

## Review Article

# Bael (*Aegle marmelos* L. Corrêa), a Medicinal Tree with Immense Economic Potentials

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Bael (*Aegle marmelos* L. Corrêa) is an economically valuable tree species in South Asia. The ripen bael fruits are popular among people because of the delicious fruit pulp, which is ideal for making jam, syrup, and pudding. Bael possesses many medicinal values and therefore used as an ingredient in ayurvedic herbal medical preparations. The fruits, bark, leaves, seeds, and roots of bael contain bioactive compounds such as coumarin, xanthoxol, imperatorin, aegeline, and marmeline. These compounds can provide antidiabetic, anticancerous, antifertility, antimicrobial, immunogenic, and insecticidal activities. Bael is also essential as a species for reforestation, especially in the unfertile marginal lands. Bael seeds possess a unique fatty acid (12-hydroxyoctadec-cis-9-enoic acid or ricinoleic acid), a convertible item into biodiesel. Bael is an underutilized fruit species in South Asian countries. However, numerous studies report the medically significant properties and industrially vital characteristics of bael in India. The present review focused on summarizing and discussing the essential details and potentials of bael for industrial applications towards economic development.

## 1. Introduction

Bael, *Aegle marmelos* (L.) Corrêa, is one of the medicinally treasured tree species [1] out of the 250,000 living terrestrial plant species on earth. Bael is also known as begal-quince, golden apple, and stone apple in India [2] and a sacred tree in places where Hindus live. Bael trees are usually planted near temples dedicated to Lord Shiva and routinely worshipped by the devotees [3]. Bael is one of the most appreciated plants used in ayurvedic medicine by the Indian and other South Asian inhabitants in ancient history [4]. According to the historical records, bael is used as a medicinal and food item since 5000 B.C. [5] and known to human beings even when writing the famous Sanskrit epic-poem Ramayana [6]. Bael mentioned in the renowned book Charaka Samhita, a comprehensive compilation of all the essential ayurvedic information, which identified bael as a necessary item in ayurvedic medicine [6]. The tree is

aromatic, and all the parts are medicinally important [2]. Fruits, leaves, bark, roots, and seeds are used in ayurvedic and folk medicine systems to treat various ailments [2, 5].

Herbal medicines are heavily used and immensely popular in developing countries [7]. Bael fruits and leaves are used to treat dysentery, dyspepsia, mal-absorption, neurological diseases, edema, vomiting, and rheumatism [1]. In addition to the essential medicinal values, bael is reported as an important item in industrial food processing and an excellent source for extracting pharmaceuticals and many other economically important herbal compounds. Unfortunately, bael is still considered an underutilized tree fruit species in South Asian countries, and its real economic potentials have not been exploited.

The genetic characterization of the superior mother plants for large-scale propagation, biochemical characterization for essential phytochemicals, and tissue culture protocols for effective multiplication process is necessary to

utilize bael as a cash crop, significantly to develop the rural economies in South Asian countries. We conducted the present review to document the essential biological features and economic potentials of bael. This review also discussed the reported and potential biotechnological approaches to improve bael as a profitable cash crop. We used the Google Search Engine to search peer-reviewed published data in the period from 1990 to 2020. We also included key research papers from 1935 to 1989 to enrich the discussion with essential information reported in the past.

## 2. Ecology and Distribution

The believed origin of bael is India. The species reached the nearby countries in prehistorical times and recently to the other faraway lands through human movements [8]. The bael trees thrive well in dry, mixed deciduous, and dry dipterocarp forests and soils of India, Sri Lanka, Thailand, Pakistan, Bangladesh, Myanmar, Vietnam, the Philippines, Cambodia, Malaysia, Java, Egypt, Surinam, Trinidad, and Florida (S Figure 1). Bael occurs in India since 800 B.C. as a crop according to the historical reports [9]. Bael is a subtropical species, although it can grow well in tropical environments. Bael can thrive well in high altitude as high as 1,200 m and withstand without any significant growth retardation at 50°C and -7°C. In the prolonged droughts, fruiting may cease, but the plant can survive with shallow soil moisture. Bael trees generally require well-drained soil (pH: 5–8), but many studies and grower-reports suggest that it can grow equally well in alkaline, stony, and shallow soils. Bael grows well and produces bountiful harvests of fruits in the “oolitic-limestone” soils of southern Florida. In India and Sri Lanka, bael is famous as a fruit species, which can grow in very tough soils where other trees and other crops cannot grow [6].

**2.1. Botanical Description.** The comprehensive descriptions of the biological features of bael are available [10–12]. The size and the architecture of the bael tree are highly variable depending on the soil and climatic factors; however, the essential botanical features remain constant regardless of the climatic factors. From an agricultural standpoint, growers must prune and manage the tree to a convenient size and maintain a suitable number of branches for maximum fruit production.

**2.2. Tree Morphology.** Bael tree is deciduous, and the crown is compact or dense, with no weeping branches (S Figure 2). Sometimes the lower limbs are drooping. The tree is tough and widely adaptable to adverse soil and climatic conditions. The bael tree can grow up to 10 m or higher with medium or large sizes with numerous branches. The fruits mainly occur in the periphery of the canopy (S Figure 3). The trunk is short and thick with narrow oval shape ends (S Figure 4(A)). The wood is rigid and slow-growing. The young wood has a central pith (S Figure 4(B)). Under natural habitats, the trees are smaller and irregular. The trees possess short, sturdy, nonspiny, or piercing-spiny branches (S Figures 4(C) and

4(D)). The straight shaped spines are 3 cm in length when fully grown and originate from the leaves' axis (S Figure 4(D)). The tree's bark is flaking, bluish-grey, soft, and contains irregular furrows on the younger branches (S Figures 4(A), 5(A), and 5(B)).

