Anti-Acne Cream Containing Aegle marmelos Leaf Extract: *A Phytopharmaceutical Review and Formulation Approach*

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Abstract- Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit affecting an estimated 80–85% of adolescents and young adults worldwide, driven by four interlinked pathogenic factors: androgen-driven sebaceous hyperactivity, follicular hyperkeratinization, colonization by Cutibacterium acnes (formerly Propionibacterium acnes), and perifollicular inflammation. Long-term use of conventional anti-acne agents — topical retinoids, benzoyl peroxide, and oral/topical antibiotics — is constrained by cutaneous irritation, photosensitivity, and rising antimicrobial resistance, sustaining interest in standardized herbal alternatives. Aegle marmelos (L.) Corrêa (Rutaceae), the Indian Bael tree, is a rich source of furoquinoline alkaloids (aegeline, skimmianine), furanocoumarins (marmelosin, umbelliferone, marmesin), and flavonoids/phenolic acids (rutin, quercetin, gallic and ferulic acids) with documented antioxidant, broad-spectrum antibacterial, anti-inflammatory, and wound-healing activity, and an existing, if limited, precedent in the formulation literature as an anti-acne cream active. This review consolidates the botanical, phytochemical, and pharmacological evidence on A. marmelos leaves as it relates to acne, maps that evidence onto the four-factor acne pathogenesis model, and proposes a Quality-by-Design (QbD) based approach for developing an A. marmelos leaf extract anti-acne cream. A central, and explicitly flagged, evidence gap emerges from this mapping: although A. marmelos extracts show broad-spectrum activity against Staphylococcus aureus, Escherichia coli, Bacillus subtilis, and several dermatophytic fungi, no study identified in this review has directly tested a leaf extract against C. acnes/P. acnes itself, and no dedicated sebostatic, anti-androgen, or comedolytic data exist for the plant. These gaps, together with the absence of human clinical efficacy data, are incorporated as mandatory confirmatory steps within the proposed formulation and quality-control strategy rather than glossed over.

Index-terms: Aegle marmelos; Bael; acne vulgaris; Cutibacterium acnes; furoquinoline alkaloids; marmelosin; anti-acne cream; Quality by Design

1. INTRODUCTION

1.1 Acne vulgaris: clinical burden and current therapeutic landscape

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit and one of the most common skin disorders worldwide, affecting an estimated 70–85% of adolescents and young adults to some degree, with prevalence exceeding 80% among 11- to 30-year-olds; most cases first appear at or shortly after puberty, with girls most often affected between 14 and 17 years and boys between 16 and 19 years. The disease presents along a spectrum from comedonal (blackheads/whiteheads) to inflammatory lesions (papules, pustules, nodules, and cysts) and can leave permanent scarring and post-inflammatory hyperpigmentation, with substantial documented impact on self-esteem and psychosocial wellbeing. Its pathogenesis is now understood as multifactorial, arising from the interaction of four processes: androgen-driven sebaceous gland hyperactivity and excess sebum production; abnormal follicular keratinization leading to microcomedo formation; proliferation and dysbiosis of Cutibacterium acnes within the lipid-rich follicular environment; and a perifollicular inflammatory response involving toll-like receptor (TLR2) and NLRP3 inflammasome activation with release of pro-inflammatory cytokines.

Conventional anti-acne therapy is organized around these same four targets: topical retinoids and salicylic/azelaic acid for comedolysis; benzoyl peroxide and topical/oral antibiotics (clindamycin, doxycycline, erythromycin) for antimicrobial control; hormonal agents (anti-androgens, combined oral contraceptives) for sebum suppression; and anti-inflammatory agents including isotretinoin for severe disease. These remain effective but are limited in practice by cutaneous irritation and dryness, photosensitization, and — of growing concern — antimicrobial resistance arising from prolonged topical and systemic antibiotic use against C. acnes. This safety and resistance profile, combined with rising consumer demand for natural and herbal cosmeceuticals, continues to drive interest in standardized plant-derived antibacterial, anti-inflammatory, and antioxidant actives as adjuncts or alternatives within topical acne formulations.

1.2 Rationale for Aegle marmelos as a candidate active

Aegle marmelos (L.) Corrêa, commonly known as Bael, bili, or the Indian quince (family Rutaceae), is a medicinal tree native to the Indian subcontinent with an extensive history of use in Ayurvedic and traditional medicine. Its leaves are phytochemically rich in furoquinoline alkaloids, furanocoumarins, flavonoids, and phenolic acids, and have independently documented antioxidant, broad-spectrum antibacterial and antifungal, anti-inflammatory, and wound-healing activity — a pharmacological profile that maps plausibly onto two of the four acne-pathogenesis factors described above (microbial colonization and inflammation). A. marmelos already has a limited precedent in the cosmetic-formulation literature: published studies describe herbal anti-acne face washes and body lotions using A. marmelos leaf extract, and at least one published study describes the formulation and evaluation of an anti-acne cream using A. marmelos extract

specifically. As detailed in Section 4, however, the antibacterial evidence base for A. marmelos — while broad — has not, to our knowledge, been generated against C. acnes/P. acnes itself in leaf-extract form, and dedicated sebostatic or comedolytic data are absent altogether. This review treats these as central, explicit evidence gaps rather than incidental limitations.

The objective of this review is therefore twofold: (i) to consolidate the available botanical, phytochemical, mechanistic, and pharmacological evidence on A. marmelos leaves as it pertains to acne vulgaris, mapped explicitly onto the four-factor pathogenesis model; and (ii) to propose a Quality-by-Design (QbD) based formulation approach for an A. marmelos leaf extract anti-acne cream, building on the existing cream-formulation precedent in the literature while identifying the confirmatory studies needed before an anti-acne efficacy claim could be made with confidence.

