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Comprehensive Evaluation of Quercetin from *Bauhinia purpurea* for Its Anti-Acne and Anti-Inflammatory Potential, Including Advances in Quercetin-Loaded Nanogel Formulation

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Abstract

Acne vulgaris is among the most prevalent chronic inflammatory dermatoses in clinical dermatology, afflicting a substantial proportion of the global adolescent and adult population. Conventional pharmacotherapies – including topical retinoids, benzoyl peroxide, and systemic antibiotics – remain the therapeutic mainstay; however, their long-term utility is progressively undermined by adverse cutaneous reactions, systemic toxicity, and the rising prevalence of antibiotic-resistant Cutibacterium acnes strains. These limitations have intensified scientific interest in plant-derived bioactives as alternative or adjunctive agents. Bauhinia purpurea L. (Leguminosae–Caesalpinioideae), a medicinally revered tree indigenous to tropical Asia, harbors a diverse array of secondary metabolites, among which quercetin – a pentahydroxylated flavonol – has emerged as a particularly promising multi-target candidate. This review consolidates current knowledge on: (i) the botanical identity and phytochemical profile of B. purpurea, with emphasis on quercetin content and extraction methodology; (ii) the structural and physicochemical attributes underpinning quercetin's bioactivity; (iii) the mechanistic basis of its anti-acne and anti-inflammatory properties, encompassing NF-κB pathway modulation, MAPK signaling suppression, sebostatic activity, inhibition of C. acnes, and oxidative-stress regulation; and (iv) contemporary advances in quercetin-loaded nanogel formulations designed to overcome quercetin's intrinsic biopharmaceutical limitations. Emerging nanocarrier strategies – including carbopol-based nanogels, polymeric nanoparticle-incorporated gels, solid lipid nanoparticle gels, and nanostructured lipid carrier gels – are critically appraised. Research gaps, regulatory considerations, and a future roadmap for clinical translation are also delineated.

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INTRODUCTION

Acne vulgaris constitutes a chronic, multifactorial disorder of the pilosebaceous unit, predominantly manifesting in adolescents yet extending into adulthood across a sizeable patient cohort. Epidemiological data indicate that the condition affects nearly 85% of individuals aged 12–25 years, with global prevalence continuing an upward trajectory [1]. Clinically, the disorder

encompasses a spectrum ranging from non-inflammatory comedones to inflammatory papules, pustules, and nodulocystic lesions capable of inducing permanent scarring and post-inflammatory hyperpigmentation. Beyond cutaneous sequelae, acne imposes a disproportionate psychological burden, significantly undermining quality of life, self-esteem, and social functioning [2].

The pathogenesis of acne is orchestrated by four interrelated mechanisms: (i) androgen-mediated hypersecretion of sebum by sebaceous glands, (ii) aberrant follicular keratinization with microcomedo formation, (iii) dysbiotic colonization by Cutibacterium acnes (formerly Propionibacterium acnes), and (iv) a cascade of innate and adaptive immune-inflammatory responses involving pattern-recognition receptors and diverse cytokine networks [3]. Although first-line therapeutic agents – retinoids, benzoyl peroxide, topical and systemic antibiotics, and hormonal modulators – are mechanistically rational, their clinical utility is curtailed by well-characterized adverse effects, including retinoid teratogenicity, antibiotic resistance, and cutaneous dysbiosis. These limitations have catalyzed concerted efforts to identify safer, plant-derived therapeutic alternatives [4].

Within this framework, the genus Bauhinia (Leguminosae) has attracted sustained ethnobotanical and pharmacological interest. Comprising approximately 300 species distributed across tropical and subtropical regions of Asia, Africa, and the Americas, Bauhinia plants have been employed in traditional medicine for the management of diabetes, inflammatory disorders, dermatological conditions, and hepatic dysfunction across centuries [5]. *Bauhinia purpurea* L., commonly designated the purple orchid tree or camel's foot tree, is particularly well-documented in Indian, Thai, and Chinese traditional healing systems. Its leaves, bark, flowers, and seeds collectively yield a diverse repertoire of secondary metabolites, including flavonoids, sterols, tannins, and phenolic acids [6].