The trees possess dimorphic twigs. The regular twigs have 3–5 cm long internodes with a leaf at each node and one to two spines (S Figures 4(B) and 6). The other type of twigs, the foliage spurs, are arising on the primary branches (S Figure 7(A)). The foliage spurs are shorter than usual twigs (1–3 cm) with copious diminutive internodes. In foliage spurs, each node has a leaf; however, the spine is absent. The further twigs produced on the first-year twigs have glabrous surfaces, whereas the new twigs produced in the second- and third-year twigs have striated surfaces. The prickles are generally absent on the stem, or if present, they are not persistent. The suckers (S Figure 7(B)) originate from the main bael trees when they grow up to a sufficient height and crown width. The young suckers have the stout and sharpest spines to protect the suckers from the herbivores. Usually, gum-like sap is secreting out from the wounds. Initially, the sap secretions appear as long thick threads and later become dried up long solid crystals.

**2.3. Leaf Morphology.** The leaves are alternate, single, or compound (S Figures 6 and 8(A)), with one or occasionally two pairs of shortly stalked opposite leaflets (S Figures 8(B) and 8(C)). The leaf petioles are glabrous and long, and with no wings absent. The leaves are trifoliate and aromatic, mostly when chopped. The leaves are deciduous, alternate, and borne as single or compound. In compound leaves, the leaflets appear in 2–5 oval-ovate or ovate shaped, pointed, and frivolously toothed leaflets (i.e., shallowly serratocrenate). A leaflet is 4–10 cm long and 2–5 cm wide. The leaflets are thin, and their midribs are prominent from the beneath. The terminal leaflet has a longer petiole. The new foliage emerging after a dormant or a reproductive phase is glossy in appearance and pink or burgundy in color (S Figure 7(A)).

**2.4. Flower Morphology.** The flowers are fragrant and form 4–7 clusters along the new branches (S Figure 6). A flower has four or five recurved and fleshy petals (the exterior color is green, and the inside color is yellow) with 50 or more greenish-yellow stamens (S Figures 6 and 9(A)). The flower is 2 cm wide, sweet-scented, stalked, lax, erect, and occurred axillary or terminal cymes. The calyx is shallow, with five short, broad teeth, and pubescent outside. The stigma is capitate, and the ovary is oblong-ovoid and slightly tapering into the thick short style (S Figure 9(B)).

**2.5. Fruit Morphology.** The fruits have a hard, smooth-woody shell (i.e., pericarp), a soft rind at immature stages (S Figures 9(C)–9(E)). The crust is gray-green at early stages (S Figure 10), turns yellowish or orange at the ripening stage (S Figures 10, 11(A), and 12(A)), and becomes very hard and orange-red when dried (S Figures 11(A) and 12(B)). The bael fruit exists in diverse shapes ranging from round, pyriform,

oval, or oblong (S Figure 11(A)). The fruits are 5–20 cm in diameter (S Figure 11(B)). The aromatic tiny oil glands appear as dots on the fruit shell (S Figure 10). Inside the fruit, there is a hard central core with 8 to 20 indistinctly apparent triangular segments with thin, dark-orange walls (S Figures 9(D) and 9(E)). They contain aromatic, pale-orange, pasty, sweet, resinous, astringent pulp with a pleasing aroma (S Figures 11(B) and 11(C)). The fruits are slow ripening, and they could take one year for full ripening (S Figure 10). The ripen fruit flesh is yellowish-orange in color, mucilage, fibrous, and aromatic. The seeds embed in a pulp-adhesive transparent mucilage (S Figures 9(D), 9(E), 11(B), 11(C), and 13(A)), which solidified like a glassy crystal when dried (S Figure 13(B)).

**2.6. Seeds, Seedlings, and Budded Plants.** The number of seeds varies from 10–50 (S Figure 9(E)). A seed is 1 cm long with a flattened-oblong shape. The seeds also contain woolly hairs (S Figures 14(A) and 14(B)). The seeds encase in a sack of sticky transparent mucilage or gummy substance that solidifies after drying (S Figures 14(A) and 14(B)). The testa is white. The embryo has large cotyledons with a short superior radicle. There is no endosperm. Some seeds can get aborted during the development (S Figure 14(A)). The seeds undergo no dormancy and germinate within 2–3 weeks. The seedlings are ready for transplanting within 2–3 months (S Figure 15(A)). The seedlings used as rootstocks are ready by the next year to produce grafted/budded plants (S Figure 15(B)).

**2.7. Crop Improvement.** The studies on improving bael as a crop using agronomic and genetic approaches are limited. Some important mother plants or cultivars have been selected in India [13] and Sri Lanka [8]. The grafting is done to propagate the elite mother plants for cultivation. Besides the selected mother plants, no standard cultivar produced through breeding is available for large-scale cultivation of bael [6]. The breeding is not conducted for bael mainly because it is a long-generation species, and the plant's reproductive biology is not well understood. Cytogenetic studies have been conducted, and the ploidy level of *A. marmelos* could be diploid ( $2n = 18$ ) or tetraploid ( $4n = 36$ ) with normal and remarkably high pollen fertility at each ploidy level. The large fruits are often correlated with the tetraploid genomes [3]. The phenological events such as leaf emergence and falling, flowering, and fruiting are the same for the wild and cultivated types. Exceedingly high open pollination is observed, and common pollination agents are insects and wind. Fruiting is enhanced by insect pollinators such as honeybees. However, propagation through seeds very much lacks as ants and fungi damage seeds. Therefore, vegetative propagation through agamospermy, coppices, and root suckers are prominent (S Figure 6). However, detailed studies on bael's reproductive biology are required under local conditions before implementing any crop improvement programs. The seedlings and budded plants are shown in S Figures 15(A) and 15(B).