II. BOTANICAL PROFILE OF AEGLE MARMELOS

Table 1 summarizes the taxonomic classification of the plant, and Figure 1 illustrates the characteristic trifoliate-to-quinquefoliate compound leaf used for macroscopic identification.

Taxonomic rank	Classification
Kingdom	Plantae
Order	Sapindales
Family	Rutaceae
Subfamily	Aurantioideae
Genus	Aegle
Species	marmelos (L.) Corrêa
Common names	Bael, Bel, Bili, Sriphal (Hindi); Bengal quince, golden apple, stone apple, Indian quince (English); Vilwam/Koovalam (Tamil/Malayalam); Maredu (Telugu)

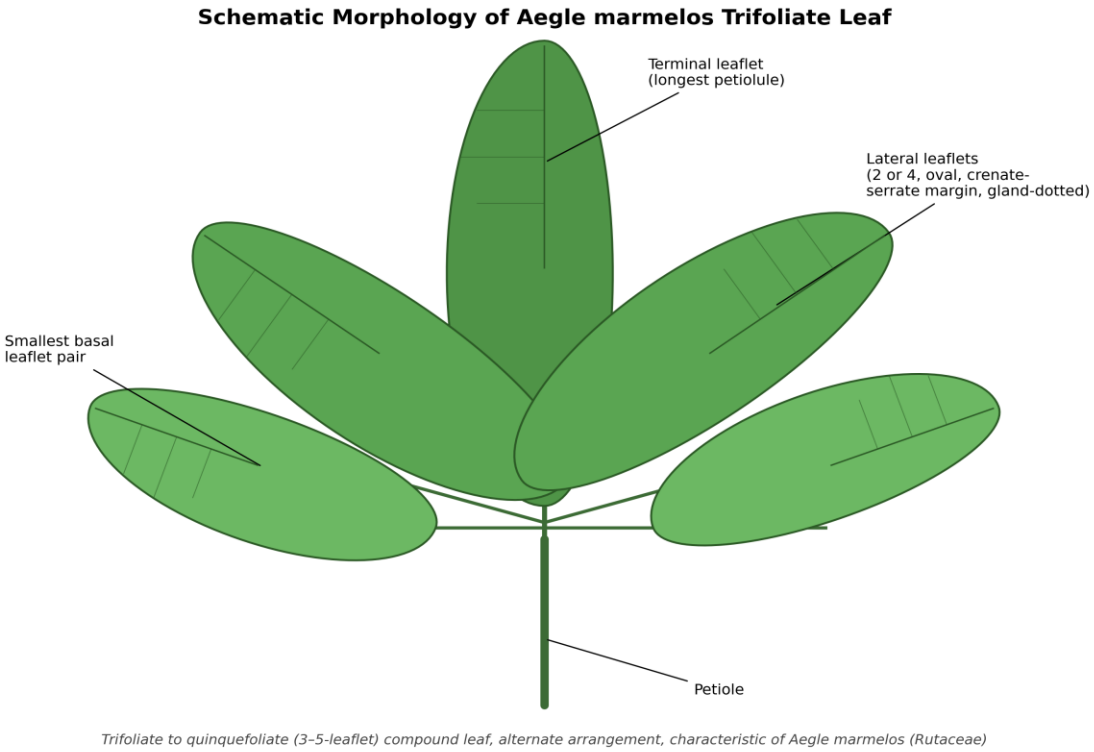

Figure 1. Schematic line diagram of the characteristic trifoliate-to-quinquefoliate (3–5-leaflet) compound leaf of Aegle marmelos. (Original schematic; an authenticated photographic plate of the fresh plant/leaf material should be inserted alongside this figure in the final manuscript.)

Aegle marmelos is a slow-growing, medium-sized deciduous tree reaching 12–15 m in height, with a short trunk, thick soft flaking bark, and spreading, often spiny branches; young suckers bear stiff straight spines. The deciduous, alternate leaves are compound, composed of three to five oval, pointed, shallowly toothed leaflets 4–10 cm long and 2–5 cm wide, with the terminal leaflet borne on a distinctly longer petiole than the lateral leaflets — the trifoliate leaf is, in fact, of religious as well as botanical significance in India, being associated with the worship of Lord Shiva. The plant is native to the Eastern Ghats and central India and grows wild along the sub-Himalayan tract from the Jhelum river eastward to West Bengal, as well as throughout central and southern India; it is also cultivated in Bangladesh, Egypt, Malaysia, Myanmar, Pakistan, Sri Lanka, and Thailand. The tree tolerates a wide pH range (5–8) and poor or stony soils, and is traditionally noted for thriving where other fruit trees cannot survive.

Across Ayurvedic and traditional medicine, virtually every part of A. marmelos — leaves, bark, root, and fruit — has documented therapeutic use, including for digestive disorders, diarrhoea and dysentery, diabetes, fever, and a range of dermatological and ophthalmic conditions; leaf extracts in particular have long been applied topically for skin infections and inflammatory skin conditions, traditional indications that anticipate the antimicrobial and anti-inflammatory pharmacology reviewed in Section 5.

III. PHYTOCHEMISTRY

The bioactivity of A. marmelos leaves derives from four overlapping groups of secondary metabolites: (i) furoquinoline alkaloids, (ii) furanocoumarins and simple coumarins, (iii) flavonoids and phenolic acids, and (iv) a terpene-rich essential oil. As with most medicinal Rutaceae, the relative yield of each group depends strongly on plant part, extraction solvent, and the particular cultivar/accession used — a comparative phytochemical screen of eighteen A. marmelos varieties found the highest alkaloid, flavonoid, and phenol content in the Pant Aparna cultivar, underscoring that "A. marmelos leaf extract" is not a single, fixed chemical entity across the literature.