Among the flavonoids isolated from B. purpurea, quercetin (3,3′,4′,5,7-pentahydroxyflavone; $C_{15}H_{10}O_7$; MW 302.24 g/mol) stands apart for the breadth and potency of its documented biological activities. Its pentahydroxy scaffold confers powerful antioxidant capacity through hydrogen atom transfer and single-electron transfer mechanisms, while its planar aromatic architecture facilitates interaction with kinase active sites, phosphodiesterases, and transcription-factor complexes relevant to inflammatory signaling [7]. The molecule's established capacity to suppress NF-κB activation, attenuate MAPK phosphorylation cascades, inhibit lipid peroxidation, and directly impair C. acnes growth positions it as a compelling multi-target anti-acne candidate [8].

Notwithstanding these pharmacological attributes, the clinical translation of quercetin has historically been constrained by its poor aqueous solubility (~0.01 mg/mL at physiological pH), photolability, rapid first-pass metabolism following oral administration, and limited transdermal permeation in conventional topical formulations [9]. Nanotechnology-based delivery platforms – particularly nanogel systems that embed nanoparticulate quercetin within a hydrophilic polymeric matrix – have emerged as a compelling strategy to circumvent these obstacles, offering enhanced solubilization, sustained release, and improved follicular targeting [10].

The present review, therefore, aims to provide a coherent, critical synthesis of evidence pertaining to: (i) the botanical and phytochemical characteristics of *B. purpurea* with relevance to quercetin; (ii) the mechanistic underpinnings of quercetin's anti-acne and anti-inflammatory activities; and (iii) the current landscape of quercetin-loaded nanogel formulations. By integrating evidence from in vitro, in vivo, and early clinical investigations, this review seeks to delineate the translational trajectory of quercetin-based nanogels and propose a framework for future research priorities.

BOTANICAL PROFILE AND TRADITIONAL USES OF *BAUHINIA PURPUREA*

Bauhinia purpurea L. (synonym: Phanera purpurea) is a small-to-medium deciduous tree attaining heights of 10–12 m, characterized by its distinctive bilobed leaves – each measuring approximately 8–15 cm in length – whose silhouette is reminiscent of a camel's hoof, a morphological hallmark of the genus. The flowers are large, fragrant, and purple-pink to lavender in coloration, appearing in terminal

racemes during the autumn season. The species is native to southern China and mainland Southeast Asia but has been naturalized throughout the Indian subcontinent and the broader tropics [11].

Within the traditional medicinal systems of India, the bark and leaves of *B. purpurea* are employed as astringents, anthelmintics, and anti-inflammatory preparations. Ayurvedic textual descriptions document the use of bark preparations for managing skin disorders, dysentery, and glandular swellings. In Thai ethnomedicine, the leaves are administered as diuretic and antidysenteric remedies, while Chinese traditional practice employs floral and foliar decoctions for febrile conditions and dermatitic complaints [6]. This cross-cultural convergence of therapeutic applications underscores the plant's multi-pharmacological reputation and provides biological plausibility for contemporary scientific investigations.

Phytochemical surveys of *B. purpurea* have identified a rich matrix of secondary metabolites (Table 1). Flavonoids – principally quercetin, kaempferol, luteolin, and their respective glycoside derivatives – constitute the dominant polyphenolic fraction in leaf extracts [5]. Additional constituents include β-sitosterol, stigmasterol, ursolic acid, oleanolic acid, tannins, protocatechuic acid, and a characteristic group of phenanthroindolizidine alkaloids. The relative abundance of individual constituents varies with plant part, developmental stage, geographic provenance, and extraction solvent, necessitating standardized phytochemical protocols for reproducible quercetin isolation [12].

Table 1. Phytochemical constituents of *Bauhinia purpurea* across various plant parts, with associated biological activities. Quercetin and kaempferol represent the dominant flavonol constituents with relevance to anti-acne applications [5, 6, 12].

