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Formulation , development and evaluation of a novel polyherbal anti-acnegel

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ABSTRACT :

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit involving follicular hyperkeratinisation, sebum production, *Cutibacterium acnes*-associated processes and inflammation[1–3]. Interest in plant-based topical products is growing, but laboratory activity must not be confused with clinical efficacy [2,4]. This review critically examines the evidence relevant to neem (*Azadirachta indica*), turmeric (*Curcuma longa*), aloe vera (*Aloe barbadensis* Miller) and tulsi (*Ocimum tenuiflorum*) as proposed components of a polyherbal anti-acne gel. Evidence for neem and tulsi is mainly review-level, in vitro or formulation-level; turmeric has a broader skin-health literature but limited acne-specific clinical data; and aloe vera has limited clinical support as an adjunct to tretinoin, not as a stand-alone treatment [5,6]. Published herbal gel studies mostly report physicochemical properties, while extract standardisation, microbiological methods and tolerability testing are often insufficiently documented[7–10]. No verified study has demonstrated synergy among the four plants, so the combination is best treated as a research hypothesis. We outline formulation, evaluation and stability requirements and the research needed before therapeutic claims can be made.

Keywords: Acne Vulgaris, Polyherbal Formulation, *Azadirachta indica*, *Curcuma longa*, Aloe Vera, *Ocimum tenuiflorum*, Topical Gel, Evidence Appraisal

GRAPHICAL & EXECUTIVE HIGHLIGHTS

- **Evidence Hierarchy:** Neem and tulsi data are mainly in vitro, review-level or formulation-level; no verified controlled clinical acne trial exists for either alone [11–13].
- **Turmeric & Aloe:** Curcuminoids show anti-inflammatory and antioxidant rationale but unclear acne-specific clinical results; aloe has been tested clinically only as a tretinoin adjunct [5,6].
- **Synergy Unproven:** No verified study has tested additive, synergistic or antagonistic effects of the exact four-herb combination [3,14].
- **Formulation Reality:** Published gel studies report appearance, pH, viscosity and spreadability; these cannot establish anti-acne efficacy or safety [7–10].
- **Roadmap:** Standardised extracts, compatibility and stability studies, validated antimicrobial assays, skin-tolerability testing and controlled trials are required [3,4].

INTRODUCTION

Acne vulgaris is a common, chronic inflammatory disorder of the pilosebaceous unit that mainly affects adolescents and young adults. Beyond active lesions, it may cause post-inflammatory change, scarring and psychosocial burden [2,3]. Pathogenesis is multifactorial, involving altered follicular keratinisation, sebum production, *C. acnes*-associated processes and inflammatory responses rather than infection alone [1,3].

Clinical expression ranges from non-inflammatory comedones (open and closed) to inflammatory papules, pustules and nodules. Lesions concentrate on the face, chest and upper back, where pilosebaceous units are numerous and sebaceous activity is high. Severity is commonly graded as mild, moderate or severe, and this grading guides the choice between topical and systemic therapy. Because acne often persists for years and may leave pigmentary change or scars, early and well-tolerated treatment is an important goal, and the effect on self-esteem and quality of life can be considerable [2,3].

Standard treatment includes topical retinoids, benzoyl peroxide and topical antibiotics, with systemic therapy chosen by severity. Selection must weigh tolerability, contraindications and antimicrobial stewardship. These limitations have encouraged research into plant-derived ingredients [15–17]; however, traditional use or in vitro antimicrobial activity does not establish clinical benefit or safety [2,4].

Each conventional topical option has practical limitations. Retinoids and benzoyl peroxide commonly cause dryness, erythema and burning during the first weeks of use; topical antibiotics are generally advised in combination with other agents rather than alone because of concern about bacterial resistance; and adherence tends to fall when treatment is irritating or slow to act. These concerns explain why plant-derived adjuvants for mild acne are

widely investigated [15,16], although patient acceptability of a natural product must not be confused with proof that it works [4].

A gel is an attractive dosage form for acne-prone skin. Hydrogels are transparent or translucent, non-greasy, easy to spread and wash off, and give a cooling feel; compared with creams and ointments they leave little occlusive residue on oily skin. A hydrophilic gel base can also carry aqueous or hydroalcoholic herbal extracts, which makes the form convenient for botanical preparations. The same water-rich character, however, creates a risk of microbial contamination and limits the incorporation of lipophilic constituents, points that recur throughout this review.

Neem, turmeric, aloe vera and tulsi have been proposed for a topical polyherbal gel because of reported antimicrobial, anti-inflammatory, antioxidant or soothing effects. The central question is whether current evidence supports investigating them together in one dosage form. This review summarises acne biology, appraises the evidence for each plant, considers formulation and evaluation requirements, and identifies research gaps. It does not report experimental results for a newly formulated gel.

Approach of this review. This is a narrative, critical appraisal of 21 sources comprising systematic and narrative reviews, a Cochrane review, one randomised clinical trial, in vitro studies, medicinal-chemistry papers and small herbal gel formulation studies. Findings were classed on a simple evidence hierarchy: (i) controlled clinical data in acne; (ii) systematic or narrative reviews that summarise clinical or preclinical work; (iii) in vitro or mechanistic data; and (iv) formulation-level reports in which the physical characteristics, and sometimes laboratory antimicrobial activity, of a herbal gel are described. Higher levels were given more weight, and statements of efficacy were restricted to what the study design can support. Wording such as “identified” refers only to the sources reviewed here and not to an exhaustive database search.

PATHOPHYSIOLOGY OF ACNE & TARGETS FOR TOPICAL INTERVENTION

Acne lesions arise from interacting processes. Follicular hyperkeratinisation promotes obstruction and comedone formation; sebum creates a follicular environment favourable to microbial growth; *C. acnes* interacts with the host and may form biofilms; and inflammatory pathways, including macrophage-mediated responses, drive papules, pustules and nodules and contribute to scarring [1,3]. Because these processes are related but distinct, antimicrobial action alone is unlikely to address every aspect of acne.

A herbal ingredient may be relevant through antimicrobial or anti-inflammatory activity, antioxidant effects or improved skin comfort. However, the reviewed sources did not establish direct sebum-regulating or comedolytic activity for the four selected plants. A multi-ingredient rationale is therefore a hypothesis to test, not evidence of effectiveness.

Follicular hyperkeratinisation and comedone formation

In a normal follicle the keratinocytes of the infundibulum are shed and cleared together with sebum. In acne this process is altered: cells become more cohesive and proliferate, producing a keratin and lipid plug that distends the follicle and forms the microcomedone, the earliest recognised lesion. Open and closed comedones develop from this lesion and may later evolve into inflammatory lesions [1,3]. A topical product intended to act at this stage would need to reach the follicular opening and influence keratinocyte behaviour, an activity that was not established for the four plants in the reviewed sources.