3.1 Alkaloids

The two most extensively characterized alkaloids from A. marmelos leaves are aegeline (N-[2-hydroxy-2-(4-methoxyphenyl)ethyl]cinnamamide), an N-acylated phenethylamine derivative, and skimmianine (4,7,8-trimethoxyfuro[2,3-b]quinoline), a furoquinoline alkaloid also widely distributed across the Rutaceae. Additional minor alkaloids reported from the leaves include marmeline, dictamine, and several cinnamamide derivatives. Alkaloids as a class are reported to account for a substantial share of the plant's secondary metabolite pool, and plant-derived alkaloids in general are recognized for anti-inflammatory activity through suppression of pro-inflammatory protein complexes; skimmianine itself has documented anti-inflammatory and acetylcholinesterase-inhibitory activity in non-cutaneous models, though it has also shown phototoxicity to some bacteria and yeasts under long-wavelength UV in unrelated Rutaceae species — a property that, while not directly tested for A. marmelos leaf alkaloids, is a reasonable photostability/photosafety consideration for a topical formulation (Section 8.4).

3.2 Coumarins and furanocoumarins

A. marmelos is unusually rich in coumarin derivatives, with marmelosin, marmesin, umbelliferone, marmin, scopoletin, psoralen, imperatorin, and related furanocoumarins reported across different plant parts; marmelosin and koenimbine-type markers are commonly used for HPLC-based quality control of Bael extracts and dietary supplements. Marmelosin in particular has documented anti-inflammatory activity, lowering nitric oxide and TNF-α production, while umbelliferone (7-hydroxycoumarin) is a well-characterized antioxidant and UV-absorbing coumarin already used as a sunscreen ingredient in its own right — a useful complementary property for a topical acne formulation given that several conventional anti-acne actives (retinoids, in particular) increase photosensitivity.

3.3 Flavonoids and phenolic acids

HPLC analysis of A. marmelos leaf extracts has confirmed the presence of gallic acid and rutin as major markers, with quercetin, ferulic acid, and caffeic acid also reported; total phenolic and flavonoid content, quantified against gallic acid and rutin calibration curves respectively, is

comparable to that reported in other studies of the species. These compounds are well-characterized antioxidants and are independently associated with anti-inflammatory and skin-conditioning effects in the broader cosmetic-ingredient literature.

3.4 Essential oil

The essential oil of A. marmelos leaves, twigs, and fruit has been extensively studied since the 1950s and is typically dominated by the monoterpene α-phellandrene (reported as high as 56% in some leaf-oil analyses) together with p-cymene and, in other reports, limonene as the principal marker compound used to authenticate A. marmelos oil samples; the oil itself has documented antibacterial and antifungal activity against several plant and skin-relevant pathogens.

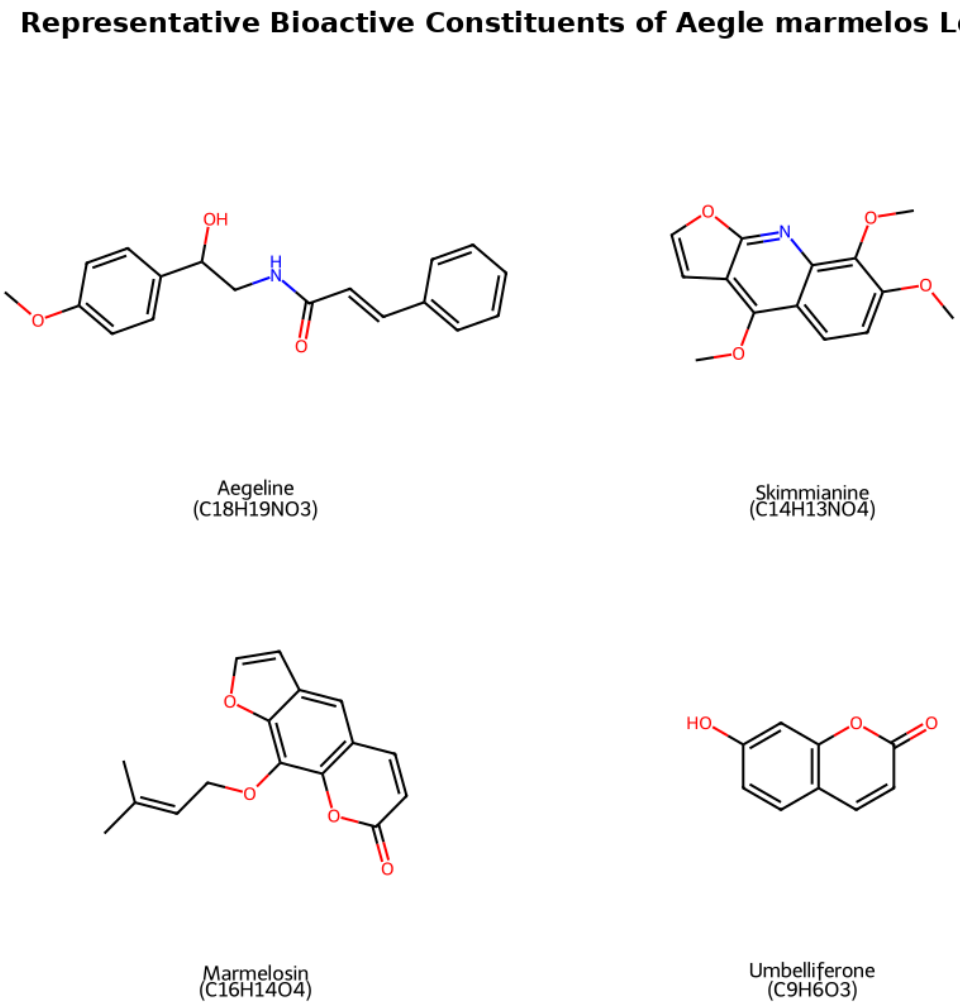

Figure 2. Two-dimensional structures of representative bioactive constituents of Aegle marmelos leaves: the alkaloids aegeline and skimmianine, and the furanocoumarins marmelosin and umbelliferone (structures generated from validated PubChem-deposited SMILES; molecular formulae confirmed against literature/CAS data).

