in comparison to other trees. They also act as a sink for chemical pollutants as it absorbs toxic gases from the atmosphere and make them inert or neutral [9]. Beal possesses antiviral, antiheltinthic, anti-inflammatory, antibilious, antiparasitical, antipyretic, antiscorbatic, digestive, aphrodisiac, aromatic, astringent, febrifuge, hemostatic, antidiarrheal and nutritive properties.

Ethno-medicinal uses

The ethnic community played a vital role in preserving traditional knowledge of this plant which was used to cure several ailments. The ripe and unripe fruit has been used in traditional medicine to cure chronic diarrhea and dysentery. Fresh fruit pulp juice is prepared and taken twice in chronic dysentery [10]. The green fruit is sliced and dried in sun; the powder of dried fruit slices is taken in diarrhea and dysentery [11]. Ripe fruit sharbat prepared from pulp, milk and sugar is taken to relieve from constipation [12]. Fine powder of unripe fruit is taken with water to cure intestinal parasites like *Entamoeba histolytica* [13]. The trifoliate leaves (bilva-patra) of this tree are offered to Lord Shiva since prehistoric times. This signifies the importance of leaves and even today is being used to cure diabetes, abscess, eye diseases, backache etc. Ripe fruit juice is very useful in treating inflammation of rectum [14].

Bael leaves paste kept on infected part and tied with bandage to cure abscess [15]. Poultice made from leaves is used as remedy in opthalmia and eye diseases [16]. Bael tea prepared from leaves good for health and is used for flatulence, gastrointestinal problems, cough and chronic intestinal diseases in children [17].

Leaves are used in abscess and backache [18]. Decoction of leaves is used in eliminating fever and also helps in removal of mucous secretion from bronchial tubes [19]. Small amount of grinded leaves taken with one glass of water in morning for few days is used to control diabetes [20]. In order to control peptic ulcer the leaves are soaked overnight in water and this water is strained and drinks the morning for few weeks [21]. The juice of leaf is mixed in warm water with little pepper and taken as drink to get relief from sneezing cough and respiratory spasm [22]. Extract of leaves is applied on injuries caused by animal bite [18]. The decoction of leaves is useful in jaundice [23]. One table spoon juice extracted from bael leaves is taken daily on a regular basis is used by tribes of Jharkhand to cure diabetes [24]. Extract of bael root, pyaz and haldi are mixed in equal proportion and is put in ear to relive carache [25]. Dry powder of fruit mixed with mustard oil (1:2) is applied externally to treat burn cases [26]. An ethno-botanical survey of Gujjar community inhabiting Rajaji National Park, Uttarakhand was conducted by us which revealed that *A. marmelos* is being used for treating jaundice, diarrhea, fever, diabetes. Leaves juice taken in early morning having empty stomach is effective in diabetes while leaf juice taken with honey is helpful in prevention of fever. A teaspoon of dried and powdered bael leaves taken for three days help in increasing appetite. Bael leaves extract taken with honey for one week is used to cure jaundice. Jaundice can also be cured by consuming a teaspoon of crushed bael leaves added with a pinch of black pepper and then drink a cup of butter milk. The treatment is to be followed three times a day. Moreover, fruit juice is useful in the treatment of diarrhea and dysentery. Panda and Kala (2006) [27] gathered data on various medicinal formulations of bael used by traditional herbal healers and practitioners of the Ayurveda (Vaidyas) across Uttarakhand state. The roots of bael as an ingredient of dasamula (ten roots) are useful in recovering the loss of appetite. Bael root decoction is given twice daily to cure fever and cold. Root and bark decoction is used in the treatment of intermittent fever and heart palpitation. Rife bael fruit powder exhibits anti-cancerous and anti-proliferative activities. Unripe fruit pulp mixed with boiled rice water is taken twice a day to cure vomiting in pregnancy but when mixed with sugar and taken with milk twice daily cares urinogenital disorders.