Sebum and the follicular microbiome

Androgen-driven sebum production rises at puberty and supplies the lipids that support the follicular microbiota. *Cutibacterium acnes*, formerly *Propionibacterium acnes* and still reported under that name in older studies [13], is a lipophilic Gram-positive bacterium that belongs to the normal skin flora. Acne is associated less with the mere presence of the organism than with changes in its activity, its growth in biofilm-like communities and the response of the host [1,3]. This is one reason why a reduction in bacterial counts in a laboratory assay does not by itself predict a reduction in lesions.

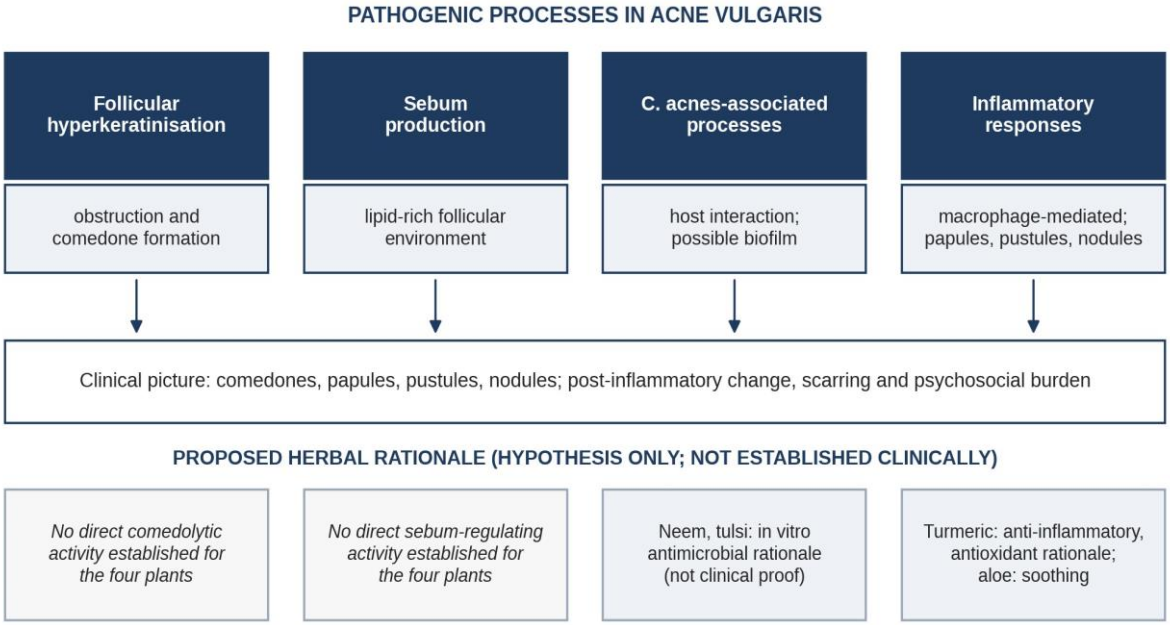
Inflammation and the host response

Components and metabolites of *C. acnes* can be recognised by innate immune receptors on keratinocytes and on monocytes and macrophages, leading to the release of inflammatory mediators and the recruitment of further immune cells. Macrophages take part in phagocytosis, in amplifying inflammation and in the tissue remodelling that leads to scarring [1]. Targeting inflammation is therefore a legitimate aim for a topical product, but anti-inflammatory activity measured in cells or in chemical assays must be shown to translate into reduced lesion counts in people [3].

Implications for topical herbal intervention

The processes above suggest three questions for any herbal gel: whether the active constituent reaches the pilosebaceous unit rather than remaining on the skin surface; whether the proposed activity (antimicrobial, anti-inflammatory, antioxidant or soothing) is relevant to the lesion type being treated; and whether the vehicle itself is non-comedogenic and non-irritating. Irritation deserves particular attention because inflamed skin may worsen with sensitising ingredients and post-inflammatory pigmentation can follow. Figure 1 summarises the main pathogenic processes and the hypothesised herbal rationale for each.

FIGURE 1: PATHOGENIC PROCESSES IN ACNE AND THE PROPOSED HERBAL RATIONALE



Schematic prepared for this review from the processes described in Section 2[1,3]. The lower row states the rationale reported for the four plants and is a hypothesis to be tested, not evidence of clinical effect.

PHYTOCHEMISTRY AND PHARMACOLOGICAL RATIONALE

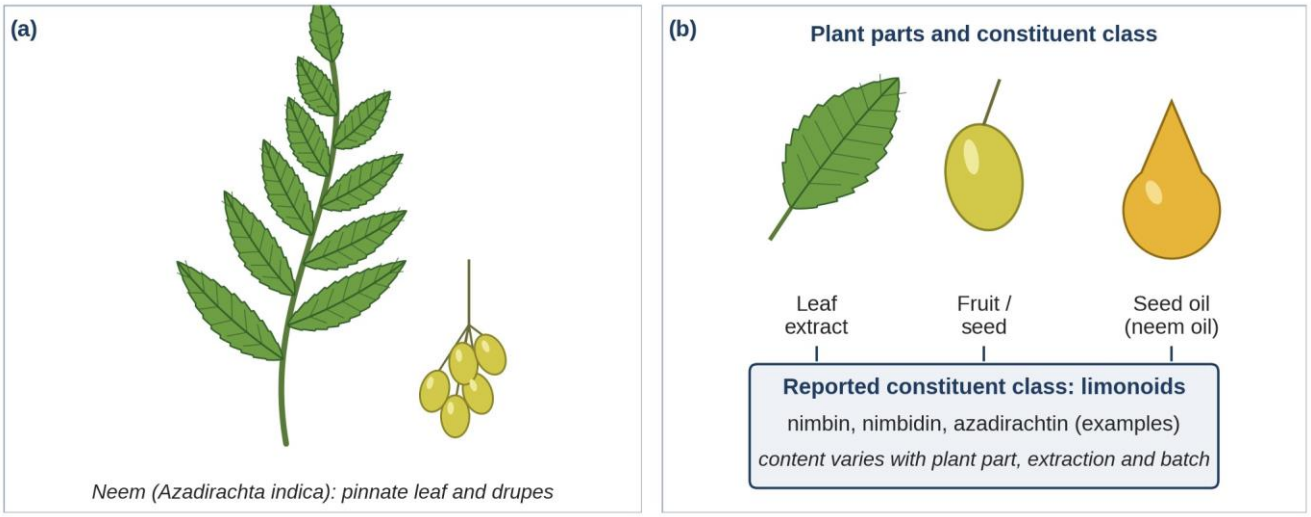
The four plants selected for the proposed gel belong to different botanical families and supply different kinds of material: leaf, seed oil or bark (neem), rhizome (turmeric), leaf gel and latex (aloe vera) and leaf or essential oil (tulsi). Their constituent profiles are therefore not interchangeable. Figures 2 to 5 present each plant together with a representative constituent or constituent class. The illustrations are schematic drawings prepared for this review and are not photographs of authenticated specimens.