Compound class	Representative constituents	Plant part	Reported activity	Reference
Flavonols	Quercetin, Kaempferol, Quercitrin	Leaf, Flower	Anti-inflammatory, antioxidant, antimicrobial.	[5, 17]
Flavonoid glycosides	Isoquercitrin, Rutin, Quercetin-3-O-rutinoside	Leaf, Bark	Improved aqueous solubility; anti-inflammatory.	[16, 17]
Sterols	β-Sitosterol, Stigmasterol	Seed, Bark	Anti-inflammatory; 5α-reductase inhibition.	[5]
Triterpenoids	Ursolic acid, Oleanolic acid	Leaf, Bark	Anti-inflammatory; hepatoprotective.	[6]
Tannins	Condensed tannins (proanthocyanidins)	Bark	Astringent; antimicrobial; anthelmintic.	[6]
Phenolic acids	Protocatechuic acid, Gallic acid	Leaf	Antioxidant; antibacterial.	[12]
Alkaloids	Phenanthroindolizidine alkaloids	Leaf, Seed	Cytotoxic; anti-inflammatory (characterized).	[5]

CHEMISTRY AND PHYSICOCHEMICAL PROPERTIES OF QUERCETIN

Quercetin belongs to the flavonol subclass of flavonoids, defined by a 3-hydroxyflavone backbone, with the systematic name 3,3′,4′,5,7-pentahydroxyflavone. Structurally, it comprises two benzene rings (A and B) bridged by a heterocyclic pyranone ring (C), with hydroxyl substitutions at positions 3, 5, 7, 3′, and 4′ (Figure 1). The catechol moiety on ring B (3′,4′-dihydroxy groups) principally governs radical-scavenging capacity, while the 3-hydroxyl group on ring C, in conjunction with the 4-oxo function and the 2,3-double bond, facilitates chelation of transition-metal ions relevant to oxidative stress pathogenesis [13].

In the context of topical dermal delivery, quercetin's physicochemical profile presents a paradox: its moderate lipophilicity (log P ≈ 1.75) initially appears favorable for stratum corneum partitioning, yet its propensity to crystallize and aggregate in aqueous vehicles dramatically limits bioavailability at the dermal–follicular interface (Table 2). This necessitates deliberate formulation engineering, most effectively realized through nano-scale encapsulation strategies maintaining quercetin in an amorphous, molecularly dispersed state throughout the delivery process [9].

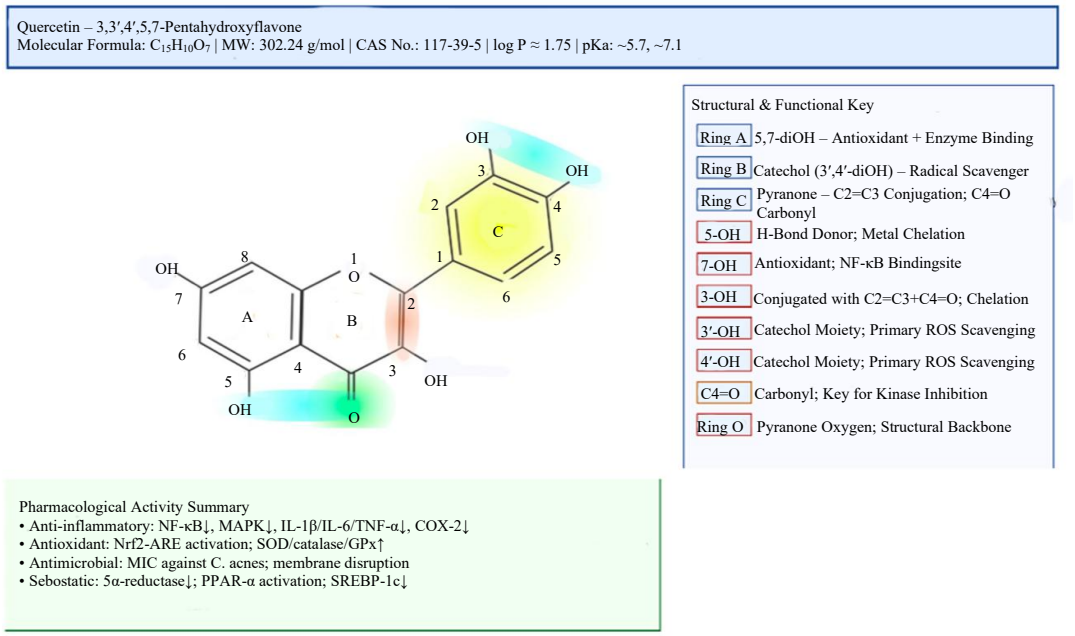

Figure 1. Structural organization of quercetin, illustrating the three aromatic ring systems (A, B, C) and the key functional groups contributing to antioxidant, anti-inflammatory, and antimicrobial activities. The catechol moiety of Ring B constitutes the primary radical-scavenging site [7, 13].