The branches and buds taken for budding and grafting are shown in S Figures 16(A)–16(C).

### 3. Morphological Characterization of Bael Varieties/Accessions

Sing et al. [14] characterized different bael selections under the rainfed tropical semi-arid western India environment. They reported a higher degree of variation in vegetative, reproductive, yield, and phytochemical characters. Fourteen bael genotypes were characterized in Bangladesh, and four varieties were identified as the superior genotypes [15]. Although the morphological variations of bael have been observed in Sri Lanka, no systematic studies to characterize the entire germplasm within the country are available.

**3.1. Genetic Characterization and DNA Fingerprinting.** Bayer et al. [12] has conducted a molecular phylogenetic study for the subfamily of bael, Aurantodeae of family Rutaceae, using chloroplast DNA sequences and identified bael a monophyletic group. The bael is located significantly distant to the Citrus clade, consisting mostly of the known Citrus species [8]. This finding is in line with the inferences made by Swingle and Reece [10], where bael was considered as the bael-fruit group. However, the samples studied by then were taken from ex situ germplasm collections, and it seems that they do not contain samples from Sri Lanka. Pathirana et al. [8] have estimated that *A. marmelos* is evolutionary related to African genus *Afraegle* arguing that the genus *Aegle* would have been evolved in Africa and later disseminated to South Asia.

Large-scale genetic characterization using DNA markers is remote for bael. Furthermore, the National Center for Biotechnology Information (NCBI) nucleotide sequence citations for *A. marmelos* are only 253 by the year 2020 (<http://www.ncbi.nlm.nih.gov>). The true-to-typeness of the tissue-cultured bael plants was confirmed by using randomly amplified polymorphic DNA (RAPD) marker, OPA2, and inter-simple sequence repeat (ISSR) marker, MP2-based DNA fingerprinting [16]. Nayak et al. [17] used RAPD markers for genetic diversity assessment of a selected set of bael germplasm and which is the only study published on molecular characterization of bael germplasm. As RAPD markers are not very robust in assessing genetic diversity, they are not currently used in molecular diversity studies. Therefore, detailed molecular diversity assessment efforts are required using robust DNA markers such as microsatellite and SNPs. The use of molecular marker-based DNA fingerprinting is crucial for bael germplasm to understand the domestication events, to determine the effective population sizes for conservation, to accurately tag the superior cultivars for large-scale clonal propagation, and to map genes and Quantitative Trait Loci (QTL) [18].

**3.2. Economic Importance/Value and Underutilized Status of Bael.** In addition to the food and medicinal values, activated carbon produced from bael fruit shells can be used as an efficient, low-cost adsorbent to remove heavy metals such as

chromium from polluted or drinking water [19]. The use of activated carbon derived from bael rinds could be a novel approach to detoxify the heavy metal contaminated drinking water in Dry Zone, Sri Lanka, to combat chronic kidney disease of unknown etiology (CKDU). Bael leaves could also be used as a potential biosorbent. The noxious lead ions were demonstrated to be removed from an aqueous solution by absorbing them into the bael leaves [20]. An unusual fatty acid, 12-hydroxyoctadec-cis-9-enoic acid (ricinoleic acid), is present in the bael seed oil, which has the potential to be manufactured as biodiesel [21] in the future. The structure of bael exudate gum was also determined [21–23] which could be further characterized for various industrial applications. Bael is highlighted as a natural purifier of the environment and can be used as a supporting tree for wildlife and key species in reforestation of urban, rural [24], and dryer areas, and also it is useful as a shedding tree [25] for nutrient recycling.

**3.3. Food Value.** Consumption of fruits and vegetables is considered in the modern context as the best way to acquire essential antioxidants and micronutrients for a healthy life [26]. In the contemporary world, fruits are often appreciated as rich sources of health-promoting nontoxic natural food additives [27]. Bael nicely fits into this context as a nutritionally rich fruit species. Bael is mainly consumed as a fresh fruit in which the inner fleshy layer of the pericarp and placenta are edible [25]. These parts are also used to make pudding, juice, jam, and cakes [5, 28]. Bael fruit is rich in colorants and flavoring agents, which could be used as additives in the food industry [29]. The extracted nectar of fruit can also be used as a value-added product [6]. Bael fruits are also characterized by a higher abundance of soluble dietary fiber, volatile compounds with reducing sugars, carotenoids, and antioxidants [29]. The nutrient composition of bael fruits is given in Table 1 [30]. The detailed content of the elements present in ripe bael fruits is reported in Pathirana et al. [8].

**3.4. Biologically Active Phytochemicals Present in Bael.** A comprehensive review of phytochemicals is available at Lambole et al. [31]. All the parts of the bael tree are rich in phytochemicals such as coumarins, scoparone, scopoletin, umbelliferone, and marmesin [32, 33]. Table 2 provides a summary of key alkaloids, coumarins, and terpenoids.

**3.5. Phytochemicals in Fruits.** Bael fruits contain xanthoxol, imperatorin, alloimperatorin,  $\beta$ -sitosterol [38], tannins, and alkaloids such as aegeline and marmeline. Tannin was found to increase during ripening, where the highest tannin content was found in fully ripe fruits. Riboflavin, an essential vitamin, is only found in fully ripe fruits. However, the ascorbic acid content decreases significantly with fruit ripening [39], implying a marked reduction of antioxidant activity with maturation. A glycoprotein was discovered in bael, and its partial structure was proposed by Mandal and Mukherjee [22]. Bael has phenyl propanoids, which are

proven to be anticancerous [2]. The profile of the phytochemicals present in unripe bael fruits is given in Sharma et al. [40], in which marmelin is presented as the key bioactive compound. The main volatile compounds present in bael are monoterpenes and sesquiterpenes [29]. Another compound known as shahidine is also present, which is a newly reported molecule having very high labile oxazoline activity against few Gram-positive bacteria [41]. The gum of the surrounding environment of the seeds in bael fruit also contains phytochemicals [23].