Azadirachta indica (Neem)

Azadirachta indica A. Juss. (family Meliaceae) is a fast-growing evergreen tree native to the Indian subcontinent and now cultivated across the tropics. It bears pinnate leaves with serrate leaflets, small white fragrant flowers in panicles and olive-like drupes whose seeds yield neem oil. In Ayurvedic practice leaf, bark and seed preparations have long been applied to the skin, which accounts for the interest in neem for acne and other dermatoses [11,12]. Neem is discussed in dermatology and dermocosmetic reviews for traditional topical use and reported antimicrobial activity [11,12]. Limonoids such as nimbin, nimbidin and azadirachtin are frequently cited, but their presence and concentration depend on plant part, extraction method and batch and must not be assumed without analytical characterisation. Acne-specific evidence is mainly in vitro or formulation-level. Neem has been included in multi-herb gels, often with turmeric [7–10], but its individual contribution cannot be isolated in such products. No verified controlled clinical trial of neem alone for acne was identified. A report of rash associated with neem oil further shows that tolerability is preparation-dependent and needs product-specific evaluation [18].

For gel development the choice of plant part decides the chemistry. Aqueous or hydroalcoholic leaf extracts are comparatively hydrophilic, whereas neem seed oil is lipophilic, has a strong characteristic odour and is not readily miscible with a hydrogel without a surfactant or emulsifying system. The reported rash with neem oil [18] is a reminder that crude oils and concentrated extracts should not be assumed to be benign on inflamed skin. A neem extract intended for a leave-on gel should therefore be characterised by plant part, solvent, extraction ratio and at least one marker class, and its irritation potential should be tested at the intended concentration. Because neem in the published gels was combined with other herbs [7-10], dose–response data for neem itself are missing.

FIGURE 2: NEEM (AZADIRACHTA INDICA): PLANT MATERIAL AND REPORTED CONSTITUENT CLASS



Schematic illustration. Limonoids are named as reported in dermatology and dermocosmetic reviews [11,12]; their content depends on plant part, extraction method and batch.

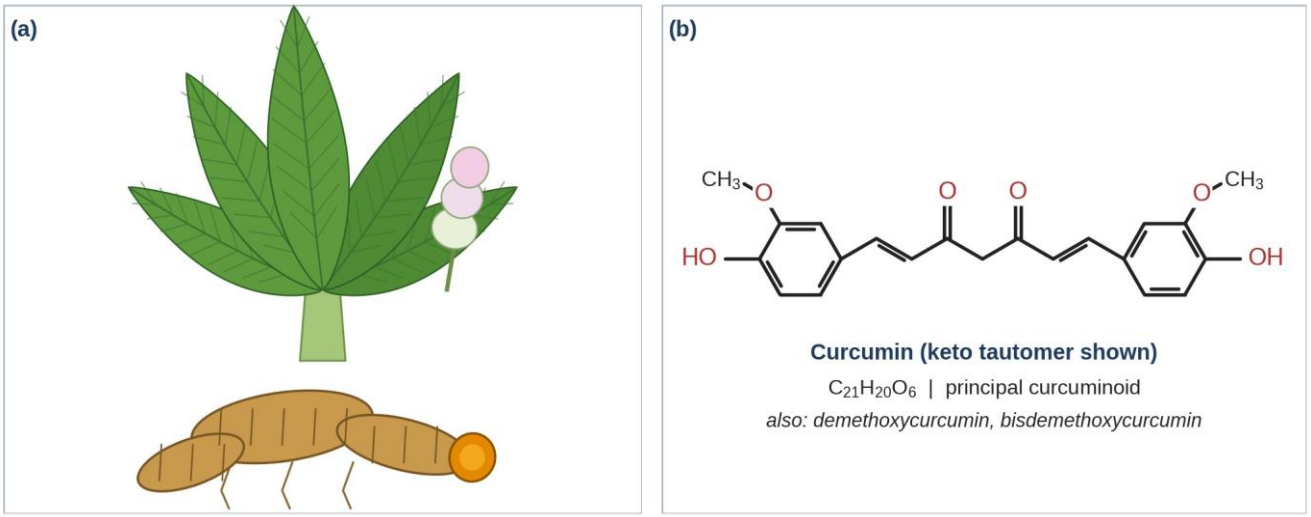
Curcuma longa (Turmeric)

Curcuma longa L. (family Zingiberaceae) is a perennial herb propagated by rhizomes, which are boiled, dried and powdered to give turmeric, the spice and dye of South Asian cuisine and traditional medicine (Sanskrit *haridra*). The orange-yellow colour of the rhizome is due mainly to its curcuminoids, and the rhizome also contains a volatile oil rich in sesquiterpenes. These two fractions differ in polarity and volatility and are recovered by different extraction methods [6,14].

Turmeric contains curcuminoids, including curcumin, demethoxycurcumin and bisdemethoxycurcumin. Reviews describe anti-inflammatory, antioxidant and antimicrobial properties, but these mechanisms are not proof that a turmeric gel reduces acne lesions [6,14]. A systematic review of human studies covered multiple skin conditions, with acne among them, but the accessible summary did not provide condition-specific results sufficient to establish efficacy for a topical anti-acne gel [6].

Curcumin also poses formulation challenges: poor aqueous solubility, chemical stability concerns and intense colour [19,20]. Its behaviour in a water-rich gel (precipitation, colour change, uniformity, stability) must be evaluated in the intended vehicle, and evidence from other skin conditions should not be extrapolated directly to acne.

FIGURE 3: TURMERIC (CURCUMA LONGA): RHIZOME, LEAVES AND THE PRINCIPAL CURCUMINOID



Schematic illustration. Curcumin is drawn in its keto tautomer; the curcuminoid fraction also contains demethoxycurcumin and bisdemethoxycurcumin [6,14]. The cut surface of the rhizome shows the characteristic orange interior.

The medicinal-chemistry literature draws attention to the chemical instability of curcumin, its tendency to interfere with assay readouts, and its low aqueous solubility and poor systemic bioavailability [19,20]. Two consequences matter for this review. First, activity seen in a biochemical or cell-based assay should be interpreted with caution, because compounds of this type can give apparently positive results through non-specific mechanisms. Second, in a topical gel poor solubility means that curcuminoids may be present as suspended or precipitated material rather than in solution, which affects