Table 2. Physicochemical characterization of quercetin relevant to topical anti-acne formulation design. These properties collectively define the biopharmaceutical challenges necessitating nanoformulation strategies [9, 13, 14].

Parameter	Value / range	Pharmaceutical significance
Molecular formula	$C_{15}H_{10}O_7$	Five hydroxyl groups; pentahydroxyflavone scaffold.
Molecular weight	302.24 g/mol	Small molecule; membrane-permeable potential.
Melting point	316–317 °C	Thermally stable; suitable for hot-melt processing.
Aqueous solubility (pH 7.4)	~0.01 mg/mL	Very low → nanotechnology required for topical delivery.
log P (lipophilicity)	≈ 1.75	Moderate; stratum corneum partitioning favoured but crystallization risk.
pKa values	~5.7 and ~7.1	pH-dependent ionization affects membrane partitioning across skin layers.
UV absorption maxima	256 nm (Band II); 370 nm (Band I)	Characteristic flavonol chromophore; photostability concern.
DPPH IC_{50}	Substantially < ascorbic acid (reported conditions)	Superior radical-scavenging activity; potent antioxidant.
Crystal form	Pale yellow orthorhombic crystals	Tendency to aggregate in aqueous vehicles → amorphous form preferred.
First-pass metabolism (oral)	~17% absolute bioavailability (preclinical)	Extensive hepatic and intestinal metabolism → topical route preferred.

EXTRACTION AND ISOLATION OF QUERCETIN FROM *BAUHINIA PURPUREA*

Quercetin isolation from *B. purpurea* generally follows a multi-step procedure commencing with maceration or Soxhlet extraction of dried plant material – typically leaves – using polar solvents, such as 80% aqueous methanol or ethanol, which optimize flavonoid yields. Successive liquid–liquid partitioning employing solvents of increasing polarity (n-hexane, ethyl acetate, n-butanol) enriches the quercetin content in the ethyl acetate fraction. Column chromatography on silica gel, with gradient elution using hexane–ethyl acetate or chloroform–methanol systems, affords quercetin as a pure crystalline compound [15].

Structural confirmation relies on a combination of complementary analytical approaches. Ultraviolet–visible spectroscopy reveals characteristic absorption maxima at approximately 370 nm (Band I) and 256 nm (Band II), consistent with the flavonol chromophore. Fourier-transform infrared spectroscopy identifies hydroxyl stretching vibrations (3200–3500 cm^{-1}) and carbonyl absorption (~1660 cm^{-1}). High-resolution ^{1}H and ^{13}C NMR spectra confirm the aromatic proton environments and the pentahydroxy substitution pattern. HPLC-DAD provides quantitative assessment, with quercetin typically eluting at 15–20 minutes under standard reversed-phase C18 conditions at 370 nm detection [12].

Several Bauhinia species allied to *B. purpurea* – including *B. malabarica*, *B. variegata*, *B. racemosa*, and *B. acuminata* – have been reported to contain quercetin and quercetin-3-O-glycosides as major flavonoid constituents [16, 17]. A pharmacognostic investigation on *B. malabarica* by Thetsana et al. (2019) quantified quercetin content at 0.18 g per 100 g dry weight in dried leaves using validated RP-HPLC [18]. Comparable studies on *B. purpurea* leaves under equivalent extraction conditions have consistently yielded quercetin as the predominant flavonol aglycone, reinforcing the species' phytochemical significance as a quercetin source for pharmaceutical applications.

