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Phytochemical and pharmacological profile of *Aegle marmelos* (L.) Correa: A comprehensive review of therapeutic potential, mechanisms of action, and translational relevance

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ABSTRACT

Aegle marmelos (L.) Correa, commonly known as Bael, is a botanically and culturally significant plant of the Indian subcontinent, widely valued for its therapeutic versatility. This review presents a comprehensive synthesis of *in vitro*, *in vivo*, and clinical evidence on the pharmacological potential of Bael and its bioactive compounds, including marmelosin, aegeline, imperatorin, gallic acid, and rutin. A systematic literature search was conducted across PubMed, Scopus, and Google Scholar covering 1990–2025, restricted to English-language studies. Eligible studies included *in vitro*, *in vivo*, clinical, and translationally relevant investigations, and data were extracted and thematically synthesized to evaluate phytochemical composition, pharmacological functions, mechanisms of action, and clinical applications. Bael extracts from various plant parts have demonstrated therapeutic effects in inflammation, cancer, diabetes, microbial infections, neurodegeneration, wound healing, and mood disorders. Mechanistic insights highlight modulation of critical biological pathways such as Nuclear Factor kappa-light-chain-enhancer of activated B cells, Vascular Endothelial Growth Factor, DPP-4, aldose reductase, HO-1, and β-catenin. Notably, molecular docking studies reveal interactions with diverse targets, including HSULF-2, MAO-A, SARS-CoV-2 proteins, and SpaP, supporting its multifunctional pharmacological relevance. However, translation to clinical practice is challenged by limited high-quality clinical trials, variability in bioactive content across extracts, and a lack of standardized dosing and formulation strategies. Despite these gaps, Bael exhibits a favorable safety profile and holds promise as a complementary agent in integrative medicine. This review underscores the importance of advancing clinical research and formulation science to fully harness Bael's potential in evidence-based healthcare and nutraceutical innovation.

1. INTRODUCTION

Aegle marmelos (L.) Correa, commonly known as Bael, is a deciduous subtropical tree belonging to the Rutaceae family and is the sole species within the genus *Aegle*. Native to the Indian subcontinent, it is widely distributed across Southeast Asia and valued for its resilience in arid climates and cultural prominence in traditional medicine systems [1,2]. The Bael fruit, encased in a hard shell and filled with mucilaginous pulp, has been consumed for centuries as both a dietary and therapeutic resource. In India, Bael is revered as a "divine tree" in Ayurvedic texts, underscoring its integration into rituals, functional foods, and household remedies [3].

Phytochemical studies confirm that nearly all parts of the tree—fruit, leaves, bark, roots, seeds, and flowers—contain diverse classes of bioactive compounds including coumarins, flavonoids, terpenoids, phenolic acids, and alkaloids [4,5]. These metabolites are linked with wide-ranging pharmacological effects such as antimicrobial, anti-inflammatory, antidiabetic, anticancer, and neuroprotective activities, supporting its traditional claims [2,6].

Despite this long-standing ethnomedicinal use and growing pharmacological evidence, translation of Bael into modern phytopharmaceuticals remains limited. Existing reviews often provide fragmented insights into either its

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phytochemistry [1] or specific pharmacological activities [3], but a comprehensive synthesis that integrates mechanistic pathways, molecular docking evidence, clinical findings, and translational gaps is lacking. Moreover, inconsistencies in extraction methods, variability in phytoconstituent profiles, and the paucity of standardized clinical trials further constrain its clinical relevance [7,8].

This review seeks to bring together existing research on Bael, focusing particularly on its phytochemical components and the mechanisms through which they exert therapeutic effects. Our objectives are threefold: (1) to classify the main types of bioactive compounds isolated from different parts of the plant, including but not limited to coumarins, flavonoids, terpenoids, and phenolic acids; (2) to interpret their biological activities in relation to health outcomes; and (3) to examine the clinical relevance and application potential of Bael-based products in modern healthcare and dietary formulations. In addition, this article emphasizes the importance of advancing molecular-level research—such as docking studies and formulation optimization—to fully harness Bael's medicinal promise.

2. METHODS

This narrative review was conducted to consolidate current knowledge on the pharmacological activities and bioactive constituents of Bael, with emphasis on mechanisms of action, therapeutic relevance, and research gaps. An extensive literature search was carried out using electronic databases including PubMed, Scopus, and Google Scholar. The search was limited to original research works in English-language publications, published from January 1990 to June 30th, 2025. Relevant additional articles were further identified through manual screening of the bibliographies of key reviews and research works. Keywords used for the search included combinations of "*Aegle marmelos*," "Bael," "bioactive constituents," "mechanisms of action," "pharmacological effects," and "therapeutic applications," utilizing Boolean operators (AND/OR) to enhance precision.

For clinical insights, the search was further refined with terms such as "clinical studies," "randomized controlled trials," "human trials," and "nutraceuticals." Studies were considered eligible if they included clinical trials, observational studies, *in vitro* or *in vivo* studies with translational significance, systematic reviews, or reputable institutional reports. Articles without full-text access, non-English papers, and preclinical studies lacking relevance to human health were excluded.

Due to the qualitative nature of the review, data extraction was performed manually rather than using software tools. Two independent reviewers primarily screened the literature from [PubMed (n = 713), and Scopus (n = 818)]. In addition, a supplementary search was also conducted on Google Scholar to identify any additional relevant articles. After screening for relevance, 82 peer-reviewed sources were included in the synthesis. The consistency and accuracy were ensured by mutual discussion and resolving any possible disagreements.

The extracted data were analyzed descriptively and thematically organized according to compound class and pharmacological categories with the aim of exploring and interpreting existing literature rather than calculating statistically. Consideration of study design, methodological rigor, and reporting transparency was integrated into the interpretation of the findings. This methodology facilitated a structured and holistic synthesis of available evidence on Bael, identifying key areas for further investigation and application in healthcare and nutrition.