Table 2 summarizes the principal phytoconstituents discussed above together with their reported bioactivity relevant to this review.

Constituent	Class	Reported activity relevant to acne/skin
Aegeline	Phenethylamine alkaloid (cinnamamide)	Major leaf alkaloid; anti-inflammatory, antidiabetic, anti-hyperlipidemic activity reported in systemic models
Skimmianine	Furoquinoline alkaloid	Anti-inflammatory (COX-1/COX-2 interaction reported in silico); acetylcholinesterase inhibitor; potential phototoxicity reported in related species — relevant photosafety caveat
Marmelosin	Furanocoumarin	↓ nitric oxide and TNF-α; used as an HPLC marker compound for extract standardization
Umbelliferone	Simple coumarin	Antioxidant; UV-absorbing (used in sunscreens); antibacterial activity reported
Marmesin, marmin, scopoletin, psoralen	Coumarins/furanocoumarins	Antioxidant and antimicrobial contributions to overall extract activity; some (psoralen) are photosensitizing and relevant to formulation photosafety
Gallic acid, rutin, quercetin, ferulic/caffeic acid	Phenolic acids / flavonoids	Free-radical scavenging (DPPH/FRAP); anti-inflammatory; standard HPLC markers for leaf-extract quality control
Essential oil (α-phellandrene, p-cymene, limonene)	Monoterpenes	Antibacterial/antifungal activity against several pathogens; characteristic aroma; limonene used as an oil-authentication marker

IV. MECHANISTIC BASIS: ACNE PATHOGENESIS AND PROPOSED SITES OF PHYTOCHEMICAL ACTION

4.1 Overview of the four-factor acne pathogenesis model

Contemporary dermatological consensus describes acne vulgaris as arising from the interaction of four pathogenic factors. First, androgens (chiefly testosterone and dihydrotestosterone, acting from puberty onward) drive sebaceous gland hyperactivity and excess sebum production, which both increases ductal hypercornification and provides a nutrient-rich, lipid environment for bacterial

colonization. Second, abnormal keratinization of the follicular infundibulum — with increased keratinocyte proliferation and reduced desquamation — produces the follicular horny plug that constitutes the earliest visible lesion, the microcomedo. Third, the resulting anaerobic, sebum-rich follicular environment favours proliferation of the commensal bacterium Cutibacterium acnes; current evidence suggests it is not bacterial overgrowth per se but a loss of C. acnes phylotype diversity, together with secretion of hydrolytic lipases, proteases, and hyaluronidases, that triggers pathological inflammation. Fourth, this microbial activity — together with hydrolyzed, irritant free fatty acids released from sebum — activates toll-like receptor 2 (TLR2) and the NLRP3 inflammasome in keratinocytes and monocytes, driving the perifollicular inflammatory cascade responsible for the clinically visible papules, pustules, and nodules of inflammatory acne, and ultimately for scarring and post-inflammatory hyperpigmentation. Figure 3 maps this four-factor model against the pharmacological evidence available for A. marmelos leaf extract, factor by factor.