MECHANISTIC BASIS OF QUERCETIN'S ANTI-INFLAMMATORY ACTIVITY

Inhibition of NF-κB Signaling

Nuclear factor kappa B (NF-κB) is a pleiotropic transcription factor complex orchestrating the expression of pro-inflammatory cytokines, chemokines, adhesion molecules, and inducible enzymes including cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). In acne pathogenesis, C. acnes activate TLR-2 on keratinocytes and macrophages, initiating downstream IκB kinase (IKK) activation, phosphorylation and proteasomal degradation of IκBα, and nuclear translocation of p65/p50 NF-κB dimers [3]. Quercetin suppresses this pathway at multiple nodes: it inhibits IKKβ kinase activity, stabilizes IκBα against degradation, and directly attenuates p65 nuclear translocation, thereby reducing NF-κB-driven gene transcription [7]. Experimental evidence from C. acnes-stimulated HaCaT keratinocytes and THP-1 monocytes demonstrates significant reductions in NF-κB activity following quercetin treatment in the micromolar range, with concomitant decreases in TNF-α, IL-1β, IL-6, and IL-8 secretion [8].

MAPK Pathway Modulation

Mitogen-activated protein kinase (MAPK) cascades – specifically the ERK1/2, p38, and JNK sub-pathways – represent central signal transduction routes linking microbial stimuli to cytokine gene expression in skin cells. Kim et al. (2021) demonstrated that quercetin treatment of C. acnes-stimulated HaCaT and THP-1 cells significantly attenuated phosphorylation of p38, ERK1/2, and JNK, alongside suppression of TLR-2 protein expression and MMP-9 mRNA levels [8]. These findings collectively indicate that quercetin interferes with both receptor-proximal events and downstream kinase cascades, producing multi-nodal dampening of the inflammatory amplification loop characteristic of acne lesion development.

Cytokine and Mediator Regulation

Beyond NF-κB and MAPK targeting, quercetin exerts broad-spectrum cytokine regulatory effects particularly relevant in acne-associated inflammation. Studies in C. acnes-exposed RAW264.7 macrophages have confirmed effective suppression of IL-1β, IL-8, IL-6, and TNF-α upregulation, while one investigation reported a near 100-fold induction of the anti-inflammatory cytokine IL-10 in quercetin-treated keratinocytes [10]. This cytokine-rebalancing effect may be mechanistically linked to quercetin's capacity to facilitate macrophage polarization from the pro-inflammatory M1 towards the anti-inflammatory M2 phenotype – a shift that would theoretically favor resolution of acne lesions and mitigate post-inflammatory scar formation [19].

COX-2 and Prostaglandin Suppression

Quercetin inhibits COX-2 and 5-lipoxygenase (5-LOX), the key enzymatic mediators of eicosanoid biosynthesis. By reducing prostaglandin E2 (PGE_2) and leukotriene B4 (LTB_4) production, quercetin attenuates vasodilation, oedema, and neutrophil chemotaxis in inflamed sebaceous follicles. This

eicosanoid-modulatory property complements its cytokine-suppressive effects, providing convergent anti-inflammatory coverage across both the cyclooxygenase and lipoxygenase arms of the arachidonic acid cascade [20].

Antioxidant and Oxidative Stress Mitigation

Reactive oxygen species (ROS) generated by C. acnes-stimulated neutrophils and macrophages contribute significantly to acne pathogenesis by amplifying the inflammatory cascade and inducing lipid peroxidation of sebum components. Quercetin's pentahydroxy structure confers exceptional radical-scavenging capacity via hydrogen atom donation, with reported IC_{50} values in DPPH assays substantially below those of standard antioxidants such as ascorbic acid under comparable conditions [13]. Beyond direct radical scavenging, quercetin activates the Nrf2–ARE transcriptional pathway, upregulating endogenous antioxidant enzymes – superoxide dismutase (SOD1, SOD2), catalase, and glutathione peroxidase (GPx) – thereby bolstering the cellular antioxidant defence network (Table 3) [21].

Table 3. Schematic representation of the stepwise pathogenic cascade in acne vulgaris and the corresponding molecular intervention points of quercetin. Each pathogenic step is cross-referenced with the established quercetin mechanism of action [3, 7, 8, 10, 13, 20, 21].

Pathogenic step	Pathway	Quercetin intervention
Cutibacterium acnes / Androgen stimulation	*TRIGGER*	–
TLR-2 Activation → IKK → IκBα degradation	NF-κB Pathway	Quercetin inhibits IKKβ, stabilizes IκBα, blocks p65 nuclear translocation.
p38 / ERK1/2 / JNK phosphorylation	MAPK Cascade	Quercetin reduces p38/ERK1/2/JNK phosphorylation; suppresses TLR-2 expression.
COX-2 ↑ / 5-LOX ↑ → PGE_2 + LTB_4 ↑	Eicosanoid Synthesis	Quercetin competitively inhibits COX-2 and 5-LOX active sites.
IL-1β / IL-6 / IL-8 / TNF-α secretion	Cytokine Surge	Quercetin downregulates cytokine gene transcription; induces IL-10 (~100×).
ROS generation → lipid peroxidation	Oxidative Stress	Quercetin activates Nrf2-ARE → SOD, catalase, GPx; direct H• donation.