**3.6. Phytochemicals in Leaves, Stem, and Roots.** Leaves (S Figure 17(A)) contain alkaloids, mermesinin, rutin, phenylethyl cinnamides, anhydromarmeline, and aegelinosides [32, 33, 42–44], sterols, and essential oils [32]. Stem barks and roots (S Figures 17(B) and 17(C)) contain a coumarin as aegelinol. Roots also contain psoralen, xanthotoxin, coumarins, tembamide, mermin, and skimmianine. The hemicellulose fraction of the bael bark was characterized by Basak et al. [45].

**3.7. Medicinal and Pharmacological Values.** All parts of the bael plant consist of immense medicinal properties. The herbal medicinal preparations of bael are used to treat chronic diarrhea, dysentery, peptic ulcers, laxative for astringency, and respiratory ailments [5]. The medicinal properties of herbal preparations of bael are tested using animal models such as rats [46], rabbits [47], and mouse [48].

Cancer is one of the significant causes of death worldwide, and novel drugs are required for efficient treatments. A total of reported 187 plant species from 102 genera and 61 families have proven antitumor properties [2]. However, only 15 species from 10 genera from nine families are currently used in clinical studies. Bael has more considerable significance as it has many compounds with anticancerous properties. Bael samples collected from different agroclimatic regions showed similar biological activities, indicating the synthesis of bioactive compounds in the plant is not environmentally dependent.

Bael fruits, leaves, and other parts of the tree have phytochemicals that possess numerous pharmacological values. The anti-inflammatory activity was demonstrated by preparations of bael roots [49]. Antioxidant potential of alcoholic and aqueous extracts of bael bark was able to scavenge target radical species such as  $O^{2-}$ , NO, 2, 2'-azino-bis-3-ethylbenzothiazoline-6-sulphonate (ABTS+) [50, 51]. All parts of the bael tree can be prepared as ideal tonics and reported to be good for the brain [52]. Gopalan et al. [30] argued that marmelosin is the therapeutically active compound in bael, and Shailajan et al. [53] further supported that argument, validating marmelosin as the primary therapeutic bioactive compound in bael using high-performance liquid chromatography (HPLC). Marmelosin is reported to possess toxic, restorative, astringent, and laxative properties and is also mentioned as an excellent substance for the heart and brain [54].



TABLE 1: Nutrient profile of the bael fruits.

Component	Amount present in 100 g of bael fruit flesh*
Protein	1.8 g
Fat	0.4 g
Minerals	1.7 g
Carbohydrates	31.8 g
Carotene	55.0 mg
Thiamin	0.1 mg
Riboflavin	1.2 mg
Niacin	1.1 mg
Vitamin C	8.0 mg

\*Source: Gopalan et al. [30].

**3.8. Antidiabetic Activity.** Bael extracts are shown to have significantly higher antidiabetic activities [55] when tested using animal models. The fruit extracts of bael have demonstrated protective effects on pancreatic tissues of diabetic rats [56]. Aqueous and alcoholic extracts of fruits administered at a dose of 500 mg per kg of body weight produced hyperglycemia in rabbits [23, 57]. An elevation of vitamin C content was also accompanied by hyperglycemia when rats were administered with bael fruit extracts [58]. Further observation of hyperglycemic activity [59, 60] and antihyperglycemic activity of the bael aqueous extracts were made using rat models [60]. These antidiabetic and hyperglycemic effects were further confirmed by Choudhary et al. [61] using aqueous extracts of bael seeds. Bael leaves have also shown the hyperglycemic impact [62]. According to Gireesh et al. [63], bael leaf extracts can decrease Mi receptor gene expression and inhibit aldose reductase activity, anticataract activity, and free radical scavenging activity, and all of them are related to diabetics. The compound Aegeline-2 in bael leaves is the responsible compound for antihyperglycemic activity [64].

**3.9. Anticancerous Activity.** Cancers are the most nuisance of all noninfectious diseases. The phytochemicals in herbs often hailed as a gold mine for discovering anticancerous drugs. A considerable amount of work is reported on the anticancer activity of bael. The anticancerous potential of bael has been conducted using brine shrimp lethality assay, sea urchin eggs assay, hemolysis assay, and 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) assay using tumor cells, and significant toxic effects were obtained [65]. The compounds isolated from bael showed in vitro antitumor activity in cancer cell lines, Ehrlich ascites carcinoma (EAC) (LK562), body cavity-based lymphoma cell line (BC) (MCF7), and mast cell line (MC) (Colo38) [2, 66, 67]. The bioactive molecules present in the bael extracts were later identified by gas chromatography-mass spectrometry (GC-MS) as cisplatin, chromomycin, cytosine arabinoside, 5-fluorouracil, butyl-p-tolyl sulfide, 6-methyl-4-chromanone, and 5-methoxypsolaren [67]. Like many other bioactive molecules, bael extracts can modulate reactive oxygen species, increase immunity, and minimize inflammation and angiogenesis. High tech state-of-the-art imaging techniques such as single photon emission computed tomography (SPECT), positron emission tomography

(PET), and nuclear magnetic resonance (NMR) were used to prove the anti-inflammatory and antiangiogenesis activities of bael [68].

Chemo and radiotherapies are the routinely used procedures to kill the cancerous cells progressively. Oncologists are often facing a massive problem in determining the effective doses of chemo and radiation therapies to minimize the cytological and genetic damages on the healthy cells. It is rather complicated as individual patients respond variably to these therapies. Herbs such as bael have been found to possess protective effects against chemo and radiotherapy treatments. Doxorubicin, a potent drug, is frequently used in chemotherapy, which can also cause irreversible damages to the DNA of healthy cells. However, the fruit extract of bael was found to inhibit the doxorubicin-induced genetic damage [69]. Sagar and Wong [68] reviewed the usefulness of botanicals to improve tissue repair following radiation therapy and listed the potential radioprotective mechanisms [4, 66, 70].