3. RESULTS AND DISCUSSION

3.1. Phytoconstituents

Bael contains a wide array of secondary metabolites distributed across different plant organs. Based on our comprehensive literature survey of 78 studies, leaves were the most frequently investigated organ (48.7%), followed by fruit pulp (30.8%) and bark (9.0%). In comparison, roots (5.1%), seeds (3.8%), and flowers (2.6%) remain comparatively underexplored. The percentage distribution suggests that research focus should expand to the underexplored organs to ensure a more comprehensive pharmacological profile of the plant.

The most frequently reported bioactive classes are coumarins (marmelosin, imperatorin, and psoralen), alkaloids (aegeline), flavonoids (rutin, quercetin), and phenolic acids (gallic acid and ferulic acid). These were identified across multiple studies and are repeatedly linked to key pharmacological activities such as antidiabetic, antioxidant, anticancer, and wound-healing effects. Coumarins and flavonoids, in particular, emerge as dominant contributors to the therapeutic potential of Bael, consistent with their wide occurrence in Rutaceae plants.

This frequency-based descriptive assessment enriches the narrative review by highlighting which organs and metabolites dominate the literature, while also identifying underexplored plant parts (e.g., flowers and seeds) that may offer novel therapeutic insights.

3.1.1. Coumarin compounds

Among the different phytoconstituents, coumarins are the most extensively studied group. Coumarin compounds isolated from different parts of Bael exhibit diverse pharmacological properties. Marmelosin ($C_{16}H_{14}O_4$), primarily found in the fruit, has potent antioxidant and anti-inflammatory effects [6]. Aegeline ($C_{18}H_{19}NO_3$), sourced from the leaves, demonstrates anti-obesity and anti-diabetic activities [9]. Psorlen ($C_{11}H_6O_3$) and xanthotoxol ($C_{11}H_6O_4$), both derived from the seeds, possess anticancer properties [10,11]. In addition, the bark yields marmin ($C_{19}H_{24}O_5$) and marmenol ($C_{19}H_{24}O_6$), known for their anti-inflammatory and hepatoprotective roles [12,13].

It is important to note that the detection and activity of coumarins can be influenced by experimental conditions. Psoralen and imperatorin, for instance, are photosensitive and can degrade upon UV exposure, which may affect their reported yields [10]. Similarly, extraction efficiency varies with solvent polarity, with methanol and ethanol generally producing higher recovery compared to aqueous solvents [14]. Recognizing these methodological factors provides essential context for

interpreting pharmacological outcomes across studies. The presence of these compounds across different plant parts highlights the medicinal versatility of Bael.

3.1.2. Terpenoids compounds

Terpenoids isolated from Bael are distributed across various parts of the plant and exhibit a wide range of bioactive properties. Limonene and p-cymene, found in the fruit, display antioxidant and anti-inflammatory effects [15,16]. α-Phellandrene and β-myrcene, also present in the fruit, contribute to its anti-cancer and analgesic properties [17,18]. The leaves are rich in α-pinene and caryophyllene, known for their anti-inflammatory and antimicrobial properties [19,20]. Linalool and terpinolene, sourced from the essential oils of the leaves, exhibit sedative and anti-microbial effects [21,22]. These terpenoids highlight the therapeutic significance of various parts of Bael in traditional and modern medicine.

3.1.3. Flavonoids compounds

Flavonoid compounds isolated from different parts of Bael offer a wide range of health benefits. Quercetin, predominantly found in the leaves, exhibits potent antioxidant and anti-inflammatory properties [23]. The fruit is rich in rutin and catechin, both known for their cardiovascular protective and anti-diabetic effects [24,25]. Kaempferol, extracted from the bark, has demonstrated anticancer and anti-inflammatory potential [26]. The seeds yield 5,7-dimethoxyflavanone, which shows promise in anti-cancer research [27]. Epigallocatechin, found in the flowers, offers neuroprotective benefits [28]. In addition, phellamurin, isolated from the root, has shown antimicrobial and anti-inflammatory effects [29]. These diverse flavonoids highlight the therapeutic versatility of Bael, supporting its traditional use in various medicinal applications.

3.1.4. Other constituents

Bael contains a variety of other bioactive constituents distributed across different plant parts, contributing to its medicinal value. The fruit is particularly rich in phenolic acids such as gallic acid ($C_7H_6O_5$) and chlorogenic acid ($C_{16}H_{18}O_9$), both known for their antioxidant and antimicrobial properties [30,31]. Leaves contain caffeic acid, ferulic acid, and p-coumaric acid, which exhibit strong anti-inflammatory and hepatoprotective effects [32–34]. The seeds are sources of essential fatty acids such as linoleic, palmitic, and linolenic acids, beneficial for cardiovascular and skin health [35–37]. In addition, amino acids such as phenylalanine, tyrosine, and arginine have been isolated from the bark and roots, playing roles in protein synthesis and metabolic regulation [38,39].

3.2. Pharmacological activity of Bael

The Bael plant harbors a diverse array of phytochemicals that exhibit a wide spectrum of pharmacological activities. Extracts derived from its leaves, fruits, roots, bark, seeds, and flowers have been extensively studied for their therapeutic potential in treating various diseases. Multiple *in vitro* and *in vivo* studies have reported significant antimicrobial, anti-inflammatory, anticancer, wound healing, antidiabetic, and antidepressant properties of Bael. Table 1 summarizes the key pharmacological activities of Bael as reported in recent scientific literature, highlighting its role as a valuable medicinal plant with multifaceted health benefits [14, 40–62].

3.2.1. Antimicrobial activities

3.2.1.1. Anti-fungal activity

Bael exhibits promising antifungal potential, attributed to bioactive compounds present in various parts of the plant. Acetone extracts of Bael fruit have yielded several coumarin derivatives such as marmesiline, marmelonine, 6-(4-acetoxy-3-methyl-2-butenyl)-7-hydroxycoumarin, 6-(2-hydroxy-3-hydroxymethyl-3-butenyl)-7-hydroxycoumarin, and 8-hydroxysmyrindiol. These compounds possess unique structural features that contribute to their antifungal activity [14]. In addition, an ethyl alcohol extract of Bael leaves demonstrated significant inhibition against dermatophytic fungi *in vitro*. Though the specific compounds were not identified, the results suggest potential for developing antifungal remedies, particularly for dermatophytosis, pending compound isolation and *in vivo* validation [40]. Furthermore, petroleum ether and methanol extracts of Bael seeds led to the isolation of 1-methyl-2-(3′-methyl-but-2′-enyloxy)-anthraquinone, which exhibited strong antifungal effects, particularly against pathogenic strains of *Aspergillus* spp. and *Candida albicans* [41]. Collectively, these findings support the candidacy of Bael as a natural source of antifungal agents.