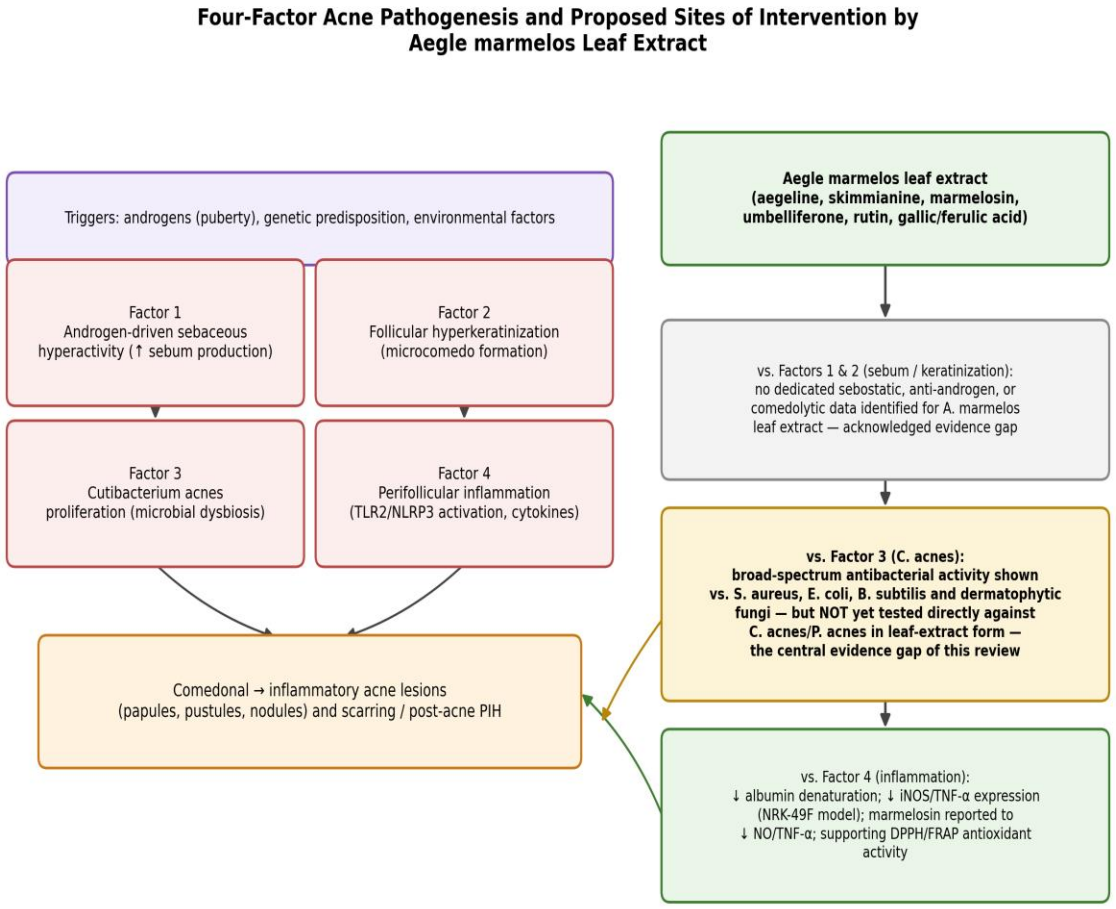

Figure 3. Four-factor acne pathogenesis model (left) and the evidence available for Aegle marmelos leaf extract against each factor (right). The amber box marks the central, explicitly flagged evidence gap of this review: broad-spectrum antibacterial data exist, but not against C. acnes/P. acnes itself.

4.2 Factors 1 and 2: sebum and follicular keratinization — an acknowledged evidence gap

No study identified in the course of this review has evaluated A. marmelos leaf extract for sebostatic activity (e.g., effects on sebocyte lipogenesis or 5α-reductase activity), anti-androgenic activity, or comedolytic activity (e.g., effects on follicular keratinocyte desquamation). This is a genuine and significant gap: two of the four recognized drivers of acne pathogenesis are, at present, simply unaddressed by the available pharmacological literature on this plant. Any anti-acne positioning of an A. marmelos cream should therefore rest on its antimicrobial and anti-inflammatory actions (Factors 3 and 4 below) rather than on an assumed, but currently undemonstrated, effect on sebum production or comedone formation.

4.3 Factor 3: microbial colonization — broad-spectrum evidence, but not against the acne organism itself

A. marmelos leaf extracts have repeatedly demonstrated antibacterial activity in disc-diffusion and MIC/MMC assays against a broad panel of organisms — Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Salmonella paratyphi A/B, Vibrio cholerae, and Pseudomonas aeruginosa — as well as antifungal activity against several dermatophytes (Trichophyton mentagrophytes, Microsporum canis, T. rubrum, Epidermophyton floccosum) using methanolic, aqueous, and petroleum-ether extracts. This is a genuinely broad antimicrobial spectrum, and the activity against skin-relevant dermatophytes in particular is encouraging for a topical dermatological application. However, none of the leaf-extract studies identified in this review tested activity specifically against Cutibacterium acnes (Propionibacterium acnes) or Staphylococcus epidermidis, the two organisms most directly implicated in acne pathogenesis — the organism panels used were chosen for general antimicrobial/antidiarrhoeal screening, not for acne-specific relevance. (A related study using silver nanoparticles synthesized with A. marmelos fruit extract did specifically target P. acnes, but this combines a fruit-derived reducing agent with a metallic nanoparticle active, and is not direct evidence for a plain leaf-extract cream.) Closing this gap with a direct C. acnes/P. acnes susceptibility and MIC study on the specific standardized leaf extract proposed for the cream (Section 6.1) is, in our assessment, the single most important confirmatory experiment needed before an antimicrobial anti-acne claim can be made with confidence — and it is built into the proposed formulation workflow (Section 6.3, Step 3) accordingly.

4.4 Factor 4: perifollicular inflammation — the strongest evidence

The most direct and mechanistically relevant pharmacological evidence for A. marmelos in this context is its anti-inflammatory activity. Leaf extract has reduced albumin denaturation (a standard in vitro anti-inflammatory assay) and, in a normal rat kidney fibroblast (NRK-49F) cell model under high-glucose stress, reduced expression of inducible nitric oxide synthase (iNOS) and tumour necrosis factor-alpha (TNF-α), alongside reduced intracellular reactive oxygen species generation. Separately, marmelosin — one of the plant's principal coumarin markers — has been

specifically reported to lower nitric oxide and TNF-α production, both central mediators of the perifollicular inflammatory cascade described in Section 4.1. These anti-inflammatory findings, together with the antioxidant activity summarized in Section 5, constitute the most defensible pharmacological basis for an A. marmelos anti-acne cream at present, independent of the unresolved Factor 3 question.

V. SUPPORTING PHARMACOLOGICAL EVIDENCE RELEVANT TO SKIN HEALTH

Beyond the acne-specific evidence mapped in Section 4, A. marmelos leaves have a broader pharmacological profile of indirect relevance to a topical cream formulation, particularly for skin barrier repair, oxidative protection, and the management of post-acne sequelae. Table 3 summarizes the principal supporting activities and their caveats.