Pharmacological Activities

Anti-inflammatory

Ghangale *et al.,* (2008) [28] studied aqueous extract of *A. marmelos* with the help of rat paw oedema model and assured that *A. marmelos* have anti-inflammatory activity [29]. The various extracts of the leaves of bael were evaluated for anti-inflammatory activity. The alcoholic extract of bael leaves antagonized the histamine–induced contractions and demonstrated positive relaxant effect in isolated guinea pig ileum and tracheal chain, suggesting inhibition of H1-receptor activity this extract may underlie these effects [30].

Antifertility activity

The antifertility effect of the aqueous extracts of leaves of *A. marmelos* was reported in male Albino rats. The rats were administered with aqueous extracts (250 mg/kg body weight) of leaves of *A. marmelos* for 45 days and treatment resulted in reduction in the weights of testis, epididymes and seminal vesicle. The extract also resulted in reduction of testicular sperm count, epididymal sperm count and motility and abnormal sperm count [31].

Antidiarrheal activity

Antidiarrheal activity is one of the major medicinal properties of *A. marmelos* and traditionally it is extensively used to control chronic diarrhea and dysentery. The *in vitro* antidiarrheal activity of dried fruit pulps of *A. marmelos* was reported. The ethanolic extract showed good activity against *Shigella boydii, S. sonnies* and *S. flexneri,* moderate against *S. dysenteriae* [32].

Antioxidant activity
A. marmelos is extensively reported to possess antioxidant activity against a variety of free radicals. Antioxidant activity and free radical scavenging activity of the ripe and unripe fruit of *A. marmelos* was compared. Results indicated that the enzymatic antioxidants increased in ripe fruit when compared to unripe fruit extract (except glutathione peroxidase). The percentage of free radical inhibition was also high in unripe fruit than that of the ripe fruit [33].The antioxidant activity of the fruit of *A. marmelos* was reported. The aqueous extract of *A. marmelos* fruit was showed antioxidant activity by the DPPH radical scavenging [34].

Hepatoprotective activity
The hepatoprotective activity of the leaves of *A. marmelos* was reported in alcohol induced liver injury in Albino rats. Rats were administered with 30% ethyl alcohol for a period of 40 days. The induced rats were fed with leaves of *A. marmelos* for 21 days. The TBARS values of healthy, alcohol intoxicated and herbal drug treated animals were 123.35, 235.68 and 141.85 g/g tissue respectively. This indicates the excellent hepatoprotective effect of the leaves of *A. marmelos* [35].

Antiulcer activity
A. marmelos is known to show gastro protective activity. Unripe bael fruit extract produced a noteworthy inhibition of absolute ethanol induced gastric mucosal damage in rats. This activity is due to the presence of luvangetinin the fruit. Gastric ulcer is usually mediated by progress of oxidative stress. Luvangetin might act by inhibition of oxidative stress producing compounds in the gastrointestinal tract thus preventing ulcer formation [36].

Anti-diabetic and antihyperlipidaemic activity
A. marmelos extract, when administered at a dose of 250 mg/kg of body weight, shows better result than glycenamide. This antidiabetic effect may be due to the coumarins present in the fruit which induce the beta cells of islet of Langerhans to produce insulin. Aqueous extract of bael seeds reduces blood glucose level in case of severe diabetic patients [36-37]

Anti-hyperlipidemic activity
Oral administration of aqueous extract of bael fruits and seeds separately at a dose of 250 mg/kg of body weight to diabetes induced rats has shown significant decrease in the blood lipid level. The effect may be due to fat mobilization from deposits which is caused due to hydrolysis of triglycerides. The extract also increases glucose utilization [36-38]. *A. marmelos* leaves extract showed significant effect on lipid peroxides, lipids, lipoproteins and antioxidant enzymes, concluding antihyperlipedic activity in rats with isoproterenol induced myocardial infarction.