3.2.1.2. Anti-bacterial activity

Bael demonstrates significant antibacterial properties, particularly through extracts and novel formulations derived from its leaves and unripe fruits. Aqueous leaf extracts were used to synthesize copper oxide (CuO) nanoparticles via green synthesis, which exhibited notable antibacterial effects. The mechanism involves the positively charged CuO nanoparticles interacting electrostatically with negatively charged bacterial cell walls, leading to structural disruption and inhibition of bacterial growth [43]. Methanolic extracts of Bael leaves, rich in tannins and phenolic compounds, also showed antibacterial activity—specifically against *Acinetobacter baumannii*. These compounds are believed to interfere with bacterial protein synthesis by binding to adhesins and proline-rich proteins, thereby inhibiting bacterial adherence and proliferation [42]. In addition, the aqueous extract of unripe Bael fruit was found to contain marmelosin, which reduced bacterial colonization, likely by modulating the metabolic activity of HEp-2 cells, supporting its use in managing bacterial diarrhea [44] (Fig. 1). Beyond these, other studies report activity against additional clinically relevant species such as *Staphylococcus aureus*, *Enterococcus faecalis*, and *Shigella dysenteriae*, suggesting a broad-spectrum antibacterial potential [40,45,63]. This cumulative evidence indicates that Bael's antibacterial activity is not restricted to a single pathogen but extends across both Gram-positive and Gram-negative bacteria.

3.2.1.3. Antiviral activity

Bael has shown promising antiviral potential, particularly against the dengue virus. A study utilizing extracts

Table 1. Compilation of studies on pharmacological activity of Bael extract.

Pharmacological activity	Plant part used	Solvent used	Chemical constituent isolated	Formulation	Mechanism of action	Research outcome	References
Anti-fungal	Leaves	Ethyl alcohol	-	-	-	*Significant inhibition of dermatophytic fungi → potential remedy for dermatophytosis upon compound isolation and in vivo confirmation*	[40]
	Fruit	Acetone	Marmesiline, Marmelonine, 6-(4-acetoxy-3-methyl-2-butenyl)-7- hydroxycoumarin, 6-(2-hydroxy-3-hydroxymethyl-3-butenyl)-7-hydroxycoumarin, 8-hydroxysmyrindiol	-	-	Unique coumarin structures → antifungal activity	[14]
	Seed	Petroleum ether and Methanol	1-methyl-2-(3′-methyl-but-2′-enyloxy)-anthraquinone	-	-	Inhibition of *Aspergillus spp.* and *C. albicans*	[41]
Anti-bacterial	Leaves	Methanol	Tannins and Phenols	-	Binds adhesins, interferes with protein synthesis	Effective against *A. baumannii*	[42]
	Leaves	Water	-	Nanoparticles	Electrostatic interaction → cell wall disruption	Green-synthesized CuO nanoparticles → strong antibacterial activity	[43]
	Unripe Fruit	Water	Marmelosin	-	Affects HEp-2 cell metabolism → reduces bacterial colonization	Antidiarrheal activity through antibacterial mechanism	[44]
	Leaves	Methanol	Marmelosin, Cuminaldehyde, Tannins, Marmin, Terpenoids	-	Antibiofilm activity attributed to phytochemicals; slow-acting with peak efficacy on day 7	Significant antibacterial effect observed; potential alternative to standard intracanal medicaments	[45]
Anti-viral	Flower	-	-	-	↓ Replication of dengue virus serotypes DV1–DV4	Potential candidate for pan-serotype dengue virus inhibition	[46]
Anti-inflammatory	Bark	Hydro alcoholic extract	Marmelosin, Umbelliferone, Para-coumaric acid	-	↓ Inflammatory mediators	Demonstrated anti-inflammatory potential	[47]
	Fruit	Ethyl acetate	Marmelosin	-	↓ TNF-α, ↓ NF-κB expression	Significant anti-inflammatory effect	[48]
	Roots	Water	Marmin, Marmesin, Umbelliferine and Skimmianine	-	↓ Histamine, prostaglandins, serotonin	Positive effect in inflammation control	[49]
	Leaves	Water	-	Nanoparticles	↓ Neutrophil lysosomal release (via inhibition of heat-induced hemolysis)	Good anti-inflammatory response via phytofabrication approach	[50]
	Fruit	Methanol (HPLC-grade for analysis), Water (juice extraction)	Marmelosin, Umbelliferone, Luvangetin	Probiotic-fermented juice	↓ TNF-α, ↓ IL-6, ↑ SOD activity, ↓ Disease Activity Index (DAI); enhanced bioavailability via microbial biotransformation	Fermented juice improved antioxidant status, reduced inflammatory cytokines, and showed protective effects in DSS-induced UC model	[51]