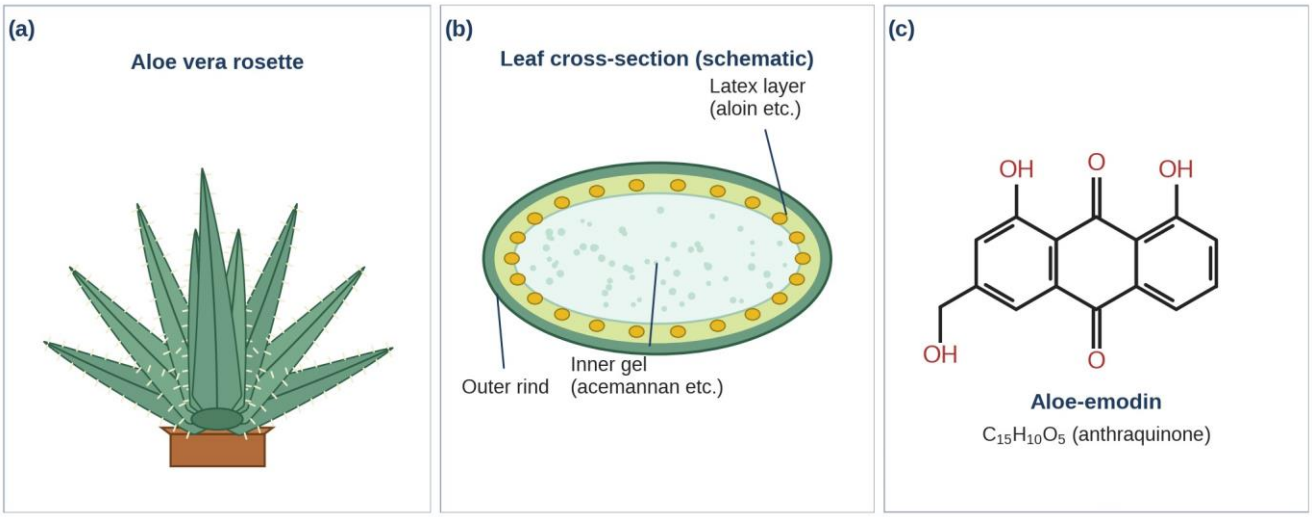
uniformity, colour and release. The intense yellow colour also stains skin, clothing and packaging, and the colour of curcumin is pH-dependent, shifting towards orange-red in alkaline media. pH control, light-protective packaging and monitoring of colour during storage therefore form part of stability testing.

Aloe barbadensis Miller (Aloe Vera)

Aloe barbadensis Miller (also treated as *Aloe vera* (L.) Burm.f.; family Asphodelaceae) is a succulent perennial with a rosette of thick, lance-shaped leaves with spiny margins. Two materials are obtained from the leaf and should not be confused: the clear, mucilaginous inner gel, rich in water and polysaccharides, and the yellow latex of the outer leaf layer, which is rich in anthraquinone derivatives such as aloin [21]. Topical products are generally based on the inner gel, and purified or decolourised preparations are commonly used to limit the anthraquinone content.

Aloe vera is widely used for skin-soothing and wound-related applications. Its constituents vary with plant material and processing; the literature discusses aloin, aloe-emodin, aloesin and polysaccharides such as acemannan [21]. General soothing or wound-healing evidence does not itself establish anti-acne efficacy. The most directly relevant clinical evidence is an 8-week randomised, double-blind trial (60 participants) of aloe vera gel combined with tretinoin in mild-to-moderate acne [5]. Because aloe was combined with a conventional treatment, the study does not show that aloe alone is effective, nor does it test a four-plant gel. If fresh aloe gel is used, batch variability, microbial quality, preservative effectiveness and polymer compatibility require attention.

FIGURE 4: ALOE VERA (ALOE BARBADENSIS MILLER): ROSETTE, LEAF ANATOMY AND ALOE-EMODIN



Schematic illustrations. Panel (b) shows the inner gel and the latex-bearing cells near the rind; anthraquinones such as aloin and aloe-emodin belong to the latex fraction, whereas acemannan is a gel polysaccharide [21].

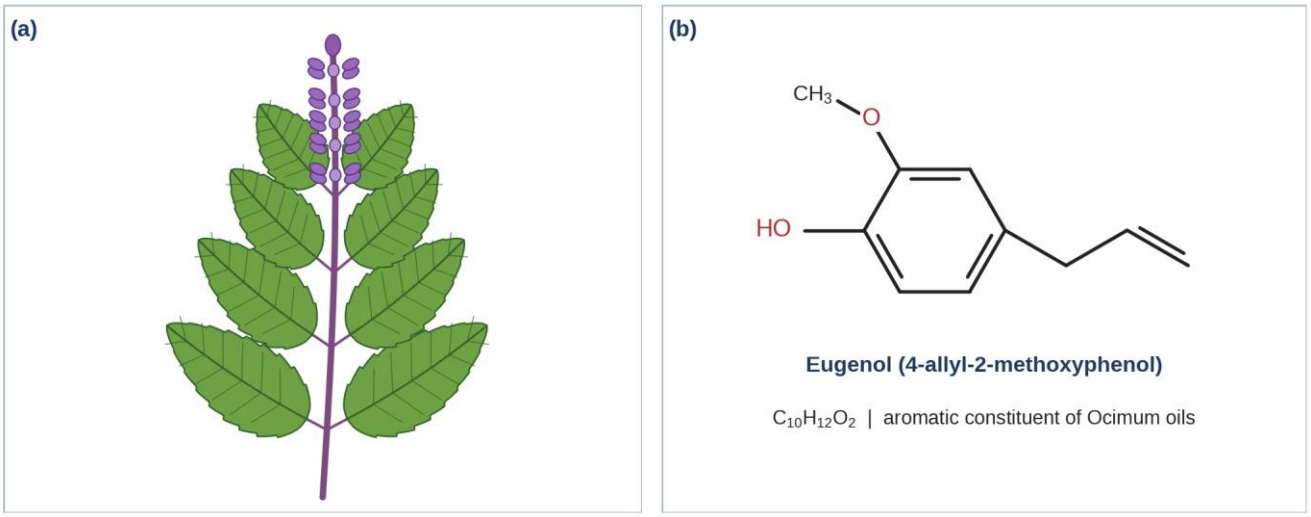
Aloe gel is largely water. It contributes hydration and a soothing feel, but it is also an excellent medium for microbial growth. Fresh gel is variable and prone to enzymatic and oxidative change after harvest, and its polysaccharide viscosity can fall with storage, heat or contamination, so a stabilised gel or powder of defined quality may be preferable to fresh pulp when reproducible batches are required [21]. Aloe polysaccharides can also interact with the gelling polymer and with electrolytes and alter viscosity, so compatibility should be tested before the base is fixed. The use of aloe alongside tretinoin [5] is consistent with a soothing or supportive role, but the trial design does not allow that role to be separated from any direct effect on acne.

Ocimum tenuiflorum (Tulsi)

Ocimum tenuiflorum L. (family Lamiaceae), known as holy basil or tulsi, is an aromatic, branching herb of the Indian subcontinent that is widely grown for religious and medicinal use. Glandular trichomes on the leaves store an essential oil in which phenylpropanoids such as eugenol and sesquiterpenes such as β-caryophyllene are commonly reported; the proportions vary with species, cultivar, harvest and extraction method [13].

Tulsi (synonym *O. sanctum*) must be distinguished from other *Ocimum* species such as *O. gratissimum* and *O. basilicum*; essential-oil composition varies with species, plant part, origin and extraction method. An in vitro study reported activity of holy basil essential oil against the organism then called *Propionibacterium acnes* [13]; this concerns a particular essential oil and does not establish activity of an aqueous or hydroalcoholic extract in a gel. Tulsi appears in some multi-herb formulations [7,9], but its contribution cannot be separated when several ingredients are combined. No controlled clinical trial of tulsi for acne was identified. Eugenol-containing preparations may raise sensitisation concerns, so the final extract and formulation require tolerability testing.

