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AEGLE MARMELOS: A COMPREHENSIVE REVIEW OF ITS ETHNOPHARMACOLOGY, PHYTOCHEMISTRY, THERAPEUTIC APPLICATIONS, AND NETWORK-PHARMACOLOGY INSIGHTS

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ABSTRACT:
Aegle marmelos, commonly known as bael, is a culturally significant medicinal plant extensively used in Ayurveda and traditional medicine systems of South and Southeast Asia. Its leaves, fruits, roots, and bark possess therapeutic value for gastrointestinal, metabolic, inflammatory, microbial, and neurological disorders. The plant contains a rich array of phytochemicals, including coumarins, alkaloids, flavonoids, terpenoids, and phenolic compounds, which underpin its pharmacological activities. Recent approaches such as network pharmacology and molecular docking have revealed multi-target mechanisms involving key signaling pathways such as PI3K/AKT, MAPK, and inflammatory cytokine networks. This review consolidates classical and modern knowledge on A. marmelos, highlighting its historical background, chemical constituents, pharmacological relevance, and new in-silico insights.

KEYWORDS: Aegle marmelos, bael, phytochemistry, pharmacology, network pharmacology, molecular docking, ethnomedicine.

INTRODUCTION

Aegle marmelos (L.) Corrêa, known as bael or Bilva, is a medium-sized aromatic tree of the family Rutaceae and is native to India and Southeast Asia. It is widely used in Ayurveda, Siddha, and Unani systems for ailments such as gastrointestinal disturbances, diabetes, inflammation, infections, and respiratory conditions [1–3]. The plant holds both medicinal and cultural significance, particularly within Hindu traditions.

Scientific interest in A. marmelos has intensified due to its broad phytochemical spectrum and multi-target therapeutic mechanisms. Recent studies employing network pharmacology, molecular docking, and bioinformatics have helped clarify its role in complex, multifactorial diseases such as inflammatory bowel disease, metabolic disorders, and neurodegeneration [4,5].

2. Historical and Traditional Uses

References to A. marmelos appear in Ayurvedic classics including the Charaka Samhita and Sushruta Samhita, where Bilva is described as digestive, anti-inflammatory, and restorative. Traditionally, it is used for:

- Diarrhoea and dysentery: unripe fruit pulp as an astringent [6]
- Constipation: ripe fruit as a mild laxative
- Fever and inflammation: leaf and bark decoctions
- Diabetes: leaf extracts used in formulations such as Bilvadi Lehya
- Respiratory disorders: expectorant effects of leaf preparations

Its sacred significance has contributed to its widespread cultivation, aiding its continued use in traditional medicine.

3. Phytochemistry

A. marmelos contains diverse secondary metabolites responsible for its therapeutic effects.

3.1 Alkaloids

Aegeline, skimmianine, halfordin, and other alkaloids contribute to anti-inflammatory, antidiabetic, antimicrobial, and cardioprotective properties [7].

3.2 Coumarins and Furocoumarins

Compounds including imperatorin, psoralen, bergapten, marmelosin, marmesin, and scopoletin exhibit antioxidant, anti-inflammatory, antiviral, and anticancer effects [8,9].

3.3 Flavonoids and Phenolic Compounds
Quercetin, rutin, gallic acid, ellagic acid, and protocatechuic acid display strong free radical scavenging and neuroprotective effects [10].

3.4 Terpenoids and Essential Oils
Limonene, citral, cineole, and β-caryophyllene contribute to antimicrobial, gastroprotective, and anti-inflammatory activities [11].

3.5 Other Constituents
Tannins, steroids, pectins, sugars, and fatty acids enhance the plant's therapeutic potential and nutraceutical applications [12].

Table 1. Major Phytochemicals Identified in Aegle marmelos and Their Reported Biological Activities