Activity	Key finding	Relevance / caveat
Antioxidant	DPPH and FRAP assays confirm radical-scavenging activity correlating with total phenolic/flavonoid content; alkaloid content notably high in some accessions	Supports mitigation of inflammation-associated oxidative stress (Factor 4); well replicated across multiple independent studies
Antibacterial (broad-spectrum)	Activity vs. S. aureus, E. coli, B. subtilis, Klebsiella, Proteus, Salmonella, Vibrio, Pseudomonas across leaf, bark, fruit, and root extracts	Plausible but indirect support for Factor 3; NOT yet tested against C. acnes/P. acnes (see Section 4.3) — central gap
Antifungal	Methanol/petroleum-ether leaf extracts active against dermatophytes (T. mentagrophytes, M. canis, T. rubrum, E. floccosum)	Relevant to skin health generally; not specific to acne but supports a general dermatological antimicrobial rationale
Anti-inflammatory	↓ albumin denaturation; ↓ iNOS/TNF-α (NRK-49F model); marmelosin ↓ NO/TNF-α	Directly supports Factor 4 (Section 4.4); the strongest mechanistic evidence available
Wound healing	Methanolic leaf extract accelerated excision/incision wound repair in rats, improving wound contraction, tensile strength, and hydroxyproline content	Supports a skin-barrier-repair rationale for post-acne/post-lesion skin recovery

Activity	Key finding	Relevance / caveat
Antibiofilm (fruit extract)	Methanolic fruit extract disrupted biofilm formation by multidrug-resistant S. aureus; silver nanoparticles from fruit extract specifically targeted P. acnes growth and inflammation	Encouraging precedent, but derived from fruit (not leaf) extract and, in the AgNP study, combined with a metallic nanoparticle component — not directly transferable evidence for a plain leaf-extract cream
Cytotoxicity / systemic safety signals	Some A. marmelos leaf extract preparations have shown cytotoxic and antiproliferative effects in selected systemic/cell-based assays at higher concentrations; aluminium-toxicant-protective and reproductive studies exist for other extract types	Underscores the need for a conservatively chosen topical concentration and dedicated dermal safety testing rather than an assumption of automatic safety because the source is a traditional food/medicinal plant

VI. PROPOSED FORMULATION APPROACH FOR AN AEGLE MARMELOS LEAF EXTRACT ANTI-ACNE CREAM

A directly relevant formulation precedent already exists in the literature: Kumbhar et al. (2020) describe the formulation and evaluation of an anti-acne cream using a 70% ethanolic maceration extract of A. marmelos (in their case, fruit pulp) incorporated at 5–10% w/w into a conventional oil-in-water emulsion base (stearic acid, cetyl alcohol, liquid paraffin, glycerin, triethanolamine, methylparaben), evaluated for pH, homogeneity, spreadability, washability, after-feel, type of smear, and three-temperature stability over two months. This section adapts that precedent specifically to a standardized leaf extract, and builds in the confirmatory C. acnes testing identified as the central gap in Section 4.3.

6.1 Extract selection and standardization

- Plant material and part: authenticated, shade-dried A. marmelos leaves (not fruit pulp, to align the active rationale with the leaf-specific phytochemical and pharmacological evidence reviewed in Sections 3–5).
- Extraction method: hydro-ethanolic maceration or Soxhlet extraction (e.g., 60–70% ethanol–water), broadly following the validated maceration approach used for A. marmelos fruit in the existing cream precedent, concentrated under reduced pressure to a dry extract.
- Standardization marker(s): total phenolic content (Folin–Ciocalteu) and/or a validated HPLC assay for umbelliferone and/or marmelosin, the two most widely used chemical markers for A.

marmelos quality control, so that batch-to-batch variation in alkaloid/coumarin yield (Section 3) does not translate into inconsistent antimicrobial or anti-inflammatory performance.

- Mandatory confirmatory bioassay: each standardized extract batch should be tested for direct antibacterial activity (MIC/MBC) against C. acnes and S. epidermidis specifically, in addition to the routine antioxidant and general antibacterial assays — directly addressing the gap identified in Section 4.3, rather than relying on the plant's activity against unrelated organisms as a proxy.

6.2 Representative formulation composition

Table 4 outlines a representative oil-in-water cream composition, adapted from the published A. marmelos cream precedent and standard topical cream excipient practice.

Phase / role	Representative ingredient(s)	Indicative function
Active	Standardized A. marmelos hydro-ethanolic leaf extract (~5–10% w/w, to be optimized)	Primary antibacterial / anti-inflammatory / antioxidant active
Oil phase — emulsifier	Stearic acid (~4% w/w)	Primary emulsifying agent for the o/w cream base
Oil phase — stabilizer	Cetyl alcohol (~1.6% w/w)	Co-emulsifier; stabilizes the emulsion and improves texture
Oil phase — emollient	Liquid paraffin (~1.6% w/w)	Lubricant/emollient; non-comedogenic grade should be specified
Humectant	Glycerin (~2% w/w)	Moisture retention, improves spreadability
Neutralizer	Triethanolamine (~2% w/w)	Neutralizes stearic acid to complete emulsification
Preservative	Methylparaben (~0.15% w/w)	Microbial stability
Vehicle	Distilled water, q.s.	Aqueous phase

6.3 QbD-based development workflow

Figure 4 outlines the proposed stepwise development workflow, beginning from the Quality Target Product Profile (QTPP) and proceeding through risk assessment, formulation design, and finished-product evaluation to a documented control strategy.

