A brief review on potential therapeutic benefits of Aegle marmelos

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Abstract- Aegle marmelos is useful for a variety of medicinal purposes because it contains a number of phytoconstituents. From the leaves, aegelin, rutacine, y-sitosterol, agelemine, and aegeline were found. Coumarins like umbelliferone, scoparone, scopoletin, marmesin, and skimmin are found in roots and fruits. Furthermore, fruits contain alkaloids such as aegeline and marmeline as well as xanthotoxol, imperatorin, and alloimperatorin. Considering the vast opportunities and potential of Aegle marmelos for a variety of uses, this will support the financial empowerment of impoverished and landless farmers in addition to serving as a foundation for research and development. A number of illnesses in humans, including diabetes, liver toxicity, fungal infections, microbial infections, inflammation, pyrexia, and pain relief, can be treated with the plant or any of its individual parts. Even so, a great deal of work needs to be done to examine the Aegle marmelos’ mechanism of action in relation to other therapeutic activities. The current review seeks to complete the medicinal values of Aegle marmelos that were discovered during the research project by utilizing cutting-edge scientific methods and instruments. The present review aims to complete medicinal values of Aegle marmelos generated through the research activity using modern scientific approaches and innovative scientific tools. The review would also like to point out that the fruits and leaves offered in temples can undoubtedly be reused for better development and healthcare. Planning and possibilities are required to be identified for reuse the leaves and fruits by integrating various technology and ecosystem conservation strategies.

Keywords: Aegle marmelos, aegeline, rutacine, coumarins.

Introduction:
Aegle marmelos, commonly known as Bilva or Aegle marmelos tree (in Hindi), Bilipatra (in Gujarati), and Golden apple (in English); is a sacred Indigenous tree; that grows wild throughout India in any climate. Bilva is one of the holy trees of Hindus. Aegle marmelos is one of the most appreciated plants used in ayurvedic medicine by Indian and South Asian inhabitants in ancient history.[1-2] According to historical records, Aegle marmelos has been used as a medicinal and food item since 5000 B.C. The tree is aromatic, and all parts are medicinally important. Fruit, leaves, bark, roots, flowers, and seeds are used in Ayurvedic folklore systems to treat various ailments.[1] It is also traced in Agada Tantra (the branch of toxicology in Ayurveda) in the context of the treatment of toxic conditions. From the leaves, aegelin, rutacine, y-sitosterol, agelemine, and aegeline were found. Coumarins like umbelliferone, scoparone, scopoletin, marmesin, and skimmin are found in roots and fruits. Furthermore, fruits contain alkaloids such as aegeline and marmeline as well as xanthotoxol, imperatorin, and alloimperatorin. In recent studies; the hepatoprotective, nephroprotective, anti-inflammatory, antimicrobial, antifungal, antioxidant and anti-toxic activity of Bilva has been proven and holds an important role in toxic conditions.[2] In the present time, we all know that herbal or natural products are more used than allopathic medicine and, it’s all because of the awareness among people regarding natural medicines, and natural products. Lord Shiva is offered the leaves of A. marmelos because without these leaves, his worship is incomplete. Shivadurme, the Shiva tree, is another name for it. Our ancient literature like Rgveda, Yajurveda, Charak Samhita, and Sushrut Samhita describes a range of plants used to heal various health problems and diseases. Only 350 species of the 6000 plants specified in the ancient medical system used, the majority of which herbs, Aegle marmelos(L.) Corr is very important in everyday life is mentioned in Figure 1 and Table 1.[3-4]
### Table 2. Chemical Constituents of Aegle marmelos