FIGURE 5: TULSI (OCIMUM TENUIFLORUM): LEAFY FLOWERING SPRIG AND EUGENOL



Schematic illustration. Eugenol is shown as a representative aromatic constituent of Ocimum essential oils; its proportion in any extract or oil must be measured, not assumed [13].

Because essential oil is lipophilic it cannot simply be stirred into an aqueous gel. It needs solubilisation, for example with a surfactant or co-solvent, or formulation as a microemulsion, the approach examined for basil oils against *C. acnes* (then *P. acnes*) in vitro [13]. Volatile constituents may also be lost during processing or storage. If an aqueous or hydroalcoholic leaf extract is used instead, its chemistry will differ from that of the oil, and in vitro oil data cannot be transferred to it. Patch testing of the finished gel at the intended extract level is a minimum safety step.

Comparative tolerability considerations

Herbal origin does not exclude irritation or allergy, and the four plants raise different issues. Neem oil has been associated with rash [18]; eugenol-containing tulsi preparations may sensitise; turmeric stains and its colour can complicate the visual assessment of erythema; and aloe-containing products may carry anthraquinone residues if the latex is not removed [21]. Tolerability must also be evaluated for the whole finished gel, because excipients such as preservatives and polymers can themselves irritate. Finished-product testing, rather than inference from the history of use of each ingredient, is the appropriate standard.

TABLE 1: COMPARATIVE EVIDENCE FOR THE FOUR PROPOSED PLANTS

Species	Reported Constituents / Rationale	Evidence Relevant to Acne	Main Limitations
A. indica (Neem)	Limonoids (nimbin, nimbidin, azadirachtin); antimicrobial and anti-inflammatory potential [11,12].	Review-level, in vitro and multi-herb formulation reports [7–10].	Variable extracts; neem's contribution not isolable; limited verified clinical evidence.
C. longa (Turmeric)	Curcuminoids; anti-inflammatory and antioxidant mechanisms [6,14].	Skin-health reviews and formulation-level reports [6].	Acne-specific clinical findings unclear; poor solubility, stability and colour [19-20] .
A. barbadensis (Aloe)	Polysaccharides (acemannan) and others; hydration and soothing rationale [21].	Limited clinical evidence as a tretinoin adjunct[5]; used in gels.	Adjunct data do not establish aloe alone or the combination; water-rich gel needs microbial control.
O. tenuiflorum (Tulsi)	Eugenol and caryophyllene in essential oil; in vitro antimicrobial rationale.	In vitro essential-oil study [13]; multi-herb formulation reports [7,9].	Oil findings may not translate to other extracts; no controlled clinical acne trial identified.

CRITICAL APPRAISAL OF THE SYNERGY HYPOTHESIS

A multi-ingredient gel may merit investigation because acne involves several interacting processes and the ingredients have different reported activities. Neem and tulsi are discussed mainly for antimicrobial activity; turmeric for anti-inflammatory and antioxidant properties; and aloe vera for hydration and soothing characteristics of the vehicle. This is a conceptual rationale only.

No verified source tested whether the exact combination acts additively, synergistically or antagonistically. The presence of several plants does not itself demonstrate synergy, superior efficacy or fewer adverse effects. Such claims require suitable single-ingredient and combination controls, matched concentrations and validated outcomes.

Formulation interactions also need study: coloured or polyphenol-rich extracts may alter colour or pH; poorly soluble curcuminoids may precipitate; extracts can alter polymer behaviour; and botanical variability may reduce batch reproducibility. Extract type, plant part, solvent and concentration should be justified and documented. The reviewed evidence does not establish an optimal concentration for the proposed gel.

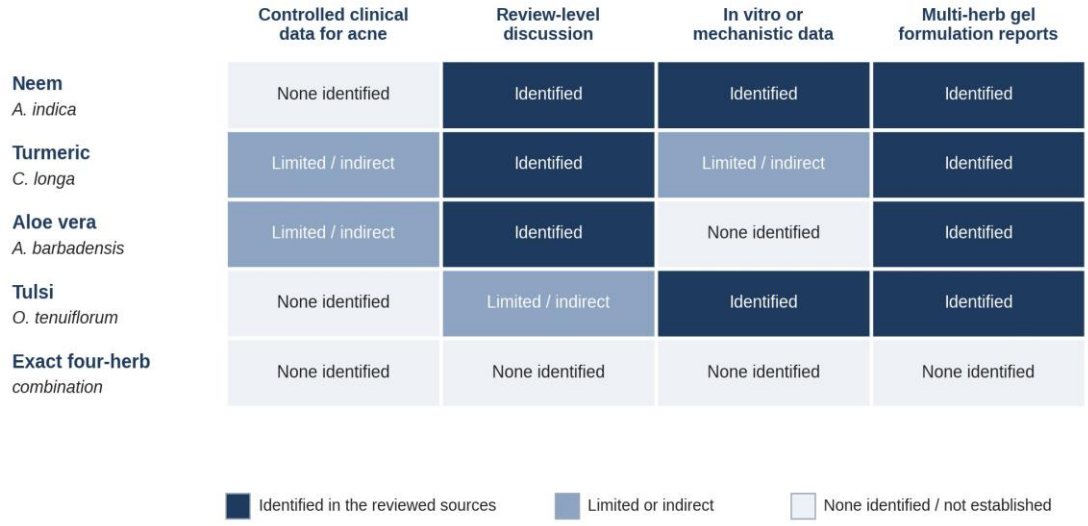
How interaction between extracts can be tested

An interaction between extracts is classed as additive (the combined effect equals the sum of the individual effects), synergistic (greater than additive) or antagonistic (less than expected). In antimicrobial work the checkerboard microdilution assay and the fractional inhibitory concentration index (FICI) are widely used: an FICI of 0.5 or lower is conventionally taken as synergy, values above 0.5 and up to 4 as additive or indifferent, and values above 4 as antagonism. Isobolograms and time-kill assays give complementary information, and comparable combination designs can be applied to anti-inflammatory endpoints. Each extract must first be tested alone over a range of concentrations, because an interaction can only be judged against the dose–response curves of its components. As noted above, no verified source has applied such a design to the exact four-herb combination.

Plausible mechanisms of interaction

Plausible interactions are chemical (complexation between polyphenols and the polymer or polysaccharides, and pH shifts that change ionisation), physical (precipitation of curcuminoids, changes in viscosity or loss of volatile oil) and biological (additive or opposing effects on the same pathway). Each of these can lower as well as raise performance, which is why compatibility screening precedes biological testing in the proposed workflow (Figure 7). Figure 6 summarises, in qualitative terms, where the evidence for each plant sits and shows that the exact combination has not been examined at any level.