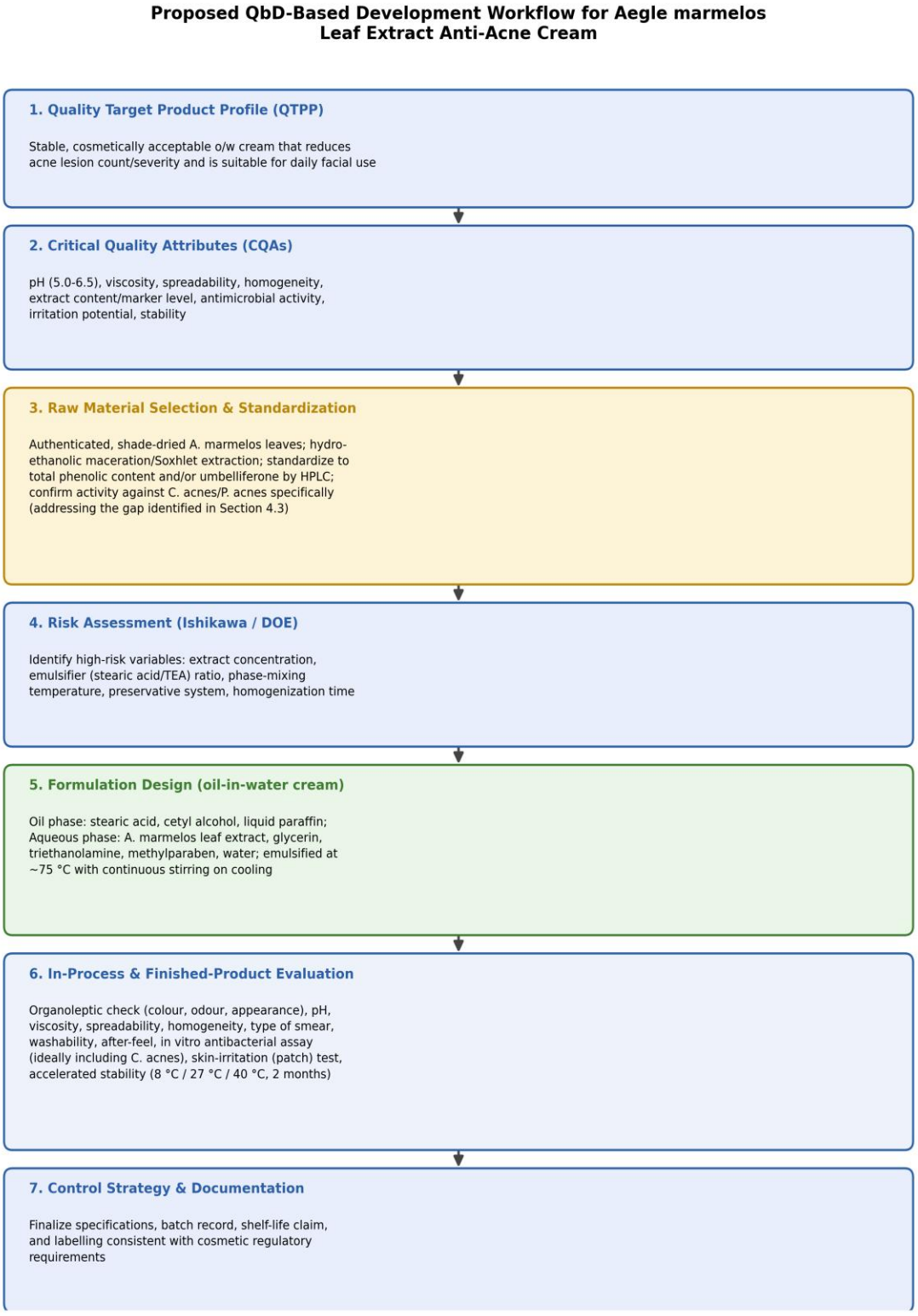

Figure 4. Proposed seven-step Quality-by-Design (QbD) workflow for development of the Aegle marmelos leaf extract anti-acne cream, incorporating the C. acnes-specific confirmatory testing identified in Section 4.3 at the raw-material-standardization step.

6.4 Evaluation parameters

Table 5 lists the evaluation parameters, drawn directly from the published A. marmelos cream precedent and standard topical cream evaluation practice, with the C. acnes-specific addition proposed in this review.

Parameter	Method / acceptance consideration
Physical appearance / colour / odour	Visual and olfactory assessment, graded for pearlescence and roughness
pH	Digital pH meter on a 0.5 g cream sample dissolved in 50 mL water; target 5.0–6.5 to match skin surface pH
Homogeneity	Visual appearance and touch; absence of particulate matter or extract aggregates
Spreadability	Standard parallel-plate spreadability method
After-feel	Emolliency, slipperiness, and residue remaining after application
Type of smear / washability	Visual assessment of film type formed on skin; ease of removal on washing with water
In vitro antioxidant activity	DPPH and/or FRAP assay on the finished cream
In vitro antibacterial activity	Disc-diffusion/MIC against S. aureus and E. coli as routine checks, AND against C. acnes/S. epidermidis specifically (addressing Section 4.3)
Dermal safety	Human repeat-insult patch test on healthy volunteers before any human-use claim
Stability	Storage at three temperatures (e.g., 8 °C, 27 °C, 40 °C) for at least two months, monitoring colour, consistency, pH, and marker-compound content

VII. EXISTING COSMETIC FORMULATION LANDSCAPE

A. marmelos already appears across several published topical cosmetic formulations, providing useful methodological precedent even where the specific plant part or indication differs from the present proposal. A herbal anti-acne face wash combining “Bael Patra” (A. marmelos leaf) with aloe vera, turmeric oil, eucalyptus oil, and other actives has been formulated and evaluated for pH, viscosity, spreadability, foamability, and irritation. A body lotion containing A. marmelos leaf extract has been formulated and stability-tested over three months at accelerated conditions, with primary skin-irritation testing conducted on thirty healthy volunteers. A cream-based exfoliating

scrub using A. marmelos fruit extract and poppy seeds has also been described. Most directly relevant, an anti-acne cream using a 70% ethanolic A. marmelos fruit extract (5–10% w/w) in a conventional stearic-acid-based oil-in-water emulsion has been formulated and evaluated, reporting a pleasant odour, good consistency and spreadability, easy washability, a non-greasy smear, and stability over two months at three storage temperatures — the direct methodological template adapted in Section 6 of this review. Across this body of work, however, antimicrobial confirmation specifically against C. acnes/P. acnes in a leaf-extract cream has not been reported, and no randomized human efficacy trial for any A. marmelos anti-acne formulation was identified, leaving room for a more rigorously substantiated product.