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Parts</th>
<th>Chemical Constituents</th>
<th>Therapeutics</th>
</tr>
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<tbody>
<tr>
<td>2.</td>
<td>Fruit</td>
<td>Marmelosin, luvangetin, Aurapten, Psoralen, Marmelide, marmin, umbelliferone, umbelliferone, skimmianine, scoporone, scopoletin, psoralen, xanthotoxol, alpha phellandrene, p-cymene, impertinol, alloimperatorin, alpha-sitosterol, tannins, fragrine, marmin, alkaloids such as aegeline, riboflavin, ascorbic acid, glycoprotein, polyphenols, flavonoids, phenolic compound, terpenoids, coumarins, polysaccharides, lupeol, carotenoids, caffeic acid, arbutin, chlorogenic acid, p-coumaric acid, p-coumaroyl, quinic acid, protocatechuic acid, saponins, sitosterol, rutin, halfordinol, phenyl ethyl cinnamamide, catechin, flavonols, flavones, lignin, oxalic acid, tartaric acid, malic acid, amino acids like phenyl alanine, tyrosine, leucine, methionine, aspartic acid, iso-leucine, arginine, alanine, feric acid, quinoline, rutaretin, gallic acid, vanillic acid, syringic acid, Gentisic acid</td>
<td>Anti-genotoxic activity, anti-spermatogenic, Anti-inflammatory, cardio-protective, anti-ulcer, anti-spasmodic, anti-diarrheal, heartbeat inhibitor, anti-cancer, anti-viral, anti-tumour activity, antioxidant, anti-dandruff activity, anti-angiallergic, anti-constipating, antiarthritic activity, anti-viral activity</td>
</tr>
<tr>
<td>3.</td>
<td>Seed</td>
<td>Palmitic acid, stearic acid, linoleic acid, linolenic acid, pyranocoumarins</td>
<td>Anti-ulcer, antimicrobial</td>
</tr>
<tr>
<td>4.</td>
<td>Bark</td>
<td>Marmin, fagarine, marmesin, umbelliferin, skimmianine, coumarin</td>
<td>Anti-inflammatory activity, anti-diabetic, antioxidant, antialgesic, anti-diarrheal, abortifacient, anti-ulcer, anti-cancer</td>
</tr>
<tr>
<td>5.</td>
<td>Root</td>
<td>Marmin, marmesin, umbelliferin, skimmianine, coumarin, psoralen, embamide</td>
<td>Anti-inflammatory activity, Antibacterial activity, anti-histaminic activity</td>
</tr>
</tbody>
</table>

**Pharmacological properties of Aegle marmelos:**

**Anti-diabetic activity:** Many studies on bilva showed that it possesses anti-diabetic property. The anti-diabetic activity of leaves of bilva was reported in alloxan diabetic rat. Chemical constituents like Umbelliferone β-D-galactopyranoside, Lupeol has hypoglycemic effect mentioned in figure 2. 3,3-dimethylallyl halfordinol, Anhydromarmeline aegelinosides A& B found in Aegle marmelos leaf extract shows glucosidase inhibitory effect. Aqueous and alcoholic extract of Aegle marmelos fruit shows...
hyperglycemia effect on rabbit at a dose of 500 mg/kg of body weight.\[^{9-13}\]

**Figure 2: Mechanism of anti-diabetic effect of Aegle marmelos**

**Anti-microbial activity:** Bilva has been traditionally used for the treatment of various infectious diseases like, bacteria, fungi and viruses.\[^{9-13}\] Marmelide extracted from *Aegle marmelos* have shown antimicrobial activity mentioned in figure-3 when experimented with coxsackieviruses B1–B6, in an assay described by plaque inhibition assay at 96 h. The extract is proved to have antiviral activity without doing any toxic effect to host cell. Chloroform extract of Aegle marmelos root shows anti-microbial effect against different bacteria causing disease like Vibrio cholera. *Aegle marmelos* seed extract 1- methyl-2-(3'-methyl-but-2'-enyloxy)-anthraquinone shows anti-microbial activity against aspergillus species & candida albicans. Extract of *Aegle marmelos* leaves and seeds shows antimicrobial activity against NK65 strain of Plasmodium berghei. Antimicrobial activity shows by α-phellandrene and α-pinene extract of Aegle marmelos. Antimicrobial activity shows against Salmonella typhi. Furocoumarin extract of *Aegle marmelos* can inhibit zinc superoxide dismutase.\[^{9-13}\]