Antioxidant supplementation would improve the efficiency of chemo and radiation therapies [71]. Therapeutic achievements in radiation therapies can be achieved by enhancing the ability to target the cancer cells, selectively destroying the malignant cells, and protecting the healthy cells from the damage caused by the radiation. Therefore, cell protectants are essential; however, chemical-based tissue protectants are toxic and cannot be tolerated by the patients frequently. Herbal-based cell and tissue protectants such as bael fruit extracts are less toxic and also act as immune enhancers, making them ideal for the target actions [68]. Bael is reported as a botanical radioprotectant in several studies [66, 72]. It has been reported that an effective route of administration is intraperitoneal administration over oral administration to protect the mice that have undergone various doses of gamma radiation. Hydroalcoholic fruit extracts of bael were found to be effective against cancer patients who have undergone gamma radiation as part of the treatment [66]. The evidence supports that bael has anticancerous activity and has cell and tissue protectant activity, which is vital in saving healthy cells when patients are undergoing chemo and radiotherapies. However, further studies are required to determine the necessary optimum doses and optimum routes of administration along with the chemo and radiation therapies.

**3.10. Antimicrobial Activity.** Bael extracts have shown antibacterial [73], antifungal [74], and antiviral [75, 76] activities. The antibacterial effect of bael was found on pathogenic *Shigella dysenteriae*, and the inhibitory activity was believed to be from coumarin compounds present in the extract [77]. An antidiarrheal activity reported in Shoba and Thomas [77] could also be due to the same or similar compounds. As an alternative to conventional antibiotics, a combination of bael and a popular antibiotic  $\beta$ -lactum was used, and inhibitory activity on  $\beta$ -lactam resistant *S. dysenteriae* and *S. flexneri* was obtained. The susceptibility was given by the differential expression of membrane porins, outer membrane protein (Omp) C and OmpF, and a

TABLE 2: A set of important phytochemicals in bael.

Name	Compound	Plant part	Medicinal property	Reference
Alkaloids	Aegelenine	Fruit, leaves	Antidiabetic, antibacterial, anti-inflammatory, and anticancerous	Shoeb et al. [33]; Chatterjee et al. [32]; Lambole et al. [31]; Rajan et al. [34]; Bhar et al. [35]; Sarkar et al. [36]
	Aegeline			
	Aegelinosides A			
	Aegelinosides B			
	Dictamine			
	Ethyl cinnamamide			
	Ethyl cinnamate			
Coumarins	Fragrine	All parts	Antidiabetic, antioxidant, anti-inflammatory, and antianalgesic	Lambole et al. [31]; Bhar et al. [35]; Sarkar et al. [36]
	Halfordinol			
	Alloimperatorin			
	Imperatorin			
	Isoimperatorin			
	Marmelide			
	Marmelosin			
	Marmesin			
	Marmin			
	Methyl ether			
	Psoralen			
	Psoralen-a			
Scoparone				
Scopolentin				
Scopoletin				
Umbelliferone				
Xanthotoxol				
Zanthotoxol				
Terpenoids	Caryophyllene	Fruit, leaf, and bark	Anticancer	Lambole et al. [31]; Bhar et al. [35]; Poonkody et al. [37] Sarkar et al. [36]
	Cineol			
	<i>cis</i> -Limonene oxide			
	<i>cis</i> -Linalool oxide			
	Cubedol			
	Elemol			
	Epi-cubebal			
	Hexanylhexanoate			
	Humulene			
	Isosylvestrene			
	Limonene			
	Linalool			
	Methyl perilate			
	Myrcene			
	P-cymene			
	Terpinolene			
	Valencene			
	Caryophyllene			
	Cineol			
	<i>cis</i> -Limonene oxide			
	<i>cis</i> -Linalool oxide			
	Cubedol			
	Elemol			
	Epi-cubebal			
	Hexanylhexanoate			
	Humulene			
	Isosylvestrene			
Limonene				
Linalool				
Methyl perilate				
Myrcene				
P-cymene				
Terpinolene				
Valencene				

cytosolic protein OmpR. When bael extract is administered, the OmpF gene was overexpressed, and OmpR was downregulated. Generally, these bacteria are resistant to  $\beta$ -lactam; however, fruit extract restores the inhibitory activity of  $\beta$ -lactam by changing porin channels' dynamics [77]. Antifungal activity is observed in essential oils extracted from bael leaves [74]. Furthermore, a potential antifungal compound anthraquinone was also isolated from bael seeds [79]. The essential oil extracts from leaves inhibit highly resistant *Fusarium udum* at 80% of efficiency under the concentration of 400 ppm included in the medium. The spore germination of *F. udum* was inhibited [74] by the bael leaf extracts. Antifungal activities were also confirmed against *Aspergillus* and *Candida* spp. using the disk diffusion assay [79]. The demonstrated antimicrobial activity implies that bael extracts can be used to control the fungal pathogens in skin diseases and the contamination of food. According to Mishra et al. [79], an array of antimicrobial compounds from bael seeds were isolated. A promising antiviral activity was also observed against the white spot syndrome virus in shrimp [75, 76].

#### 4. Other Important Properties

Bael fruit extract has shown significant antimicrofilarial activity [80] and insecticidal activity on nuisance Japanese encephalitis vector *Culex tritaeniorhynchus* [81]. Essential oils of bael are effective in fumigating stored gram and wheat samples at a concentration of 500  $\mu\text{g/ml}$ . The targeted insect pests were *Callosobruchus chinensis*, *Rhyzopertha dominica*, *Sitophilus oryzae*, and *Tribolium castaneum*.