FIGURE 6: QUALITATIVE SUMMARY OF THE EVIDENCE CATEGORIES FOR EACH PLANT AND THE COMBINATION



Prepared from the evidence discussed in Sections 3 and 7, Table 1 and Table 3 [3,4]. "Identified" means that reports exist in the reviewed sources; it does not mean that they demonstrate efficacy.

PHARMACEUTICAL DEVELOPMENT CONSIDERATIONS

This section outlines development principles, not a finished formula. General material categories include a gelling agent, humectant, preservative, pH-adjusting agent and purified water, but the literature does not establish a validated composition or optimal concentrations.

Botanical Material and Extraction

Botanical materials should be authenticated, and plant part, origin, collection conditions, solvent, extraction ratio and storage documented. Where feasible, extracts should be standardised against marker compounds or other justified quality attributes. Extraction method should reflect the intended phytochemical profile, residual-solvent limits, safety and compatibility with the gel base.

Pharmacognostic identification should combine macroscopic and microscopic examination with chromatographic fingerprinting, such as thin-layer or high-performance thin-layer chromatography, and with basic quality tests such as loss on drying, total ash, extractive values and foreign matter. Limits for heavy metals, pesticide residues and microbial load, and for rhizomes such as turmeric the control of adulterants including added dyes, should follow the applicable pharmacopoeial monographs. Candidate markers, to be justified rather than assumed, include curcuminoids for turmeric, azadirachtin or a limonoid fraction for neem, eugenol for tulsi oil or extract, and aloin together with a defined polysaccharide marker for aloe [14,21]. A marker is a practical quality tool; it does not by itself prove biological activity.

Extraction options include maceration, percolation, Soxhlet extraction, decoction and ultrasound-assisted extraction. The solvent (water, ethanol or hydroalcoholic mixtures) determines which constituents are recovered, and heat-labile constituents such as curcuminoids and volatile oil components may be lost or degraded by prolonged heating. Residual solvents must be controlled, and extracts should be dried or concentrated to a defined extract-to-herb ratio so that the amount incorporated in the gel can be expressed on a reproducible basis.

Gel Base and Excipients

The gelling polymer should be chosen for compatibility with the extracts, target viscosity, spreadability, pH range and ease of manufacture; each excipient should serve a defined purpose at a justified concentration. Preservative selection and effectiveness are especially important for water-rich botanical preparations, and packaging should protect against light and moisture.

Gelling agents used in published herbal gels include carbomers (Carbopol) and cellulose derivatives such as hydroxypropyl methylcellulose (HPMC) [8]; sodium carboxymethylcellulose and xanthan gum are alternatives. Carbomers must be neutralised to build viscosity and are sensitive to electrolytes and to some polyphenol-rich extracts, which can thin the gel, whereas cellulose ethers are less dependent on pH but may be incompatible with some high-ionic-strength components. A humectant such as glycerol or propylene glycol limits drying of the film, and a chelating agent may help where metal ions catalyse degradation. The target pH should be chosen with reference to the slightly acidic pH of normal skin, commonly cited as about 4.5 to 5.5, and to the stability of the polymer and the extracts. Preservatives must be effective at that pH, compatible with the polymer and extracts, and justified against safety limits; preservative efficacy testing is a separate requirement from antimicrobial-activity testing.

Interpreting Published Gel Studies

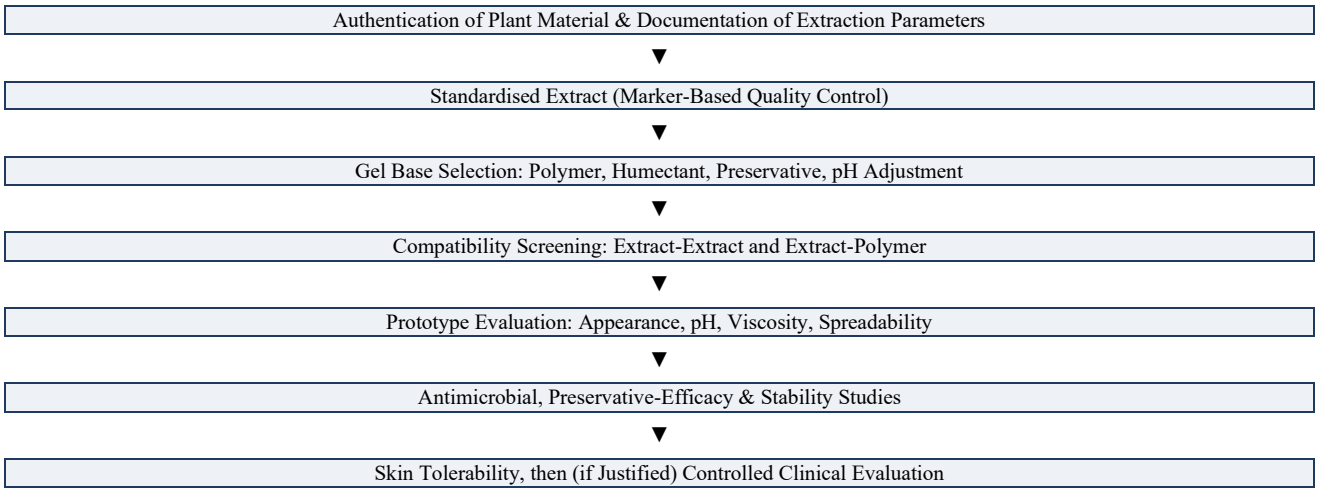
Published examples (Table 3) report compositions and outcomes that should be interpreted cautiously, as some accessible reports contain inconsistencies in extraction descriptions, pH values or formulation details. They can inform method selection but do not validate the proposed combination.

Two recurring patterns emerge from Table 3. Wash-off face-wash gels [7,8] differ from leave-on gels in contact time and skin exposure, so their performance and safety cannot be extrapolated to a leave-on product. Reports that include added volatile oils [9] or additional herbs [10] cannot attribute activity to the four proposed plants.

Delivery to the pilosebaceous unit

Conventional hydrogels act mainly at the skin surface. If follicular targeting is wanted, microemulsions, emulgels (a gel combined with an emulsion), nanoemulsions and vesicular or particulate carriers have been explored for lipophilic botanical constituents. They could address the solubility limits of curcuminoids and essential oils, as the microemulsion work on basil oils illustrates [13]. These systems add complexity, new excipients and additional stability and safety questions, so they are best considered after a simple, well-characterised gel has been shown to be stable and tolerable.

FIGURE 7: PROPOSED DEVELOPMENT WORKFLOW FOR A POLYHERBAL ANTI-ACNE GEL



EVALUATION PARAMETERS FOR A TOPICAL POLYHERBAL GEL

Evaluation should be planned before formulation optimisation and matched to the product, extracts and claims. Acceptance criteria should be justified from pharmacopeial, regulatory or validated method sources rather than invented. Physicochemical testing shows whether a gel is uniform and suitable for topical use but cannot establish clinical efficacy.