**Figure 3: Mechanism of antimicrobial activity of Aegle marmelos**

**Anti-diarrheal activity:** Bilva exhibited anti-diarrheal activity mentioned in figure 4 and it is extensively used to control chronic diarrhea and dysentery.\[^{9-13}\] Chronic diarrhea can be treated with the use of *Aegle marmelos* fruit especially half-ripe or unripe fruit.\[^{9-13}\] Ethanolic extract of fruit inhibits bacteria that cause diarrhea like, *E.Coli, Vibrio cholera* and *Shigella* sp. After consumption of fruit powder gradually mucous disappears from stool and stool becomes solid & blood. Unripe fruit extract is appeared to be effective in inflammatory bowel disease (IBD) in albino rats. Interleukin (IL1, IL6, and IL8), tumor necrosis factor (TNF)-α these inflammatory mediators are inhibited as a result of which the effect of unripe fruit extract is seen.\[^{9-13}\]
Anti-hyperlipidemic activity: Aegle marmelos extract is able to reduce the lipid level shown in figure-5. Umbelliferon, saponins and coumarin reduce the cholesterol level. Aegle marmelos fruit powder reduced free cholesterol level and ester cholesterol level.[9-14] According to the results of Sinha et al.’s study [15], ethanolic extracts of Aegle marmelos leaves can successfully lower blood triglyceride and cholesterol levels in dyslipidemic patients.

Anti-cancer activity: Bilva fruit extract is used to improve the immune system.[3,12] Because of carotenoids, polyphenols which is present in Aegle marmelos may have the ability to reduce cell mutation thus DNA damage is reduced mentioned in figure-6. Lupeol is one of the chemical constituent of Aegle marmelos effect on the sequence of RA4DNA which able to decrease the multiplication of cancer cells. Lupeol decrease the expression of cyclin D2 & D1, eDk2 thus G1-S phase cell cycle is arrested. D-limonene, eugenol, citral which obtained from Aegle marmelos extract shows anti-neoplastic effect. Marmelin (1-hydroxy-5,7-dimethoxy-2-naphthalene-carboxaldehyde) prevent the growth of epithelial cancer cell.[13] Xanthorrhizol and marmelosin isolated from Aegle marmelos is recommended to immune-compromised patient instead of chemotherapy. For skin cancer activity, Aegle marmelos peptic polysaccharide has been tested. Aegle marmelos barks extract shows antioxidant & chemo-preventive actions on Swiss albino mice. Furanocoumarin of ethanolic Aegle marmelos extract is able to fight with leukemia THP-1 cancer cells. Vijaya et al in their study identified that 50% alcoholic extract of A. marmelos exhibits strong anti-proliferative and antioxidant activities in DLA tumor-transplanted mice.[9-16]
Cardio-protective effect: Aegle marmelos leaf extract has preventing effects in isoprenaline induced myocardial infarction in albino wistar rats and it increases the levels of creatine kinase and lactase dehydrogenase enzyme and also decrease the heart of isoprenaline treated rats\(^3,14\). Methanolic Aegle marmelos root bark extract at a dosage level of 100 μg/mL can reduce up to 50% of the heartbeat rate. Aegle marmelos fruit shows protective activity against cardiovascular diseases. The enhancement of various enzymes like creatine kinase-muscle/brain (CK-MB), lactate dehydrogenase (LDH) isoenzyme, creatine kinase, LDH may be retarded by the marmesin in Serum LDH and CK levels are decreased on the other hand when leaf extract of Aegle marmelos with a dosage of 200 mg/kg is applied to isoprenaline induced myocardial rats the level is enhanced. The phytochemicals of like terpenoids, tannins and flavonoids have the ability to protect the heart from isoproterenol promoted myocardial infarction mentioned in figure-7.\(^9\)\(^{17}\)