Chemical Class	Phytochemicals	Plant Part	Reported Biological Activities	References
Alkaloids	Aegeline, Skimmianine, Halfordin, O-methylhalfordin	Leaves, bark	Antidiabetic, anti-inflammatory, cardioprotective, antimicrobial	[7,13,17]
Coumarins	Marmelosin, Marmesin, Imperatorin, Scopoletin, Psoralen, Bergapten, Xanthotoxin	Fruit pulp, seeds, roots	Antioxidant, anti-inflammatory, anticancer, antiviral, photochemotherapeutic	[8,9,20]
Furocoumarins	Bergapten, Imperatorin, Isopimpinellin	Fruit, bark	Cytotoxicity, anti-inflammatory, anti-microbial	[8,9]
Flavonoids	Rutin, Quercetin, Isorhamnetin, Kaempferol	Leaves, fruit	Antioxidant, neuroprotective, cardioprotective, anti-diabetic	[10,15]
Phenolic Acids	Gallic acid, Ellagic acid, Ferulic acid, Protocatechuic acid	Leaves, fruit, bark	Antioxidant, anti-inflammatory, hepatoprotective	[10,15]
Tannins	Tannic acid, Phlobatannins	Unripe fruit	Anti-diarrheal, astringent	[6,16]
Terpenoids	Limonene, Cineole, Citral, β-caryophyllene, α-pinene	Leaves, essential oil	Antimicrobial, gastroprotective, anti-inflammatory	[11]
Sterols/Phytosterols	β-sitosterol, Stigmasterol	Leaves, bark	Anti-inflammatory, lipid-lowering	[12]
Fatty Acids	Palmitic acid, Linoleic acid	Seeds, fruit	Antioxidant, nutraceutical value	[12]
Polysaccharides & Pectins	Pectic compounds	Ripe fruit	Laxative, gut-protective	[6,12]
Other Constituents	Saponins, Glycosides, Resin	Leaves, roots	Antimicrobial, immunomodulatory	[13,17]

4. Pharmacological Activities
4.1 Antidiabetic Activity
Leaf extracts reduce blood glucose by inhibiting α-amylase and α-glucosidase, improving insulin sensitivity and reducing oxidative stress markers in diabetic models [13].

4.2 Anti-inflammatory and Immunomodulatory Effects
Extracts downregulate TNF-α, IL-6, IL-1β, and COX-2, suppress NF-κB activation, and reduce oxidative inflammatory markers [14].

4.3 Antioxidant Activity
A. marmelos demonstrates potent DPPH, ABTS, and FRAP activity, attributed to its phenolic and flavonoid content [10,15].

4.4 Gastroprotective and Anti-diarrheal Effects
Unripe fruit reduces intestinal motility and enhances mucosal protection, confirming traditional use in diarrhea and dysentery [6,16].

4.5 Neuroprotective Activity
Extracts attenuate acetylcholinesterase activity, inhibit amyloid-β aggregation, enhance antioxidant enzymes, and improve memory parameters in animal models [17].

4.6 Antimicrobial and Antiviral Properties
Leaf and fruit extracts show activity against Escherichia coli, Staphylococcus aureus, Candida albicans, and influenza-like viruses [18,19].

4.7 Anticancer/Cytotoxic Effects

Coumarins (imperatorin, psoralen) and alkaloids exhibit cytotoxicity in breast, pancreatic, and colon cancer cell lines through apoptotic pathways [9,20].

Table 2. Summary of Pharmacological Activities of Aegle marmelos Based on Experimental and Computational Evidence

Pharmacological Activity	Active Part(s)	Key Bioactive Compounds	Mechanisms / Experimental Evidence	References
Antidiabetic	Leaves, fruits	Aegeline, skimmianine, rutin, quercetin	↓ α-amylase & α-glucosidase; ↑ insulin sensitivity; antioxidant protection	[7,13]
Anti-inflammatory	Leaves, bark, fruit	Imperatorin, marmelosin, marmesin	↓ TNF-α, IL-6, IL-1β; inhibition of NF-κB & COX-2	[14,15]
Antioxidant	Leaves, fruit	Flavonoids (rutin, quercetin), phenolic acids	DPPH, ABTS, FRAP activity; ↑ SOD, catalase	[10,15]
Gastroprotective / Anti-diarrheal	Unripe fruit, bark	Tannins, coumarins	Reduced intestinal motility; astringent effect; mucosal protection	[6,16]
Neuroprotective	Leaves, fruit	Aegeline, marmeline, quercetin	↓ AChE; anti-amyloid activity; ↓ oxidative stress; improved cognition	[17]
Antimicrobial / Antifungal	Leaves, fruit	Imperatorin, bergapten, citral, limonene	Cell membrane disruption; inhibition of microbial enzymes	[18,19]
Antiviral	Leaves	Psoralen, bergapten	Inhibits viral replication enzymes; immune modulation	[18]
Anticancer / Cytotoxic	Leaves, roots	Imperatorin, marmesin, furocoumarins	Apoptosis induction; ROS-mediated cytotoxicity; cell cycle arrest	[9,20]
Hepatoprotective	Leaves	Phenolic compounds	↓ lipid peroxidation; stabilization of hepatic enzymes	[12]
Cardioprotective	Leaves, bark	β-sitosterol, skimmianine	Lipid-lowering; vascular relaxation; antioxidant action	[7,11]