Antimicrobial testing needs a justified organism, positive and negative controls and validated conditions; *C. acnes* requires anaerobic culture. Diffusion assays are influenced by compound diffusivity and the gel base, so a smaller inhibition zone does not necessarily mean weaker biological effect. Microbial quality testing (does the product meet microbiological limits?) differs from antimicrobial activity testing (does it inhibit selected organisms?), and preservative effectiveness may also be required. Herbal origin does not exclude irritation or sensitisation, and ingredient-level testing does not replace assessment of the finished product.

Stability studies should monitor physical, chemical and microbiological attributes in the intended packaging under justified conditions, consistent with ICH Q1A(R2) principles (Table 2 lists core parameters). Marker-content testing is appropriate where validated methods exist, and release or permeation testing only where scientifically justified. Any clinical assessment requires an approved protocol, informed consent, a suitable comparator and defined outcomes.

TABLE 2: SUGGESTED EVALUATION PARAMETERS FOR A TOPICAL POLYHERBAL GEL

Parameter	Purpose	Key Considerations
Appearance, colour, odour, homogeneity	Visual quality and uniform distribution.	Record changes during storage; coloured extracts affect acceptability.
pH	Suitability for topical use and stability.	Defined method, calibrated instrument; justify range.
Viscosity / rheology	Consistency and application behaviour.	Specify instrument, spindle/geometry, speed, temperature.
Spreadability / extrudability	Ease of application or dispensing.	Reproducible protocol; report replicates.
Marker content / uniformity	Batch consistency.	A marker assay does not prove all actives are present.
Microbial quality / preservative efficacy	Protection against contamination.	Applicable pharmacopeial methods and justified limits.
Antimicrobial activity	Activity against acne-associated organisms.	Appropriate controls; anaerobic methods for *C. acnes*; not clinical proof.
Stability	Quality attributes over time.	Justified conditions, intended packaging, predefined endpoints.
Skin tolerability	Irritation or sensitisation.	Ethical, validated approaches; do not infer safety from herbal origin.
In vitro release / permeation	Release or transport where relevant.	Justified model, membrane, receptor medium, analytics.

Physicochemical characterisation

Appearance, colour, odour and homogeneity are assessed visually against a defined scale or reference. The pH is measured with a calibrated meter, either directly on the gel or on a defined dispersion, at a controlled temperature. Viscosity should be measured with a stated instrument, spindle or geometry, speed and temperature, and a flow curve is more informative than a single-point value, because a topical gel should be thick at rest and spread easily under shear. Spreadability is commonly measured by the parallel-plate method, recording the diameter reached or the time taken under a fixed load, and extrudability by the amount or force needed to expel the gel from a collapsible tube. Replicates and acceptance criteria should be reported so that batch-to-batch variation is visible.

Antimicrobial evaluation

Agar diffusion (well or disc) is a screening method. It shows whether a material diffuses and inhibits growth, but it is influenced by diffusivity, viscosity and agar depth, so a gel may appear to perform worse than the same material in solution. Broth microdilution gives minimum inhibitory and bactericidal concentrations (MIC and MBC) and supports interaction studies, and time-kill assays describe the rate of killing. For *C. acnes*, anaerobic or microaerophilic conditions and suitable media are required, and *Staphylococcus epidermidis* is often added as a second organism. Controls should include the vehicle without extract, a recognised comparator such as benzoyl peroxide or a topical antibiotic as appropriate, and an untreated growth control. Turbidimetric readouts, as used in a published face-wash study [8], are affected by coloured or particulate extracts such as turmeric, so colour and turbidity blanks are needed.

Safety and tolerability testing

Before human exposure, in vitro skin irritation methods based on reconstructed human epidermis (OECD Test Guideline 439) can be considered alongside other validated alternative methods. For finished products, human patch testing under an ethics-approved protocol assesses irritation, and repeat-exposure designs are used to assess sensitisation. Participants should be told that herbal origin does not guarantee tolerability, and adverse reactions, including erythema, dryness, burning, pruritus and allergic contact dermatitis, should be recorded systematically.

Stability programme

ICH Q1A(R2) describes long-term, intermediate and accelerated storage conditions, for example 25 °C/60% relative humidity or 30 °C/65% relative humidity for long-term studies and 40 °C/75% relative humidity for accelerated studies over six months. The climatic zone of the intended market and the container–closure system determine which conditions apply. For gels, additional stress conditions such as freeze–thaw cycling and exposure to light (important for photosensitive curcuminoids) are informative. Attributes to follow include appearance, colour, pH, viscosity, phase separation or syneresis, marker content, preservative content and microbial quality, and observed changes should be compared with predefined limits in order to propose a shelf life rather than merely described.

Study design and data handling

Laboratory studies should state the number of independent batches and replicates, report means with a measure of dispersion and use statistical tests

appropriate to the endpoint. For clinical work, sample size should be justified, allocation randomised and concealed, outcome assessors blinded and reporting made in line with accepted standards such as CONSORT. These requirements apply equally to trials of herbal and conventional products, and the lack of them is a recurrent criticism of the herbal acne literature [3,4].

COMPARATIVE LITERATURE SYNTHESIS & RESEARCH GAPS

The literature comprises reviews of medicinal plants for acne, a systematic review of turmeric across skin conditions, clinical-trial reviews of herbal treatments, small herbal gel formulation studies, and limited clinical data on aloe as a tretinoin adjunct. Differences in species, extract type, dosage form and outcomes limit direct comparison.

Reviews agree that laboratory antimicrobial and anti-inflammatory findings are more abundant than robust clinical evidence [2,14]. A systematic review of clinical trials reported encouraging outcomes for herbal medicine in acne but called for better-quality evidence and standardised methods [3], whereas a Cochrane review found inconsistent evidence for complementary therapies and noted trial-quality limitations [4]. Differences in search dates, eligibility criteria, plant selection and risk-of-bias assessment may explain these divergent conclusions.

TABLE 3: SELECTED PUBLISHED STUDIES AND INTERPRETIVE LIMITATIONS

Study	Formulation / Evaluation	Interpretation & Research Gap
Rasheed et al. (2011) [8]	*Rauvolfia serpentina*, turmeric and neem in Carbopol or HPMC face-wash gels; turbidimetric anti-acne assessment, irritation and stability reported.	Wash-off product, not a leave-on gel; accessible method details limited.
Shah & Srivastava (2015) [9]	Neem, tulsi and turmeric extracts (1% each) with tea tree, clary sage and sweet orange volatile oils; in vitro antioxidant and anti-acne evaluation against *P. acnes* and *S. epidermidis* versus a marketed gel.	In vitro only; added volatile oils prevent attributing activity to the herbal extracts alone; no tolerability or clinical data.
Rakesh et al. (2025) [7]	Aloe vera, turmeric, tulsi and neem face-wash gels (F1–F3) with different polymers; physical parameters such as pH, viscosity and spreadability.	Wash-off product; abstract and methods describe extraction differently; no microbiological or clinical efficacy shown.
Tekale et al. (2026) [10]	Green tea, neem, turmeric, aloe vera and licorice (no tulsi); appearance, pH, viscosity, spreadability, stability.	Internal inconsistencies in formulation details and pH; physicochemical data do not establish efficacy or safety.
Hajheydari et al. (2014) [5]	Aloe vera gel plus tretinoin in mild-to-moderate acne; 8-week randomised, double-blind trial (n = 60).	Adjunct design; aloe alone and the four-herb gel remain untested.