Hepatoprotective activity: Eugenol extracted from Aegle marmelos leaf has been found to exhibit hepatoprotective activity.\(^9\) Presence of rutin and other phenolic compounds taking into account all of these findings, it is conceivable to propose that A. marmelos’ hepatoprotective activity was somewhat associated with the phenolic compounds’ synergistic effect.\(^18\)

Anti-ulcer activity: Aegle marmelos fruit and Aegle marmelos seed exhibited anti ulcer activity evaluated by using various ulcer models. Aegle marmelos seed extract- Luvangetin, a pyranocoumarin shows protective activity against aspirin-induced and pylorus-ligated gastric ulcers experimented on rats. Fruit pulp extract decreases the mucosal thickness, catalase activity, superoxide dismutase and also in glutathione level.\(^9,19\)
Anti-inflammatory activity: The Aegle marmelos extracts like lupeol, citral & skimmianine shows anti-inflammatory activity shown in figure-9. [15] The Aegle marmelos extract, β caryophyllene and caryophyllene have shown an anti-inflammatory effect against lymphoma as well as neuroblastoma cells. The dried flower extract of Aegle marmelos (with optimum dosage is noted to be 200 mg/kg) shows anti-inflammatory action, when experimented on Wistar rats. Aegle marmelos fruit extract shows anti-inflammatory action, mast cell stabilization and anti-oxidant along with superoxide dismutase increase and it decreases the level of malondialdehyde which gives protection for degranulation in mast cells. The extract of bark of the Aegle marmelos gives a strong anti-inflammatory action when tested with carrageenan-induced paw oedema. The young roots of the Aegle marmelos tree show the potent anti-inflammatory action in cyclooxygenase (COX-2) inhibition, restricts pro-inflammatory cytokine. The Aegle marmelos leaf extract shows the anti-inflammatory effect (at a dose of 100 μg/ml). The Aegle marmelos fruit extract, Marmelosin possesses an anti-inflammatory effect with a reduction of nitric oxide (NO) as well as TNF-α which is a pro-inflammatory cytokine. Methanolic extract of Aegle marmelos shows analgesic activity centrally as well as peripherally. [9, 15, 19, 20]

Anti-spermatogenic activity: Aegle marmelos leaf shows anti-spermatogenic activity, it decrease the motility of sperm in rats. [14] The Aegle marmelos leaf extract shows a huge reduction in sperm count in rats. Aegle marmelos leaf extract, marmin and fragrance lowering of testicular steroidogenic enzymes in rats. Aegle marmelos bark extract shows anti spermatogenic activity with dosage 200 mg/kg and 400 mg/kg body weight which is effective from 60th day and 600 mg/kg effective from the 40th day. Changes in sperm functioning lead to infertility. The ethanolic bark extract of Aegle marmelos completely inhibit sperm motility. Aegle marmelos extract, coumarin spermicidal activity by inhibiting the calcium channel. [9] By interfering with testicular androgen levels and changing their shape, function, viability, and the concentration of spermatozoa in the cauda epididymis, Aegle marmelos can cause a reversible sterile condition in male rats. After withdrawal, the resulting effects were reversible for 120 days. This implies that the extract from Aegle marmelos may be a reversible method of male contraception mentioned in figure-10. [21]
Radio protective effect: *Aegle marmelos* leaf and fruit extract prevents the radiation induced lipid peroxidation in mice intestine, liver, kidney and spleen. To show the radio protective activity, the hydroalcoholic extract of the *Aegle marmelos* fruit is given to mice that are in exposure to gamma radiation. The extract in concentrations of 5 to 40 mg/kg is administered intraperitoneally for 5 consecutive days & after that, they are exposed to 10 Gy 60 Cobalt (Co) gamma-radiations. Most of the survivors are found on the day 10 or 30. At a concentration of 20 mg/kg, the optimum effect has been found. It has been found that *Aegle marmelos* extract possesses a radio protective effect, after 30 days of treatment. It is believed that the radio protective action of *Aegle marmelos* is a result of the lowering lipid peroxidation. *Aegle marmelos* leaf extract show a better result than fruit extract. *Aegle marmelos* leaves and *Aegle marmelos* fruit have potential free radical scavenging activity mentioned in figure-11. *Aegle marmelos* leaf extract is able in increasing the splenic lymphocyte count, thereby proving the immunomodulatory action of *Aegle marmelos*.