Sahare et al. [82] also explained that coumarin present in bael leaves possess antimicrofilarial activity. The oviposition, feeding behavior, and adult emergence were negatively affected by bael oil fumigation [83]. Bael extracts were found to reduce fertility in male rats. The administration of herbal preparations of bael to rats causes weight shedding of sexual organs and reducing the motility and density of sperms. The removal of treatment restored the fertility to normal, indicating the possible use of bael-based phytochemicals as a future birth-controlling drug [84].

Bael preparations were known to be efficient against treating respiratory ailments. The contractile activity of tracheal elements was demonstrated using guinea pig and mouse models. The antihistamine activity was also shown, indicating the usefulness of using bael extracts against respiratory ailments such as asthma [48]. Applying herbal preparations of bael modulated the expression of the I-18 gene in brachial epithelial cells showing the potential to use as an effective drug in treating cystic fibrosis in the future [85]. Bael is used to treat hepatitis [86] and  $\text{CCl}_4$ -induced hepatotoxicity in rats. The administration of bael fruit and seed extract significantly reduced the  $\text{CCl}_4$ -induced elevation of plasma enzyme and bilirubin concentration in rats [87]. It is logical to think that bael extracts could be used to treat cirrhosis, but further studies are required. Flavonoids in bael could be the attributing factor for repairing the structure and function of the liver. Oral administration of bael fruit extracts also reduced the hypovitaminosis C in rats

by the compound hesperidin, which is also contributing to the hepatoprotective role [87]. The hepatoprotective effects of bael were further confirmed by Rahiman et al. [88] and Sidana et al. [89]. Eating bael fruit ad libitum is a preventative measure and a treatment against cytotoxicity in the liver [87].

Bael has an inhibitory effect on hyperthyroidism in mice. Crushed and dried bael leaves were prepared as slowly boiled aqueous slurry and administered orally to mice at the concentration of 1 g per kg of body weight. Thyroid hormone concentrations were regulated by the administration of bael and exhibited the relative decreasing of the thyroid hormonal concentration in blood. However, the thyroxin level did not go down by the bael leaf extract [72]. The modulation of intraocular pressure (IP) is one of the treatment strategies for glaucoma. The IP ability of bael fruit extract was demonstrated using rabbit models [47]. The wound-healing property of methanol extracts of bael was tested using the formulations of ointments and injections, which facilitated the healing process, and the efficiency of the healing process is comparable to nitrofurazone [90].

Bael is long being used to treat ailments in the digestive tract, and this ability maybe because of the compound marmelosin [67] in bael extracts. Moreover, analgesic activity [48, 91] and anti-inflammatory and antipyretic activities of bael were also reported [48]. Anti-immune modulatory activity of methanol fruit extract was verified using the neutrophil adhesion test and carbon clearance assay [92]. Bael fruit extracts would augment the immune activity [92] along with the other immunity enhancement mechanisms upon exposure to the infections. Immunomodulatory activity and the augmentation of the immune activity of bael were also reported by Patel et al. [92], and an antidyslipidaemic activity was also observed [93]. Aqueous extract of bael can also act as a cardiac stimulant, smooth muscle relaxant, and uterine stimulant. However, alcoholic extracts act as a cardiac depressant implying the importance of the medium of herbal preparations [57] as one medium could ultimately reverse the intended function from the other. Antioxidant activity and the membrane effects of furanocoumarin and marmesin isolated from bael evaluated for cardiac injuries by Vimal and Devika [94] and demonstrated a protective effect against the damage. The formulations made out of bael roots were found to possess antivenom activity against snake bites [95].

The toxicity studies of the herbal preparation of bael were conducted using rat models, and it was found that higher doses of bael preparation are less toxic, and higher therapeutic indices can be achieved through administering large quantities. The very high margin of drug safety (i.e., very high LD50) in bael preparations is significant in routine treatments for various ailments [96].

#### 5. Propagation of Bael and Conventional Techniques

The seeds are the primary planting material of bael. The nurseries must be established with the fully grown seeds collected from the mature fruits. The seedlings must be

transplanted in the adequately prepared fields for better establishment and success rates. However, the seeds often show reduced germination rates, and the seedlings often display segregation of traits, especially regarding the fruit traits; thus, the superior bael trees must be propagated by using vegetative means such as budding, grafting, and micropropagation. The four-week-old buds collected in the correct phenological stage could be budded onto two-year-old health seedlings as rootstocks to obtain successful regeneration [97]. The air-layering, root cuttings, and the separation of roots with shoots that appeared separately to the mother plants can also be used to propagate bael.

**5.1. Micropropagation of Bael.** Micropropagation using tissue culture techniques is often hailed as an efficient strategy for forest tree crop improvement. Elite mother plants can be selected, mass propagated using tissue culture, and grown on a wide-scale [98]. The tissue culture requirements for the shooting of bael are explained in Surana [99]. Using 8–10 mm sized explants of auxiliary and terminal buds taken from elite bael trees were tissue cultured by Arya and Shekhawat [100]. Juvenile buds must be taken at the vegetative stage of the tree [101] to improve the success rate, and 100 mg/L ascorbic acid and 150 mg/L citric acid were used in combination to avoid browning. The Murashige and Skoog (MS) medium with 5 mg/l, 2-4D, and NAA was used for the induction of callus. Kinetin (1 mg/l) and BAP (0.5 mg/l) were used for the induction of rooting. High-frequency plantlet regeneration was achieved by using cotyledonary nodes of bael. Nayak et al. [102] explained the precise requirements of plant growth regulators for efficient shooting and rooting of bael, and the number of workers tried with different explants [103–106]. In vitro clonal propagation of bael was optimized through improved auxiliary branching of the mother plant, and the true-to-typeness of the daughter plants was confirmed from DNA fingerprinting [16].