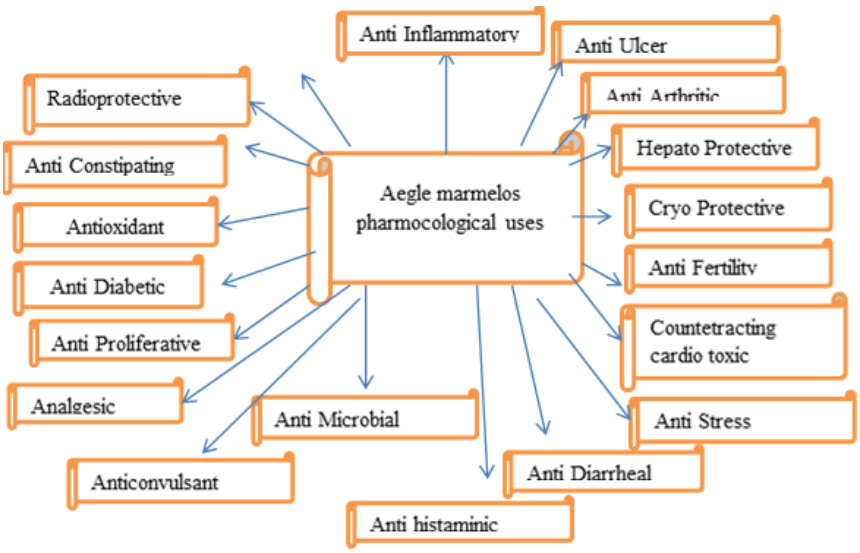

Figure 1 : Showing pharmacological role of Aegle marmelos.

5. Network Pharmacology and Molecular Docking Insights

Recent studies have used network pharmacology to identify multi-target mechanisms of A. marmelos in complex diseases.

5.1 Mechanistic Studies on Inflammatory Bowel Disease (IBD)

A 2025 network pharmacology study identified 46 active compounds and 358 target genes, with 80 core targets associated with inflammatory pathways, including AKT1, MAPK3, MAPK1, IL6, TNF, EGFR, and CASP3 [4].

Key Pathways Identified

- PI3K/AKT
- EGFR/TK signaling

- MAPK cascade
- TNF/IL-6 mediated inflammatory pathways

Top Bioactive Compounds Identified
Aegeline, imperatorin, marmesin, bergapten, and auraptene showed high binding affinity for AKT1, EGFR, MAPK3, and TNF in docking studies [4].

5.2 Neuroprotective Network Interactions
Computational studies suggest that marmeline and aegeline modulate key neurological targets such as BACE-1, PPAR-γ, CDK6, and PDE5A, thereby supporting anti-Alzheimer and cognitive-enhancing activities [17].