Wound healing activity: *Aegle marmelos* seed, *Aegle marmelos* Pulp ointment have exhibited potential wound healing activity mentioned in figure-12. *Aegle marmelos* phytoconstituents, flavonoids, alkaloids, essential oils & sterols are the reason behind the wound healing activity of *Aegle marmelos* and cause an increased rate of epithelization, wound contraction, tensile strength, and hydroxyproline content. *Aegle marmelos* was administered on topical & intraperitoneal was studied under two wound models, incision and excision in rats and it shows the same response in both models. In the excision model founds epithelialization faster and also the rate of wound contraction was higher when compared to controls wound.
Immunomodulatory effect: In animal experimental models of immunity, Aegle marmelos boosts the immune system via humoral and cellular immunity. However, Phataru et al (2010) discovered that the low dose was more effective than the high dose. [24]

Anti-anemic activity: The Aegle marmelos leaf of extract has an anti-anemic effect as they contain high iron concentration and phenolic compounds which possess antioxidant activity. It also contains a variety of vitamins and minerals, such as calcium, phosphorus, riboflavin, thiamine, vitamin C, and niacin. [9, 25]

Anti-thyroid activity: The Aegle marmelos leaf extract, Scopeletin (7-hydroxy-6-methoxy coumarin) decreased thyroid hormone level. Scopeletin (1 mg/kg for 7 days) is administered to thyroxine treated animals; it reduced thyroid hormones level in serum. Propylthiouracil (antithyroid drug) has the same activity as Aegle marmelos extract. [27]

Anti-convulsant activity: The aqueous leaves extract of Aegle marmelos shows anti-convulsant activity against Pentylene tetrazole induced seizures in mice. Ethanolic Aegle marmelos extract delayed maximal electroshock seizure (MES) and PTZ induced convulsion, thus Gabanergic mechanism giving the anticonvulsant effect. Flavonoids are found to be responsible for it which presents in Aegle marmelos. [27]

There are possibility of utilizing and incorporating leaves and fruits of Aegle marmelos in formulation of Polyherbal for optimizing better therapeutic outcomes. To proceed for further research basic information about safety reports on acute oral and sub chronic studies are always critical.

Toxicological studies: A study on different extracts of Aegle marmelos leaves in rats for their toxicity reported no histopathological changes & extract have a high margin of drug safety. [28] Consumption of Aegle marmelos have reported no such toxicity effects and are found to be safe. The Aegle marmelos extract has been administered to animal (dosage of 250 mg/kg bodyweight) for 30 days but no toxic effects has not been found. The Aegle marmelos extract administered intraperitoneally with50 mg/kg body weight has not shown any histopathological changes of liver, kidney, heart, testis, and brain. [9-17]

Anthemlinitmic activity: Aegle marmelos leaf and fruit extracts, both ethanolic and aqueous, exhibit strong anthelmintic action against tested worms, though not to the same extent as standards. But the ethanolic and aqueous extract phytochemical analysis reveals the presence of flavonoids, which may be in charge of the anthelmintic action. [28]

Nephro-protective activity: Aegle marmelos leaf extract shows nephroprotective activity by reducing the increase serum creatinine, blood urea nitrogen level. The nephroprotective activity of Aegle marmelos leaf also takes some time to get to the point where they can afford to be protected against damage to the renal tissue. [29]