ANTI-ACNE PROPERTIES OF QUERCETIN

Antimicrobial Activity Against Cutibacterium acnes

The antimicrobial efficacy of quercetin against C. acnes has been documented in multiple independent investigations employing disc diffusion and minimum inhibitory concentration (MIC) assays. The compound exerts bacteriostatic effects at low micromolar concentrations, with proposed mechanisms encompassing disruption of bacterial cell membrane integrity, inhibition of DNA gyrase and topoisomerase IV, and interference with the bacterial electron transport chain [22]. Notably, quercetin demonstrates a synergistic antimicrobial effect when combined with conventional anti-acne antibiotics, such as tetracyclines, potentially by altering membrane permeability and facilitating antibiotic intracellular accumulation – an attribute of particular clinical relevance given global antibiotic-resistant C. acnes strains [29]. Kim et al. (2021) further validated quercetin's in vivo anti-acne capacity in a murine ear model, where intradermal C. acnes injection induced erythema and oedema substantially attenuated by quercetin treatment compared to untreated controls [8].

Sebostatic Activity

Sebaceous gland hyperactivity, driven primarily by androgen receptor activation and downstream lipogenesis pathways, is a cardinal feature of acne pathogenesis. Quercetin inhibits 5α-reductase – the enzyme responsible for converting testosterone to dihydrotestosterone (DHT) within sebocytes – thereby reducing androgen-driven sebum overproduction. Additionally, quercetin activates PPARα in sebocytes, promoting lipid oxidation rather than synthesis, and suppresses SREBP-1c-mediated triglyceride biosynthesis [29]. These sebostatic mechanisms collectively suggest that quercetin may address upstream aetiological factors in acne, rather than merely managing downstream inflammatory consequences.

Anti-Comedogenic and Keratolytic Effects

Abnormal follicular keratinization, culminating in microcomedo formation, initiating the comedogenic cascade. Quercetin's capacity to modulate keratinocyte differentiation through PPARα activation and its inhibition of EGFR-mediated signaling contribute to normalization of follicular keratinization dynamics. Furthermore, quercetin's antioxidant properties may indirectly reduce comedo formation by limiting oxidative modification of sebum lipids – a process implicated in the cohesion of follicular keratocytes [1].

Post-Inflammatory Hyperpigmentation and Scar Prevention

Acne scarring and post-inflammatory hyperpigmentation (PIH) significantly compound the disease burden beyond the active inflammatory phase. Quercetin's anti-fibrotic effects – mediated via suppression of TGF-β1 signaling and downregulation of collagen type I gene expression – may mitigate excessive fibroblast activation in healing acne lesions, potentially reducing hypertrophic scar formation. Its inhibition of tyrosinase activity and melanin synthesis further positions quercetin as a candidate for PIH management, representing an added cosmeceutical benefit over conventional anti-acne agents [9].

FORMULATION CHALLENGES: RATIONALE FOR NANOTECHNOLOGY-BASED DELIVERY

Despite its impressive pharmacological portfolio, quercetin's direct clinical translation in topical anti-acne applications is impeded by a constellation of biopharmaceutical limitations. First, its extremely low aqueous solubility (~0.01 mg/mL at physiological pH) restricts drug loading in hydrophilic vehicles and generates heterogeneous, poorly stable dispersions.

Second, quercetin's tendency to aggregate and crystallize on the skin surface following vehicle evaporation limits follicular penetration. Third, the stratum corneum presents a formidable physicochemical barrier to dermal drug permeation, demanding formulation strategies that facilitate transfollicular or intrafollicular delivery, particularly as acne lesions originate in the pilosebaceous unit [23].