**5.2. A Strategic Action Plan to Uplift Bael as a Popular Cash Crop.** A detailed action plan for bael's ultimate development as a vital cash crop and to gain the world's attention on bael species is given in Figure 1. A multifaceted strategic plan is required to uplift bael as a widely popular cash crop. Such an approach should have two broad sections governing germplasm characterization and enrichment, cataloging biochemicals, and assessing their bioactivities (Figure 1).

The entire germplasm of bael must be surveyed and characterized for variations in all possible morphological characteristics. The Global Positioning System (GPS) coordinates of the tree locations must be recorded. The site owners must be convinced not to cut down or remove the trees and highlight each tree's value, given the crop's extremely high heterozygous nature. However, under unavoidable circumstances, care must be taken to bud and propagate any vital tree which is vulnerable to be cut down due to human activities.

Once the overall picture of the bael germplasm is unraveled, for the agronomically important traits, decisions must be taken to work with only local germplasm or whether

it is necessary to introduce germplasm from the center of origin, India, to have much broader genetic diversity for better success in research and development. The selected trees must then be subjected to a comprehensive phylogenetic and phylogeographic analysis by sequencing the common DNA barcoding loci to gain a holistic view of the diversity structure, origin, and distribution of the bael germplasm concerning the other members of family Rutaceae [8]. The same thing could be independently verified by genotyping the selected trees with robust and codominant SSR markers. However, this approach could be expensive and time-consuming as whole-genome coverage could be challenging because no SSR markers are specifically available for bael species; thus, we have to rely on the SSR markers designed for the other species of Rutaceae, and the chance for the success is quite low in such comparative mapping approaches. Moreover, bael is a single species genus; thus, the efficiency of comparative mapping could be further low due to the higher genetic divergence among genera. One can argue that the development of a panel SSR markers for *A. marmelos* would be an important future direction. However, with the advent of next-generation sequencing technologies and low prices of whole-genome sequencing, SNP or genotype by sequencing (GBS) markers must be preferred rather than heading back to low throughput wet lab-based markers.

Based on the molecular phylogenetic analysis, at least 1000 different trees must be selected as a panel or a core-collection, which represents 80% of the genetic diversity detected in the exploration step of the germplasm and the genotypes introduced if a germplasm enrichment was initially decided. For the better and fast acquisition of absolutely correct data for valid inferences, the selected 1000 trees must be subjected to a state of the art trait measuring phenomics platform and the genomic diversity assessment using a GBS platform. These two steps will yield metadata for all possible critical phenotypic characteristics and SNP/INDEL variations across all the genomes of the bael trees assessed. The genome-wide association (GWAS) analyses must perform to identify the marker-trait associations to declare haplotypes for marker-assisted seedling selection (MASS) and the characterization of underlying genes. The marker-assisted breeding (MAB) can also be implemented; however, given the crop's long-generation nature, MASS could be a more pragmatic approach for the fast release of the improved cultivars. With the selected seedlings multiplied through micropropagation, orchards, home gardens, and medicinal plots must be established, and any interested growers must be helped out with whatever the necessary resources to popularize the crop. Even container and bag cultures of bael plants for urban areas, multistory apartments, and fragmented lands must be promoted. The established micropropagation technique is essential to mass propagate the elite plants selected through MASS without touching the purity of the heterotic genomes providing excellent trait values.

On the other hand, further characterization attempts must be taken to elucidate more antipathogenic, anticancerous, antioxidant, anticholesterol, and antidiabetic