Insecticidal activity: Aegle marmelos leaf extracts have the potential to be a perfect environmentally friendly method of controlling Anopheles subpictus. A study conducted in 2009 by Elango G et al. examined the oviposition, ovicidal, and repellent properties of Aegle marmelos leaf extracts against Anopheles subpictus, the malaria vector. [30] Fortunately the plant Aegle marmelos’s leaf extracts were found to function against the larvae of Anopheles stephensi, Culex quinquefasciatus, and Aedes aegypti in a study conducted by Kaliyamoorthy Dass et al. (2014). [31]

Ant-malarial activity: Aegle marmelos leaf and immature bark extract of shows anti-malarial activity against Plasmodium falciparum(IC50–48.2μg/mL). Aegle marmelos root barks decoction may be used for treating malaria. Aegle marmelos root extracts shows anti-malarial activity against Plasmodium falciparum. [29]

Anti-arthritis activity: Aegle marmelos extracts shows anti arthritic activity. In arthritic rats, steroids, saponins, and alkaloids of Aegle marmelos extracts can retard articular swelling lowering arthritic index. It inhibits cyclooxygenase enzymes which in turn retard prostaglandin synthesis which is a reason for arthritis. In anti-arthritis activity flavonoids and triterpenoids are considered main reason for anti-arthritis activity study. [32]

Anti-asthmatic activity: The Aegle marmelos leaf decoction shows anti-asthmatic activity because it is effective in reducing phlegm in cold and asthma. The Aegle marmelos leaf extract aegeline helps to prohibit the release of histamine from mast cells. Another study proves that the Aegle marmelos root extract skimmianine release histamine from rat mast cell. [29]
Aegle marmelos is most frequently used in Indian Lord Shiva Temple. This leaf has many symbolic meanings. For example, the tripatra, or trifoliate, leaves are thought to symbolize the three trinities of creation, preservation, and destruction. Other symbolic meanings include the three guns, or qualities of sattva, rajas, and tamas, or the three syllables that make up AUM, the primordial sound that embodies Shiva. The trishul, which is Mahadeva's symbolic weapon, is thought to represent his three eyes, represented by the three leaves. Now a day’s many startups have grown to utilized flowers from river Ganga and preparing Fragrance materials or formulations. Similar way till date no such initiatives are taken to consider the topmost medicinal plants with high symbolic meaning society. There are more than 10000 temples of Lord Shiva in India. If the leaves after worshiped utilized for making fresh juice, pesticides/insecticides or at least a provision should be designed to recycle or utilized the Aegle marmelos leaves by Temple authorities for its valuable phytochemicals. Our Government or nonprofit able organization should also think over it to utilize the Aegle marmelos leaves if it is possible to do so. The concern over making and preparing this review on Aegle marmelos is to highlight possible opportunities are still open to work on this plant. Many research conducted on leaf, fruit and seed of the plant but no research work strongly recommend the use of it and generated importance of utilizing as leaves and fruits that form sacred offerings at temples and shrine. It increases the spiritual worth of our products while also preventing polluting water bodies from being near the temples. Both the general public and enthusiasts would purchase the manufactured goods. The authors of this review already have had startup on such initiative.

**Conclusion:** The pharmacological activities mentioned above demonstrate that Aegle marmelos (bilva), one of the auspicious plants, possesses valuable and therapeutic characteristics. To treat a wide range of illnesses, it has been widely utilized in folk medicine. Many diseases can be treated with the various parts of this plant, including the leaves, fruits, roots, bark, and seeds. Owing to the numerous phytochemicals it contains, this plant has a wide range of therapeutic benefits, including the ability to treat diabetes, diarrhoea, infections, cancer, heart disease, hypolipidemia, ulcers, inflammation, hepatoprotection, radioprotection, anti-spermaticogenic effects, wound healing, immunomodulatory effects, insecticidal effects, and anthelmintic activity. Numerous preclinical studies on Aegle marmelos have demonstrated its efficacy for a range of clinical symptoms and diseases. This review mainly focused on several phytochemical and reported pharmacological studies of A. marmelos. It concluded that despite of potential therapeutic benefit and religious values possible opportunities are still open to work on this plant.

**Conflict of Interest:** Authors affirm no conflict of interest.

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