Continued

Pharmacological activity	Plant part used	Solvent used	Chemical constituent isolated	Formulation	Mechanism of action	Research outcome	References
Anticancer	Leaves	Water	Flavonoids	Nanoparticles	Cytotoxicity against MDA-MB-231 breast cancer cells	Silver nanoparticles showed potent anticancer activity	[52]
	Fruit	Ethanol	Marmelin, Marmelosin	-	↓ VEGF, ↓ IL-8 (angiogenesis inhibition)	Suppressed breast tumor growth	[53]
	Fruit	Hydroalcoholic extract	-	-	↓ Carcinogen-induced lipid peroxidation	Protective effect against skin carcinogenesis	[54]
	Leaves	Ethanol	Limonene	-	↓ Cytotoxicity on gingival fibroblasts; fibroblast viability inversely proportional to dose and exposure time	BLE at 6.3 µl/ml maintained 95.5% fibroblast viability; potential safer alternative to CHX	[55]
Wound healing	Fruit	Ethanol	-	-	↓ Free radicals & MPO → ↑ collagen synthesis	Accelerated wound healing with enhanced collagen	[56]
	Flower	Ethanol	-	-	↑ β-catenin activation in HaCaT & Hs68 cells → ↑ collagen	Promising wound repair activity from flower extract	[57]
Anti-depressants	Leaves	Hydroethanol	-	-	↓ HPA axis activity; modulated serotonergic signaling, mitochondria, cytokines	Suggests antidepressant-like effect in preclinical CUMS model	[58]
Antidiabetic	Leaves	Ethanol	Gallic acid, Rutin	-	↓ Hyperglycaemia via α-glucosidase inhibition	Effective glucose-lowering activity	[59]
	Fruit	Methanol	Coumarin	-	↓ α-amylase and proteinase activity	Potent antidiabetic effect from fruit pulp extract	[60]
	Leaves	Ammonia	Polyphenols	-	Antioxidant → improves insulin sensitivity	Shows antidiabetic potential	[61]
	Leaves	Ethyl acetate	-	-	↓ Lens aldose reductase activity	Reduction in diabetic cataract	[62]

HEp-2: Human epithelial type 2 cells; TNF-α: Tumor Necrosis Factor-alpha; NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells; MDA-MB-231: Human breast cancer cell line commonly used in cytotoxicity studies; VEGF: Vascular Endothelial Growth Factor; IL-8: Interleukin-8; MPO: Myeloperoxidase; HaCaT cells: Immortalized human keratinocytes used as a skin model in research; Hs68 cells: Human dermal fibroblasts, commonly used for studying skin regeneration and wound healing; HPA axis: Hypothalamic–pituitary–adrenal axis; CUMS: Chronic unpredictable mild stress; DV1-DV4 Dengue Virus Serotype 1-4. SOD: Superoxide Dismutase; DAI: Disease Activity Index; BLE: *Aegle marmelos* leaves; CHX: Cytotoxic substitute for Chlorhexidine.

from the flowers of Bael demonstrated significant inhibitory activity against all four major dengue virus serotypes—*DV1, DV2, DV3, and DV4* in *in-vitro* assays [46]. Although the specific chemical constituents and formulation were not identified, the broad-spectrum inhibitory effect suggests the presence of potent bioactive compounds with antiviral properties. The extract appears to interfere with viral replication or entry mechanisms, positioning Bael as a strong natural candidate for pan-serotype dengue virus inhibition. While direct comparative data with other medicinal plants are limited in the cited study, the activity of Bael extract is consistent with similar reports of *Psidium guajava and Munronia pinnata* extracts, which also inhibited dengue virus replication *in vitro* [46]. These findings support further investigation into the flower-derived antiviral components of Bael for the development of plant-based antiviral therapeutics.

3.2.2. Anti-inflammatory activity

Bael has demonstrated notable anti-inflammatory properties through bioactive compounds isolated from various parts of the plant. Hydroalcoholic extracts of the bark contain marmelosin, umbelliferone, and para-coumaric acid, which collectively contribute to the reduction of inflammatory mediators, confirming the bark's strong anti-inflammatory potential [47]. Marmelosin, isolated from ethyl acetate extracts of the fruit, has been shown to downregulate pro-inflammatory markers such as Tumor necrosis factor-alpha (TNF-α) and Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB), suggesting

its role in modulating inflammatory signaling pathways [48]. Aqueous extracts of Bael leaves have been used to phytofabricate nickel nanoparticles, which inhibit lysosomal enzyme release by preventing heat-induced hemolysis in neutrophils, thereby demonstrating significant anti-inflammatory effects at the cellular level [50]. Furthermore, water extracts of the roots, containing compounds such as marmin, marmesin, umbelliferone, and skimmianine, have shown promising outcomes by inhibiting key inflammatory mediators such as histamine, prostaglandins, and serotonin [49] (Fig. 2).

In comparison to other medicinal plants, Bael's profile is consistent with well-recognized anti-inflammatory botanicals such as *Curcuma longa* (curcumin), which suppresses NF-κB, TNF-α, and IL-6 [64], and *Azadirachta indica* (neem), which reduces pro-inflammatory cytokines including TNF-α and IL-6 [65]. This similarity suggests that Bael possesses mechanistic overlap with other established anti-inflammatory remedies, thereby reinforcing its potential therapeutic relevance.

3.2.3. Anticancer activity

Bael exhibits promising anticancer potential, supported by studies on various plant parts and formulations. Water extracts of Bael leaves, rich in flavonoids, have been used to synthesize silver nanoparticles, which demonstrated significant cytotoxicity against *MDA-MB-231* human breast cancer cells. The nanoparticle formulation enhanced the bioavailability and anticancer efficacy of the plant extract. The nanoparticle formulation improved bioavailability and increased anticancer potency *in vitro* [52].

Ethanolic extracts of Bael fruit containing marmelin and marmelosin were found to suppress breast tumor growth by inhibiting pro-angiogenic factors such as Vascular Endothelial Growth Factor (VEGF) and IL-8, thereby preventing capillary formation essential for tumor progression. Quantitative assays indicated dose-dependent reductions in VEGF and IL-8 expression, supporting angiogenesis inhibition as a key mechanism [53].

In addition, hydroalcoholic extracts of the fruit showed protective effects against skin cancer by reducing lipid peroxidation induced by carcinogens, indicating a strong antioxidant-mediated anticancer mechanism [54]. Ethanolic leaf extracts rich in limonene also demonstrated selective cytotoxicity, maintaining 95.5% gingival fibroblast viability at 6.3 µl/ml, highlighting their potential as a safer adjunct compared to conventional chemotherapeutics or antiseptics [55]. Collectively, these findings highlight both quantitative cytotoxicity outcomes and mechanistic insights—including angiogenesis inhibition via VEGF/IL-8 suppression and antioxidant pathways—as central to the anticancer potential of Bael (Fig. 3).

3.2.4. Wound healing effect

Bael has shown significant wound healing properties, particularly through extracts derived from its flowers and fruits. An ethanolic extract of Bael flowers was found to promote wound healing by activating β-catenin signaling in HaCaT keratinocytes and Hs68 fibroblast cells, leading to enhanced collagen expression and synthesis—critical factors in skin regeneration and tissue repair. The effect was observed *in vitro* at concentrations ranging from 25 to 100 µg/ml [57].