Anticancer activity
A. marmelos extract has been found successful in inhibition of *in vitro* proliferation of human tumor cell lines including leukemic K562, T-lymphoid Jurat, beta-lymphoid Raji, erythro leukemic HEL [39].

Antimalarial activity
The alcoholic extracts of the bael seeds and leaves have been tested *in vivo* and *in vitro* for antimalarial activity against the NK65 strain of *Plasmodium berghei*. The seeds have shown schizontocidal activity in both the system, whereas, the leaves have shown activity only in the *in vitro* system [40].

Antibacterial activity
The antimicrobial activity of *A. marmelos* leaves crude extracts was checked by disc diffusion method against multi-resistant strains of *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Salmonella typhi, Proteus vulgaris, Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. The chloroform, methanol and ethanol extracts exhibited moderate antibacterial activity while aqueous extract exhibited least antibacterial activity. The antimicrobial activity against gram-negative strains was higher than that of gram positive strains [41]. Aqueous, petroleum ether and ethanol extract of *A. marmelos* leaves exhibited efficient antimicrobial activity against *Escherichia coli, Streptococcus pneumoniae, Salmonella typhi, Klebsiella pneumoniae* and *Proteus vulgaris* [42]. Sarkar and Solanki (2011) [43] isolated compound (AL1) from leaves extract which displayed antibacterial activity against *Staphylococcus aureus, Bacillus subtilis* and *E. coli*. Ariharan and Prasad (2014) [44] found aqueous extract of *A. marmelos* leaves showed antibacterial activity against *V. cholerae*, *S. typhi*, *S. aureus*, *P. aeruginosa* and *B. subtilis*. The essential oil obtained from the leaves exhibited activity against *Aeromonas* sp., *E. coli*, *Pseudomonas salanacearum* and *Xanthomonas vesicatoria* [45]. The ethanolic extract of the root has shown antibacterial activity against *Vibrio cholerae, Salmonella typhimurium*, *Klebsiella pneumoniae, E. coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis* and *Staphylococcus aureus* [46]. Victoria *et al.*, (2014) [47] reported that the ethanol extract of leaves, pulp and rind exhibited maximum antimicrobial activity against *E. coli, Bacillus subtilis,* and *Klebsiella pneumoniae*. Moreover, pharmacologically active compounds i.e. di-n-octylphalate and 1,2-benzenedicarboxilic acid isolated from ethanol extract proved to possess antimicrobial activity. The ethyl acetate extract of the plant has exhibited activity against *Vibrio cholerae*, *S. typhi*, *S. aureus*, *Pseudomonas putida* and *Bacillus anthracis* [48].

Antifungal activity
The essential oil isolated from leaves exhibited 100% inhibition of fungal spore germination rapidly at 500 ppm against *Alternaria alternata*, *A. brassicae*, *A. carthami*, *Collectotrichum capsici, Curvularia lunata, Fusarium oxysporum* f.sp. *cicer, F. odum* and *Ustilago cynodontis*. The fungicidal action at lower concentrations showed slow and steady rate of inhibition [2]. Antifungal constituents, 2-isopropenyl-4-methyl-oxa-cyclopenta(b) anthracene-5, 10-dione and (+)-4-(2-hydroxy-3methylbut-3-enyloxy)-8H-(1,3) dioxolo (4,5-H) chromen-8-one, imperatorin, β-sitosterol, plumbagin, 1-methyl-2-(3-methyl-but-2-enyloxy)- anthraqu inone, β-sitoterolglucoside, stigmasterol, vanillin and salicin, isolated from seeds of *A.marmelos* exhibited significant antifungal activity against pathogenic strains of *Aspergillus* sp. and *Candida albicans* [49]. Antifungal activity of *A. marmelos* leaf extracts were carried out on dermatophytic fungi like *Trichophyton mentagrophytes, Trichophyton rubrum, Microsporum canis, Microsporum gypseum* and *Epidermophyton floccosum* using minimum inhibitory concentration and minimum fungicidal concentration. Leaf extracts significantly inhibited the growth of all dermatophytic fungi [50].