Formulation studies often focus on physical characteristics and sometimes draw safety or efficacy conclusions their data cannot support: appearance, pH, viscosity and spreadability cannot establish anti-acne efficacy, and a multi-herb formulation cannot reveal which ingredient is responsible for an effect. Priority gaps are: (i) authenticated, standardised plant material; (ii) reproducible extraction and marker-based quality control; (iii) justified concentrations and dose-response data; (iv) extract and base compatibility; (v) physical, chemical and microbiological stability; (vi) validated antimicrobial methods with controls; (vii) product-specific tolerability; and (viii) controlled clinical evidence.

Strength and consistency of the evidence

Taken together, the sources describe a pyramid with a narrow clinical tip and a broad laboratory and formulation base. Limitations commonly raised in the clinical-trial reviews of herbal acne treatment include small samples, short duration, heterogeneous preparations, unclear randomisation or blinding, variable outcome measures and incomplete description of the botanical material [3,4]. Positive laboratory findings are also more likely to be reported than null findings, which can make the preclinical literature look more favourable than it is. These factors argue for caution in interpreting any single study, including the trial of aloe with tretinoin [5], which is informative but small and of 8 weeks' duration.

Applicability of existing studies

The studies differ in species, plant part, extract, concentration, dosage form (wash-off or leave-on), comparator and outcome, and many do not describe the botanical material in enough detail to be replicated. Quantitative pooling of such data is not appropriate, and a narrative appraisal is more suitable than a meta-analysis. Evidence on a given constituent, such as curcumin, from other skin conditions or from other routes of administration should not be assumed to apply to a topical acne gel [6].

Positioning relative to conventional care

For mild acne, plant-based products are proposed mainly as adjuncts or supportive care [15] and not as replacements for established therapies. People with moderate to severe, scarring or rapidly worsening acne should be directed to medical care, because delay can increase the risk of permanent scarring. Labelling of any herbal gel should avoid implying treatment effects that the data do not support.

REGULATORY AND QUALITY CONSIDERATIONS

A polyherbal gel intended for therapeutic claims must satisfy applicable national botanical-product and drug regulations as well as international stability guidance such as ICH Q1A(R2). Regulators generally expect authenticated and reproducibly standardised botanical raw materials, validated analytical methods, demonstrated microbiological quality, and product-specific safety data before efficacy claims are accepted. Because the present evidence does not support therapeutic claims, early-stage products are better positioned as research formulations than as anti-acne treatments.

Whether a product is treated as a cosmetic, a traditional herbal or Ayurvedic preparation or a drug depends on its composition and, above all, on the claims made for it. Claims such as treating or curing acne generally require drug-level evidence and licensing, whereas cosmetic-type claims are limited to cleansing, soothing or appearance. In India the relevant provisions of the Drugs and Cosmetics Act, 1940, and the rules made under it, together with current requirements of the Central Drugs Standard Control Organisation and the Ministry of AYUSH, should be checked at the time of development because they are revised periodically.

Manufacture should follow good manufacturing practice, and botanical raw materials should be sourced under good agricultural and collection practice. Systematic recording of adverse reactions after launch (pharmacovigilance) is part of the quality system for herbal products. Clinical studies need ethics committee approval, informed consent, registration in a trial registry (in India, the Clinical Trials Registry–India) and compliance with Good Clinical Practice and the Declaration of Helsinki.

FUTURE DIRECTIONS

Study design priorities

To test synergy, studies should compare individual extracts, selected combinations and the full formulation at matched concentrations, with vehicle and positive controls. Antimicrobial assays should be followed by formulation-relevant tests, recognising that laboratory inhibition does not establish clinical improvement. If earlier safety and performance data justify it, a clinical study should use prespecified inclusion criteria, validated lesion counts or severity scales, an appropriate comparator and transparent adverse-event reporting. Negative or inconclusive findings should be reported alongside favourable ones, and batch-level quality control and transparent methods are essential for reproducibility [17].

Formulation and delivery research

Once a stable and tolerable gel exists, comparative work on delivery systems (Section 5.4) would show whether better release of lipophilic constituents translates into better antimicrobial or anti-inflammatory performance. Studies on ex vivo human or animal skin, on follicular deposition and on the effect of vehicle on irritation would help to separate the contribution of the active constituents from that of the base.

Outcome measures for clinical studies

Clinical studies should use validated and clinically meaningful outcomes: separate counts of inflammatory and non-inflammatory lesions, an investigator global assessment or a validated grading scale such as the Global Acne Grading System, and patient-reported measures of quality of life. Follow-up should be long enough to detect a response and, ideally, recurrence after treatment is stopped, and the study population should include skin types at higher risk of post-inflammatory pigmentation. Tolerability measures such as erythema, scaling, burning and itching should be recorded at each visit.

Computational approaches

Network pharmacology and molecular docking can help to generate hypotheses about the targets of plant constituents. Their results are predictions, however, and must be verified experimentally; they should not be cited as support for a product claim. This caution is particularly relevant for compounds such as curcumin, whose behaviour in assays is known to be complex [20].

Limitations of the present review

This review is a narrative, qualitative appraisal of a restricted set of 21 sources. No systematic database search with predefined criteria and no formal risk-of-bias scoring was carried out, and for some sources only accessible summaries could be appraised. Plants that appear in some published gels but are not among the four proposed here, such as tea tree, green tea and licorice, were outside its scope. The conclusions may change as higher-quality studies appear.

CONCLUSION

Neem, turmeric, aloe vera and tulsi have reported activities that may be relevant to selected processes in acne, but the evidence is uneven: neem and tulsi rest mainly on in vitro, review-level and formulation-level reports; turmeric has broader skin-health literature but limited acne-specific clinical data; and aloe vera has limited evidence as a tretinoin adjunct rather than a stand-alone treatment. Published polyherbal gel studies predominantly report physicochemical characteristics, and the literature does not establish synergy or clinical efficacy for the exact four-plant combination. The proposed gel should therefore be treated as a research hypothesis, and standardised extracts, justified formulation design, stability, microbial quality, validated antimicrobial evaluation, safety assessment and controlled clinical research are required before therapeutic claims can be made.

In practical terms, three messages follow from this appraisal. First, the plants are worth studying, but each brings its own formulation problem: variable limonoid content and odour for neem, poor solubility and colour for curcumin, microbial vulnerability and variability for aloe gel, and the lipophilic, sensitising oil of tulsi. Second, a published gel that is well formed and pleasant to use has not been shown to be effective or safe. Third, the next useful step is a carefully controlled, transparently reported programme that begins with standardised single extracts and ends, only if justified, in a controlled clinical study.

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