Similarly, ethanolic extracts of Bael fruit pulp demonstrated effective wound healing by reducing oxidative stress markers such as free radicals and myeloperoxidase activity, which in turn facilitated increased collagen deposition at the wound site. *In vivo* studies reported significant healing at doses of 200–400 mg/kg in animal

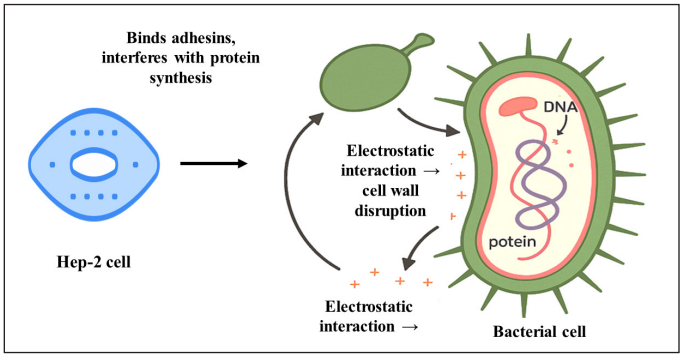

Figure 1. Mechanism of anti-bacterial action of Bael. Phytoconstituents in Bael interfere with bacterial growth by damaging membrane integrity, disrupting biofilm formation, and inhibiting microbial adhesion proteins. Abbreviations: HEp-2: Human epithelial type 2 cells; DNA: Deoxyribonucleic acid. (Image created with BioRender).

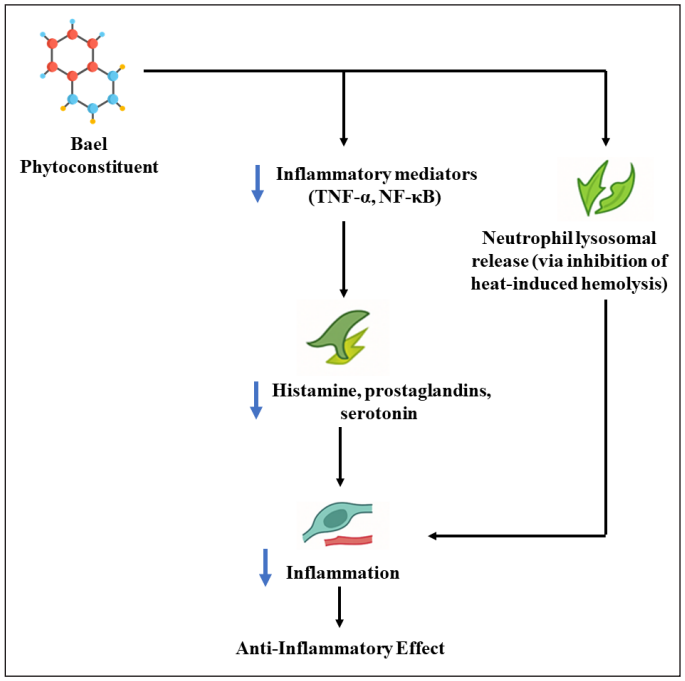

Figure 2. Mechanism of anti-inflammatory action of Bael. Bael phytoconstituents inhibit pro-inflammatory mediators such as TNF-α and NF-κB, reduce the release of histamine, prostaglandins, and serotonin, and limit neutrophil lysosomal activity via protection against heat-induced hemolysis. Abbreviations: TNF-α: Tumor Necrosis Factor-alpha; NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells. (Image created with BioRender).

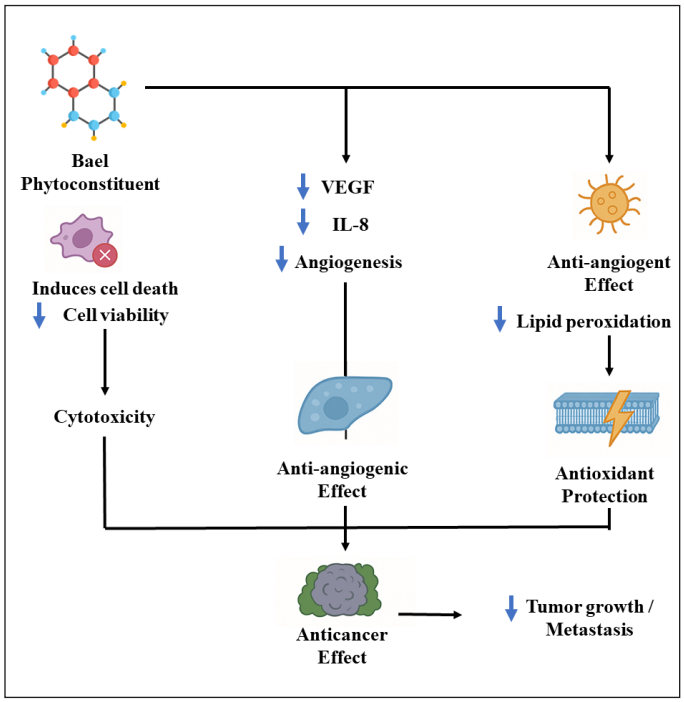

Figure 3. Mechanism of anti-cancer activity of Bael. Bael constituents exhibit cytotoxicity against cancer cells by downregulating angiogenic markers like VEGF and IL-8 and reducing lipid peroxidation. Abbreviations: VEGF: Vascular Endothelial Growth Factor; IL-8: Interleukin-8. (Image created with BioRender).