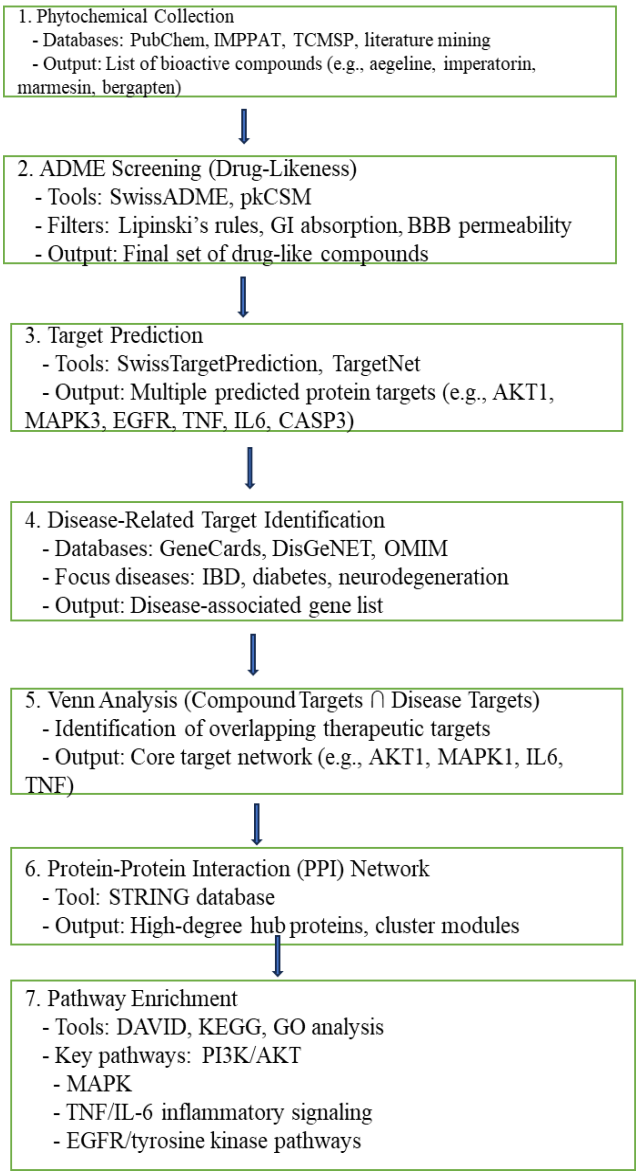

Figure 2. Network-pharmacology workflow illustrating the multi-target mechanism of *Aegle marmelos*

A stepwise computational strategy used to investigate the multi-component, multi-target interactions of *Aegle marmelos* in complex diseases.

Workflow Description:
Network pharmacology workflow for aegle marmelos analysis

6. Safety and Toxicity
A. marmelos is generally regarded as safe based on traditional and experimental evidence, but isolated compounds such as aegeline have been associated with hepatotoxicity when used in synthetic or concentrated supplement form [21]. Further standardized clinical trials are required.

7. CONCLUSION
Aegle marmelos is a versatile medicinal plant with robust historical, phytochemical, and pharmacological foundations. Advances in network pharmacology confirm its multi-target therapeutic mechanisms, especially in inflammatory and

neurodegenerative diseases. Continued research integrating clinical studies, bioinformatics, and formulation science will help unlock its full therapeutic potential.

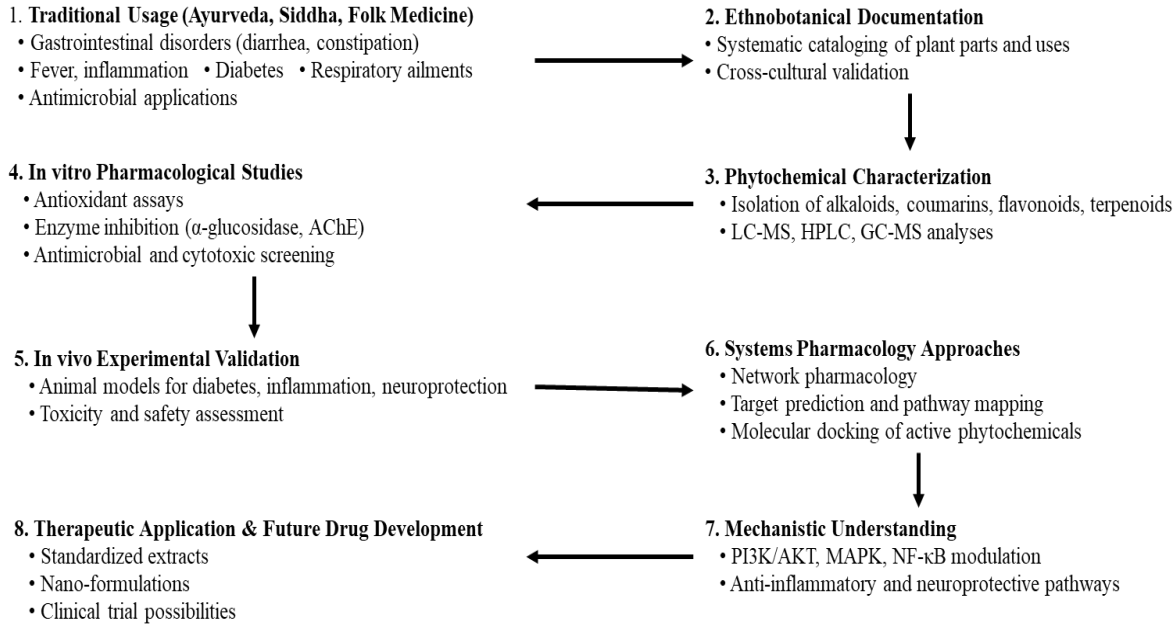

Figure 3. Flowchart Illustrating the Evidence Transition from Traditional Use to Modern Scientific Validation of Aegle marmelos

Traditional → Modern evidence translation framework

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