Antiviral activity
A. marmelos has antiviral activities in the early stages of viral replication with minimum host cytotoxicity in contrast to modern virucidal chemotherapeutic agents (that is ribavirin), which usually act in the later stages of viral replication and have potent side effect [51]. The 50% ethanolic extract of the fruits has shown antiviral activity against ranikhet disease virus [52].

Cytoprotective activity
The cytoprotective effect of the leaves of *A. marmelos* was reported in *Cyprinus carpio* (fresh water fish) exposed to heavy metals. *C. carpio* was exposed to heavy metals followed by the treatment with the dried powder of *A. marmelos* leaves. Treatment resulted in cytoprotective effect by stabilization of plasma membrane and modulation of antioxidant enzyme system [53].

Anti-thyroid activity
Panda and Kar (2006) [27] isolated scopoletin (7-hydroxy-6-methoxy coumarin) from *A. marmelos* leaves and evaluate for its potential to regulate hyperthyroidism. It was observed that scopoletin (at 1.00 mg / kg, p.o. for 7 days) to levo-thyroxine treated animals, decreased serum thyroid hormones level. It was also proved that the scopoletin have superior therapeutic activity than the standard antithyroid drug, propylthiouracil.

Phytochemistry
Various chemical constituents like alkaloids, coumarins, polysaccharides, steroids, terpenoids etc have been identified from fruits, leaves, wood, root and bark of the tree. *A.marmelos* leaves contained aegeline, rutin, lupeol, flavone, marmesinine, β-sitosterol, glycoside, oisopentenylhalforidol and phenylethylcinnamamides [54].

Alkaloids
The alkaloids are secondary plant substances. The main four alkaloids of *Aeglemarmelos*leaves are N-2- [4-(3', 3'-dimethylallyloxy) phenyl] ethylcinnamide, N-2-hydroxy-2-(4-hydroxyphenyl) ethylcinnamide, Marceline and Angeline [55]. Shahidine, an alkaloid having oxazoline core has been isolated as a major constituent from the fresh leaves of *A. marmelos* and it showed activity against a few Gram-positive bacteria [56].

Terpenoids
The essential oil of *A. marmelos* leaves was studied very much extensively in India, α-phellandrene and p-cymene were extracted from its leaves oil [57]. Limonene was reported as an important constituent from *A. marmelos* leaves and it was shown that limonene as marker for identification of bael soil samples [58].

Phenylpropenoids
Hydroxylcoumarins, phenylpropenes, lignans [59].

Tannins
The maximum tannin content in bael fruit was recorded in the month of January. There is as much as 9% in the pulp of wild fruit, less in cultivated type. Tannin is also present in leaves as skimmianine.

Coumarins
The coumarins present in bael fruit includes marmelosin, marmesin, imperatorin, marmin, alloimperatorin, methyl ether, xanthotoxol, scoparone, scopoletin, umbeliferone, marmelide and marmenol [60]. Marmelosin, marmesin, imperatorin, marmin, alloimperatorin, methyl ether, xanthotoxol, scoporone, scopoletin, umbelliferone, psoralen and marmelide [10]. Marmelon, a 7- geranyloxycoumarin [7-(2,6-dihydroxy-7- methoxy-7-methyl-3-octaenyloxy) coumari n] has also been reported [61].

Conclusion
A. marmelos is one of the important plants with several medicinal and nutraceutical properties. It is very often known as wood apple plant. It has several medicinal properties which are used in traditional medicinal system and used to cure several diseases. In last few decades *A. marmelos* is extensively studied for its medicinal properties by advanced scientific techniques and a variety of bioactive compounds have been isolated from the different part of plant and were analyzed pharmacologically. The medicinal properties of *A. marmelos* represent it as a valuable source of medicinal compound. This review summarized its various ethno-botanical and pharmacological activities i.e. antibacterial, antifungal, antiviral, antidiabetic, antimalarial, antioxidant etc.

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