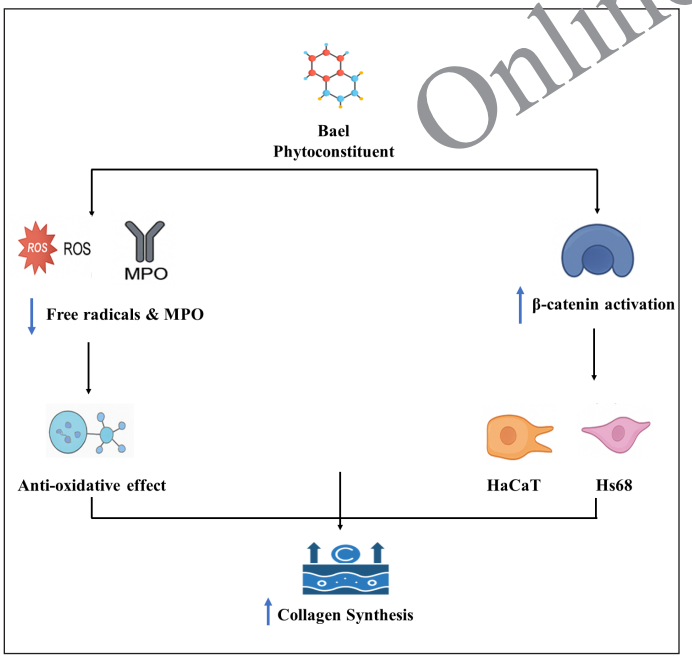

Figure 4. Mechanism of collagen synthesis and wound healing of Bael. Bael phytoconstituents reduce oxidative stress by scavenging ROS and inhibiting MPO activity, resulting in improved cellular redox status. Simultaneously, β-catenin activation in HaCaT and Hs68 cells enhances collagen gene expression. Abbreviations: ROS: Free radicals; MPO: Myeloperoxidase; HaCaT cells: Immortalized human keratinocytes used as a skin model in research; Hs68 cells: Human dermal fibroblasts, commonly used for studying skin regeneration and wound healing. (Image created with BioRender).

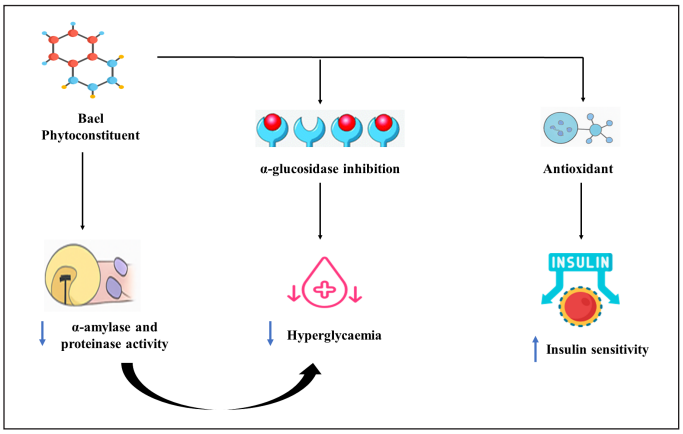

Figure 5. Mechanism of anti-diabetic action of Bael. Bioactive compounds in Bael reduce hyperglycemia through inhibition of α-glucosidase and α-amylase/proteinase enzymes, slowing carbohydrate metabolism. (Image created with BioRender).

models. This antioxidant-mediated mechanism accelerated tissue repair and improved healing outcomes [56] (Fig. 4). These studies underscore the therapeutic potential of Bael as a natural wound healing agent, warranting further exploration for topical and systemic applications in regenerative medicine.

3.2.5. Anti-depressant activity

Bael has demonstrated potential anti-depressant effects, particularly through its hydroethanolic leaf extract. In a preclinical study, administration of the extract to rats subjected to chronic unpredictable mild stress (CUMS) significantly reduced hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis—a key factor in stress-related disorders. The extract (administered orally once daily at doses of 100–200 mg/kg for 28 days) also attenuated alterations in serotonergic neurotransmission, improved mitochondrial function, and reduced the production of proinflammatory cytokines within the hippocampus and prefrontal cortex—brain regions critically involved in mood regulation [58].

These findings suggest that Bael leaf extract may exert antidepressant-like effects by modulating neuroendocrine, neurochemical, and inflammatory pathways. This is consistent with evidence from other medicinal plants such as *Withania somnifera* (ashwagandha), which reduces corticosterone levels and oxidative stress in preclinical models [66].

3.2.6. Anti-diabetic effects

Bael has been widely studied for its anti-diabetic properties, with bioactive compounds extracted from both its fruits and leaves demonstrating therapeutic potential. Methanolic extracts of Bael fruit pulp, rich in coumarins, have shown significant inhibition of α-amylase and proteinase enzymes—key targets in controlling postprandial hyperglycemia. By suppressing these enzymes, Bael extracts delay carbohydrate digestion and reduce the rapid rise in blood glucose following meals, thereby demonstrating potent antidiabetic activity [60].

Leaves of Bael have also been extensively investigated. Ammonia extracts containing polyphenols were reported to produce promising outcomes in diabetes management [61]. In addition, ethanolic extracts of leaves revealed the presence of gallic acid and rutin, both known for their glucose-lowering and insulin-sensitizing effects via α-glucosidase inhibition [59]. Another study found that ethyl acetate leaf extract effectively inhibited aldose reductase activity in rat lenses, suggesting a role in preventing diabetes-induced cataract formation [62]. Furthermore, individual phytoconstituents such as quercetin and coumarins displayed Dipeptidylpeptidase-4 (DPP-IV) inhibitory activity [67], while aegeline, citral, marmesinin, β-bisabolene, and auraptene were shown to interact with DPP-IV catalytic residues (Glu205, Glu206), highlighting Bael's promise in type 2 diabetes management [68].

When compared with other medicinal plants such as *Momordica charantia* (bitter melon), which exerts antidiabetic activity through α-amylase/α-glucosidase inhibition and improved insulin sensitivity, Bael demonstrates a similarly multitargeted profile [69]. This reinforces its relevance as a natural therapeutic candidate in diabetes management (Fig. 5).

3.3. Docking simulations of Bael bioactive compounds

Molecular docking studies have increasingly contributed to understanding the pharmacological potential of Bael by revealing the molecular mechanisms through which its phytoconstituents interact with therapeutic targets. Computational simulations have been employed to predict the binding affinity and interaction profiles of Bael-derived compounds with key proteins involved in various pathological conditions. These docking analyses provide crucial insights into the ability of Bael phytochemicals to modulate enzymatic activities and signaling pathways central to diseases such as cancer, diabetes, inflammation, and microbial infections.