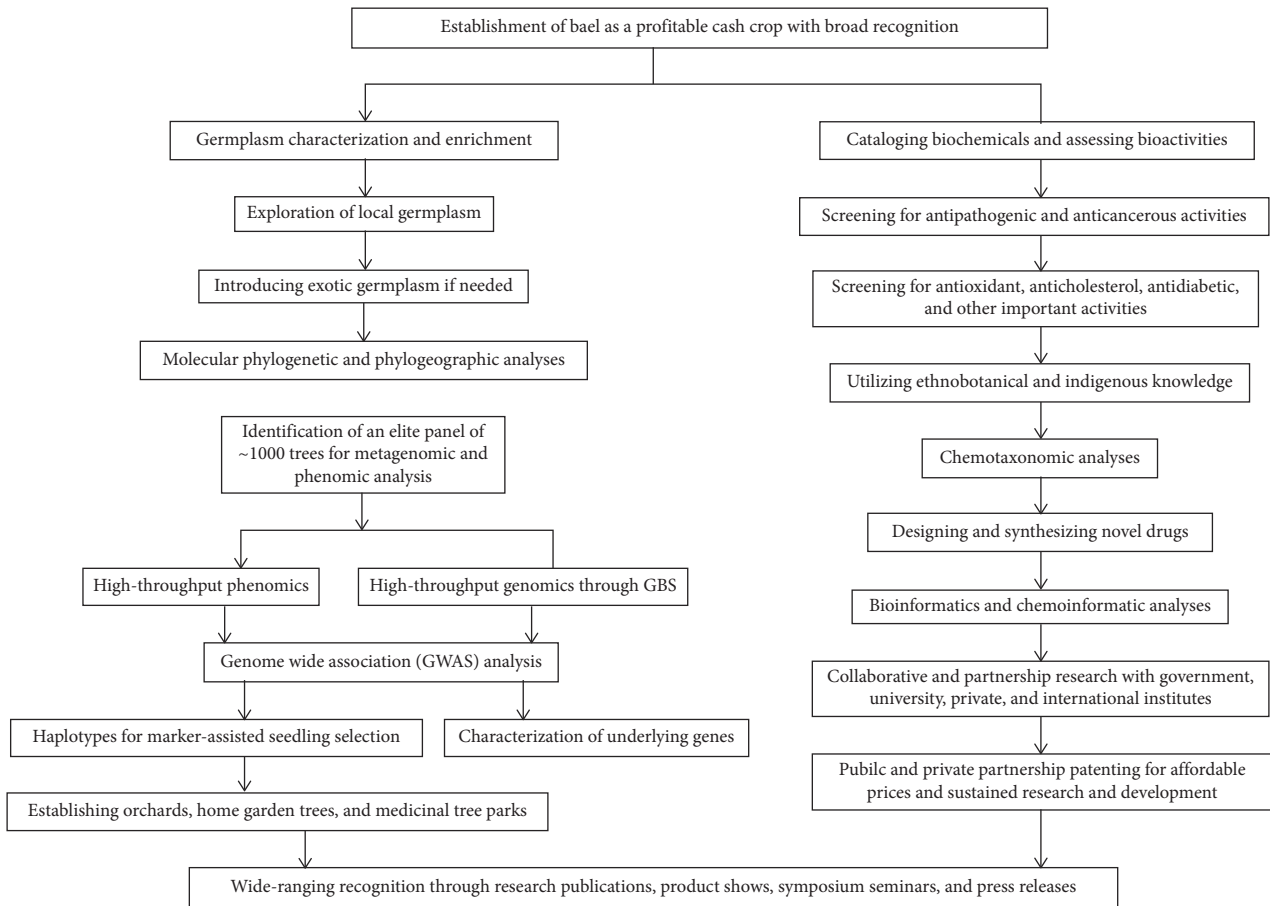


FIGURE 1: The proposed genomics, phenomic- and biochemical-based industrial strategies to develop bael as a recognized cash crop.

activities of bael fruits and other plant parts. To plan such studies, it is essential to be based on the ethnobotanical and indigenous/ayurvedic medical knowledge so that crucial leads can be taken in the research studies for a better outcome. The chemotaxonomic analysis of the elemental and biochemical profiles must also be conducted to see the similarities with phylogenetics-based diversity structures. These comparisons would also be essential to select ~1000 trees for the phenomic and genomic analyses. New leads will be available for designing and synthesizing novel drugs based on the bioactivity and chemotaxonomic study. The bioinformatics and chemoinformatic analyses are essential here to match what is in bael with what is required in the pharmacology sector.

All the proposed research directions cannot be undertaken single-handedly. The collaborative and partnership research by government, university, private, and international institutes is significant for the ultimate success. The transparent and mutually respected transfer of material across borders must be facilitated for the smooth research process. Any patentable outcome must be encouraged because the rights must be shared among public and private partnerships to ensure affordable prices and sustainably nourish the research and development with continuous funding. High-impact publications should be produced during the whole process, and the research findings must be

disseminated to stakeholders through product shows, symposiums, and press releases. All these coordinated activities undoubtedly uplift bael as a leading cash crop in the world.

## 6. Concluding Remarks

Indigenous fruit trees are significantly contributing to alleviate hidden hunger, and bael is significant in this regard. Given the numerous food, pharmacological, and other bael values, it could be considered a promising fruit tree species in large-scale agriculture. In addition to the large-scale cultivation, proper harvesting practices, appropriate storage, and transportation facilities are required for the efficient industrial processing of the fruits for efficient food and pharmaceutical industries. This would ultimately uplift bael from its underutilized statue as an important cash crop to improve rural people's livelihood and develop the economy through value-added food and pharmaceutical industries.

## Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

## Conflicts of Interest

The authors declare no conflicts of interest.

## Authors' Contributions

CP, TM, and JE conceptualized, wrote, and finalized the manuscript. JE and TM obtained funding.

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## Supplementary Materials

S Figure 1: the world distribution of bael. S Figure 2: a mature bael tree during the fruiting season. S Figure 3: a close-up view of the canopy section bearing fruits in the tree. S Figure 4: vegetative structures of bael. A: Stem or trunk; B: cross and longitudinal sections of the stem; C: thornless branch; D: thorny branch with or without leaves. The images are not shown according to a scale. S Figure 5: the bark of bael stem. A: Internal, external, and dried external views of bark; B: easy peeling of bark from the young stem. S Figure 6: line diagram of a bael twig showing trifoliolate leaves, thorns, flower buds, flowers, and early fruits. S Figure 7: thornless twig with spurs (A) and a water sucker (B) at the stage of separation. S Figure 8: leaf morphology and emergence. A: Compound leaf, top and bottom views; B: alternate leaf arrangement, top view; C: alternate leaf arrangement, bottom view. S Figure 9: reproductive structures of bael. A: Flower; B: gynoecium with a stamen (left) and L.S. of the gynoecium (right); C: T.S. of the fruit; D: L.S. of the fruit showing a carpel; E: T.S. of the fruit. S Figure 10: sequential development of fruits till ripening. Scale bar: 1 cm. S Figure 11: fruit morphology. A: Shape and size variations; B: C.S.; C: L.S. S Figure 12: bael rinds. A: Immediately after scraping flesh from ripe fruits; B: dried rinds. S Figure 13: mucilage substance in bael fruits. A: Immediately after collection; B: after four days of air-drying, mucilage became crystalized. S Figure 14: bael seeds. A: Empty (aborted seeds); B: fully developed seeds. S Figure 15: bael plant material for establishment. A: Deedlings; B: budded plants. S Figure 16: bud wood material. A: A branch harvested to obtain bud wood; B: leaves removed; C: close-up view of the bud wood. S Figure 17: bud wood material. A: A branch harvested to obtain bud wood; B: leaves removed; C: close-up view of the bud wood. (*Supplementary Materials*)

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