VIII. RESEARCH GAPS AND CHALLENGES

8.1 No direct evidence against the acne-causative organism

As established in Section 4.3, the antibacterial evidence base for A. marmelos leaf extract, while broad, has not been generated against C. acnes/P. acnes or S. epidermidis specifically. This is the single most important gap to close before an antimicrobial anti-acne claim can be substantiated, and Section 6.1 builds a direct confirmatory MIC/MBC assay against these organisms into the proposed quality-control strategy.

8.2 No sebostatic, anti-androgen, or comedolytic data

Two of the four recognized drivers of acne — excess sebum production and follicular hyperkeratinization — are entirely unaddressed by the current pharmacological literature on A. marmelos. Any claim that the proposed cream acts on these factors would be unsupported; the formulation's rationale should rest explicitly on its antimicrobial-adjacent and anti-inflammatory evidence (Sections 4.3–4.4) until dedicated sebocyte or comedolysis studies are conducted.

8.3 Cultivar and extraction variability

Phytochemical yield in A. marmelos varies meaningfully by cultivar/accession (e.g., the Pant Aparna variety showing the highest alkaloid, flavonoid, and phenolic content among eighteen varieties screened) and by extraction solvent (aqueous extract most active against S. epidermidis in one comparative study; methanolic extract most active against S. aureus in the same study). This reinforces the necessity of marker-compound-based release testing (Section 6.1) rather than reliance on unstandardized raw leaf material.

8.4 Photosafety of furanocoumarin/alkaloid constituents

Several A. marmelos constituents — psoralen most notably, and potentially skimmianine by analogy with related furoquinolines — belong to chemical classes recognized for photosensitizing or phototoxic potential under UV-A exposure. While this has not been specifically demonstrated for an A. marmelos leaf-extract cream, it is a reasonable and so-far unaddressed safety

consideration for a topical product intended for facial use, and should be assessed (e.g., via a phototoxicity assay on the standardized extract) alongside the routine dermal safety testing in Section 6.4.

8.5 Absence of clinical efficacy data

No randomized controlled trial evaluating any A. marmelos-based topical formulation for acne vulgaris in human subjects was identified in this review. All supporting pharmacological evidence is preclinical — in vitro antibacterial/antioxidant/anti-inflammatory assays, a single rodent wound-healing model, and traditional-use observation. A controlled clinical study using standardized lesion counting (comedone, papule, pustule counts) and a validated severity scale over a defined treatment period would be required before an efficacy claim could be substantiated.

IX. FUTURE PROSPECTS

- Direct C. acnes susceptibility testing: the single highest-priority next study, using the standardized leaf extract proposed in Section 6.1 against clinical C. acnes isolates, ideally including biofilm-disruption assays given the recognized role of C. acnes biofilms in treatment resistance.
- Sebocyte and comedolysis models: in vitro sebocyte lipogenesis assays and ex vivo or reconstructed-epidermis comedolysis models would directly address the Factor 1/2 gap identified in Section 4.2 and Section 8.2.
- Nanocarrier-based delivery: encapsulation of the standardized extract in nanoemulsions or phytosomes — already explored for A. marmelos fruit extract in a silver-nanoparticle gel context — could improve dermal penetration and stability of the coumarin/alkaloid actives while potentially mitigating any photosensitizing risk through controlled release.
- Controlled clinical evaluation: an 8–12-week randomized, controlled study using standardized lesion counts, a validated acne severity grading scale, and dermatologist/subject global assessment would be the appropriate next step toward a substantiated efficacy claim, following designs already established for other topical anti-acne actives.

X. CONCLUSION

Aegle marmelos leaves present a phytochemically well-characterized and traditionally well-supported, but mechanistically incomplete, candidate active for a topical anti-acne cream. The plant's anti-inflammatory and antioxidant pharmacology provides the most direct and credible support among the four recognized acne-pathogenesis factors, and an existing, if fruit-derived, cream-formulation precedent confirms practical cosmetic feasibility. However, this review has also identified a genuine and consequential evidence gap: despite broad-spectrum antibacterial activity against numerous non-acne organisms, A. marmelos leaf extract has not, to our knowledge, been directly tested against Cutibacterium acnes or Staphylococcus epidermidis, and no sebostatic,

anti-androgen, or comedolytic data exist for the plant at all. Rather than treating these as minor caveats, this review has built them into the proposed QbD-based formulation approach as mandatory confirmatory steps — specifically, direct C. acnes/S. epidermidis susceptibility testing of the standardized extract batch, alongside the routine physicochemical, antioxidant, and stability evaluation already established in the existing A. marmelos cream literature. With these confirmatory studies completed, together with resolution of the cultivar-standardization, photosafety, and clinical-evidence gaps identified in Section 8, A. marmelos leaf extract represents a scientifically plausible, though not yet clinically proven, candidate for further development as a herbal anti-acne cream.

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