For instance, marmelosin and marmesin demonstrate anticancer potential through inhibitory interactions with HSULF-2, a sulfatase linked to tumor progression, via π-alkyl, π-sulfur, and hydrogen bonding. In the context of oral health, limonene exhibits anti-*Streptococcus mutans* activity by binding to the SpaP protein, thereby interfering with bacterial adhesion. Anti-diabetic activity has been attributed to compounds such as aegeline and citral, which inhibit DPP-4 through interactions with Glu205 and Glu206 residues, thus supporting glucose homeostasis. Similarly, imperatorin shows antibacterial action against *S. dysenteriae* by targeting Cu-Zn superoxide dismutase, leading to oxidative stress-induced cell death. Quercetin and coumarins display DPP-IV inhibition, reinforcing their anti-diabetic effect, while aegeline's binding to MAO-A and iNOS suggests antidepressant properties.

Other constituents such as gallic acid, rutin, and scopoletin exhibit strong anticancer activity by targeting signaling molecules, including JUN, AKT1, and E6/E7 oncogenes, thereby inducing apoptosis in cancer cells. Notably, seselin interacts with multiple SARS-CoV-2 proteins, highlighting its antiviral potential. These findings, as summarized in Table 2, collectively emphasize the therapeutic promise of Bael and underscore the importance of docking studies in guiding future research and drug development using its bioactive principles [63, 67, 61, 70–80].

Although most studies remain at the *in silico* stage, a few have been supported by *in vitro* or *in vivo* validation—for example, quercetin's DPP-IV inhibition correlates with observed glucose-lowering activity [67], and gallic acid's pro-apoptotic docking profile is consistent with reported cytotoxicity in cancer models [75]. However, the predictive value of docking is limited by its static nature, which does not fully replicate the complexity of biological systems, such as metabolism, bioavailability, or synergistic phytochemical interactions. To date, docking studies on Bael have primarily examined compounds individually, with little exploration of synergistic docking or combined administration. While *in vivo* studies have demonstrated multicompound efficacy (e.g., polyphenol-rich extracts with antioxidant and antidiabetic effects), the docking-based prediction of synergistic interactions remains largely unexplored and represents an important future research direction.

3.4. Clinical applications and translational relevance

Although *A. marmelos* has been historically revered in Ayurvedic and Siddha systems for its wide therapeutic applications, its integration into modern clinical practice remains limited by insufficient translational data. Several studies have documented the efficacy of Bael extracts and formulations in preclinical models of diabetes, cancer, microbial infections, and inflammatory conditions; however, clinical validation is currently scarce and fragmented.

A few small-scale human studies have evaluated Bael's efficacy in gastrointestinal and metabolic disorders. For instance, decoctions of *A. marmelos* fruit pulp have shown beneficial effects in managing diarrhea and irritable bowel syndrome, attributed to its antimicrobial and mucosal protective properties. In ethnomedicinal settings, Bael fruit juice and leaf infusions are commonly consumed for blood sugar control, yet standardized clinical trials confirming glycemic outcomes, safety, and dose-response relationships are largely absent (Table 3) [7, 8, 53, 81–85].

In the context of nutraceuticals and over-the-counter herbal products, Bael has been incorporated into polyherbal formulations targeted at digestion, metabolic regulation, and immune support. However, such formulations often lack uniformity in phytoconstituent content, making bioavailability and pharmacodynamic predictability a challenge. Furthermore, interindividual differences in gut microbiota significantly influence the metabolic transformation and absorption of Bael's bioactive constituents, potentially affecting therapeutic outcomes. This highlights the need for future clinical trials to integrate microbiome profiling to better understand interpatient variability and optimize personalized interventions.

Emerging evidence from docking and *in vivo* studies suggests promising interactions with molecular targets such as DPP-4, aldose reductase, VEGF, and NF-κB, laying a foundation for future clinical trials that assess these effects in

Table 2. Docking analysis for pharmacological activity of Bael constituents.

Pharmacological activity	Chemical constituent	Mechanism of action	Research Outcome	References
Anticancer	Marmelosin, Marmesin	Binds to HSULF-2 via π-alkyl, π-sulfur, H-bonds → inhibits sulfatase activity	Potential anticancer effect via HSULF-2 inhibition	[70]
Anti-*S. mutans*	Limonene	H-bonding with C-terminal domain of SpaP protein → inhibits bacterial adhesion	Demonstrates potential anti-caries effect via SpaP inhibition	[71]
Anti-diabetic	Aegeline, Citral, Marmesinin, β-Bisabolene, Auraptene	DPP-4 inhibition via interactions with Glu205, Glu206	Promising in type 2 diabetes management	[68]
Dysentery	Imperatorin	Inhibits periplasmic Cu-Zn SOD in *S. dysenteriae* → oxidative stress-induced cell death	Potential antibacterial activity against dysentery-causing pathogens	[63]
Anti-depressants	Aegeline	Binds to MAO-A and iNOS → downregulates stress-related hypersensitivity	Shows antidepressant-like effects in preclinical model	[72]
Anti-inflammatory	Imperatorin	Targets HO-1 → reduces vascular inflammation	Effective against inflammation and oxidative stress disorders	[73]
Anti-inflammatory/ Antioxidant	Quercetin	Binds to IKKβ → modulates NF-κB pathway, ↓ p65 phosphorylation and inflammatory mediators	Shows potential in reducing inflammation and oxidative stress	[74]
Breast Cancer	Gallic acid	Inhibits JUN, AKT1, CASP3, CASP7 → induces apoptosis	Exhibits strong anticancer potential in molecular docking studies	[75]
Anti-diabetic	Quercetin, Coumarins	Inhibits DPP-IV via H-bonding with active site residues	Displays glucose-lowering effect via DPP-IV inhibition	[67]
Cervical Cancer	Rutin	Inhibits E6/E7 oncogenes → activates caspase → apoptosis in HeLa cells	Effective in cervical cancer chemoprevention	[76]
SARS CoV-2	Seselin	Binds to spike protein S2, main protease, and free enzyme of SARS-CoV-2	Potential inhibitor for multiple viral targets; candidate for COVID-19 therapy	[77]
Non-small cell lung cancer	Scopoletin	Inhibits RAS-RAF-MEK-ERK and PI3K/AKT pathways	Suppresses tumor growth by targeting key proliferation pathways	[78]
Antimicrobial (Anti-MRSA, Anti-MDR-SA)	AMP: GKEAATKAIKEWGQPKSKITH from *A. marmelos*	Binds to DHFR (−10.2 kcal/mol) and SaTrmK enzymes → stabilizes proteins (via MD simulations) → inhibits key bacterial enzymes	Demonstrated stronger binding than trimethoprim (MMPBSA: −47.69 & −44.32 kcal/mol *vs.* −13.85 & −11.67 kcal/mol); Lower MICs against MSSA, MRSA, and MDR-SA compared to trimethoprim	[79]
Antimicrobial (against *P. gingivatis*)	Rutin, Marmin, Clionasterol	Mfa1 protein → inhibits adhesion and biofilm formation	Rutin showed strongest and most stable binding; potential endodontic antimicrobial agent	[80]

HSULF-2: Heparan Sulfate 2-O-Sulfotransferase 2; *S. mutans: Streptococcus mutans*; SpaP protein: Surface Protein Antigen P; DPP-4: Dipeptidyl Peptidase-4; Glu205, Glu206: Glutamic Acid at positions 205 and 206; Cu-Zn SOD: Copper-Zinc Superoxide Dismutase; *S. dysenteriae: Shigella dysenteriae*; MAO-A: Monoamine oxidase A; iNOS: Inducible nitric oxide synthase; HO-1: Heme oxygenase-1; IKKβ: IκB kinase beta; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; JUN: Jun Proto-Oncogene; AKT1: AKT Serine/Threonine Kinase 1; CASP3: Caspase 3; CASP7: Caspase 7; DPP-IV: Dipeptidyl peptidase-4; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; RAS-RAF-MEK-ERK: Mitogen-activated signaling pathway involved in cancer cell proliferation; PI3K/AKT pathways: Phosphoinositide 3-Kinase / AKT Signaling Pathways; AMP: Antimicrobial Peptide; DBAASP: Database of Antimicrobial Activity and Structure of Peptides; DHFR: Dihydrofolate Reductase; SaTrmK: *Staphylococcus aureus* tRNA (m1A22) methyltransferase K: RMSD: Root Mean Square Deviation; RMSF: Root Mean Square Fluctuation; MMPBSA: Molecular Mechanics Poisson–Boltzmann Surface Area; MIC: Minimum Inhibitory Concentration; MSSA: Methicillin-Susceptible *Staphylococcus aureus*; MRSA: Methicillin-Resistant *Staphylococcus aureus*; MDR-SA: Multidrug Resistant *Staphylococcus aureus*; Mfa1: Minor fimbrial antigen 1.

humans. From a translational standpoint, critical gaps remain in formulation standardization, long-term safety profiling, and comparative effectiveness against existing pharmacotherapies.

Given its widespread availability, affordability, and traditional safety, Bael may represent a strong candidate for evidence-based integration into functional foods, phytopharmaceuticals, and public health strategies, particularly in low- and middle-income countries where access to conventional therapeutics is limited. However, its role in public health strategies remains exploratory and would

Table 3. Clinical and preclinical investigations of Bael across plant parts.

Sr. No.	Plant parts	Extract/Dosage	Therapeutic application	Study type/Clinical status	Reference
1.	Fruit	Ethanolic pulp extract	Exhibited antiproliferative and anti-breast cancer activity; demonstrated hepato-renal protection	Dose-response experimental study	[53]
2.	Leaves	Fresh leaf juice (20 g in 100 ml), administered for 60 days	Improved glycemic control in patients with type 2 diabetes	Randomized controlled clinical trial	[7]
3.	Fruit	AlvioLife® formulation, 200 mg/day of LI13109F versus placebo (n = 18 each)	Showed clinical efficacy in mild to moderate asthma, particularly in reducing airway inflammation	Double-blind, placebo-controlled clinical study	[81]
4.	Fruit	Fruit pulp powder (7 g/day for 21 days)	Evaluated for antidiabetic effect in type 2 diabetes patients	Phase III clinical trial	[8]
5.	Leaves	Dichloromethane (DCM) extract of leaves	Demonstrated anti-obesity potential	Observational investigation	[82]
6.	Leaves	Dried leaf powder	Exhibited antidiabetic activity	Randomized human trial	[83]
7.	Leaves, pulp and seed powder	Combined powders of leaves, pulp, and seeds	Reported benefits in diabetic individuals	Survey-based assessment	[84]
8.	Leaves	Aqueous extract (300 mg/kg body weight)	Lowered blood glucose levels	Preclinical animal model study	[85]

require validation through epidemiological studies and formal regulatory endorsement [4,5].

4. CONCLUSION

This narrative review highlights the broad-spectrum pharmacological potential of *A. marmelos* (Bael), attributed to its diverse bioactive compounds such as coumarins, flavonoids, alkaloids, and phenolic acids. Preclinical studies and limited clinical evidence support its antimicrobial, anti-inflammatory, anticancer, antidiabetic, and wound-healing effects, mediated through pathways including NF-κB, DPP-4, VEGF, and aldose reductase.

Despite promising pharmacological findings, translational challenges remain, particularly the paucity of large-scale clinical trials and the lack of standardized formulations. Future research should prioritize rigorous clinical validation, standardized extraction protocols, and exploration of delivery systems to improve bioavailability. Attention to microbiome interactions, safety profiling, and potential synergistic combinations with conventional therapies will further enhance its clinical relevance.

Given its accessibility, affordability, and favorable safety profile in traditional medicine systems, Bael shows potential as a cost-effective adjunct or preventive agent—particularly in low-resource settings. However, its public health utility requires validation through large-scale clinical and pharmacokinetic studies. With continued research bridging traditional knowledge, pharmacological insights, and clinical validation, Bael may contribute meaningfully to the development of integrative medicine and evidence-based phytotherapy.

5. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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The authors declare that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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