Fourth, quercetin undergoes rapid oxidative degradation upon exposure to light, oxygen, and alkaline conditions, necessitating protective encapsulation for adequate shelf-life. Fifth, its poor oral bioavailability (~17% absolute in preclinical models), attributable to extensive intestinal and hepatic first-pass metabolism, limits systemic dosage forms for topical indications. Nanotechnology offers versatile solutions to these challenges: nanosizing enhances dissolution and surface-area-to-volume ratios; polymeric or lipid coatings protect against degradation; and surface modification can augment selective pilosebaceous delivery [21].

QUERCETIN-LOADED NANOGEL FORMULATIONS: PRINCIPLES AND RECENT ADVANCES

Definition and Rationale for Nanogels

A nanogel is a three-dimensional, cross-linked hydrophilic polymer network swollen with an aqueous phase that physically entraps nanoparticulate drug carriers or encapsulated drug molecules within its mesh structure.

In the context of quercetin delivery, nanogels combine the patient-friendly semi-solid topical application characteristics of conventional gels – ease of spreading, non-greasy texture, extended skin contact time – with the biopharmaceutical advantages of nanoparticulate encapsulation, namely enhanced solubilization, controlled release kinetics, and improved dermal permeation [24]. The nanogel architecture creates a moist microenvironment physiologically compatible with skin, facilitating drug diffusion through the follicular infundibulum to reach the microcomedo and underlying sebaceous gland (Table 4) [10].

Table 4. Comparative evaluation of quercetin-loaded nanogel formulation systems documented in the literature, summarizing the polymer matrix, key advantages, characterization highlights, and clinical/preclinical evidence [21, 22, 24, 26, 28, 30].

System	Matrix polymer	Key advantages	Characterization highlights	Evidence summary
Carbopol Nanogel	Polyacrylic acid matrix	Bioadhesive; transparent; easy pH adjustment	pH 6.7–7.1; high viscosity; good spreadability	C. acnes inhibition ZOI: 15 ± 1.5 mm vs. 8.25 ± 2.1 mm (pure quercetin).
Polymeric (PVA/PLGA) Nanofiber Gel	Electrospun PVA, chitosan, PLGA	Biodegradable; sustained release; high surface area	EE >80%; skin deposition 28.24% ± 0.012	↓ Inflammatory lesions 61.2%; comedones 14.7%; total lesions 52.9% (clinical).
SLN / NLC Gel	Glyceryl monostearate + liquid lipid in Carbopol	Hydrophobic core; slow crystallization; high drug load	Particle size <200 nm; ZP > ± 30 mV; 2–4× dermal retention	Superior ex vivo porcine skin permeation vs. conventional gel.
Nanoemulsion Thermogel	Oleic acid + Poloxamer 407/188	Sol-gel transition at skin temp (32–37°C); prolonged contact	Mean PS ~60 nm; thermosensitive transition at 32°C	In vivo anti-acne efficacy in rabbit ear model (TQ hydrogel).
Biopolymer Hydrogel (SA / MC / CMC)	Sodium alginate, methyl cellulose, carboxymethyl cellulose	Biocompatible; biodegradable; non-comedogenic	MC variant shows highest viscosity & adhesiveness	Superior quercetin retention in porcine ear skin; propylene glycol as PE.

Note: ZOI = zone of inhibition; EE = encapsulation efficiency; PS = particle size; PE = permeation enhancer.

Carbopol-Based Quercetin Nanogels

Carbopol (polyacrylic acid) is the most widely employed gelling agent in quercetin nanogel development owing to its high viscosity at low concentrations, bioadhesive properties, and transparent appearance facilitating drug incorporation monitoring. In a representative investigation, quercetin-loaded silver nanoparticles were incorporated into a Carbopol 940 matrix to produce a composite nanogel evaluated against C. acnes by disc diffusion. The quercetin–AgNPs–Carbopol formulation produced a substantially larger zone of inhibition (15 ± 1.53 mm) compared to pure quercetin alone (8.25 ± 2.08 mm), attributable to synergistic antimicrobial activity between quercetin and the silver nanoparticle component [30]. The formulation exhibited a pH of 6.71–7.10 – within the physiologically acceptable skin pH range – alongside satisfactory spreadability and viscosity values appropriate for topical application.

Polymeric Nanoparticle-Incorporated Nanogels

Polymeric nanosystems employing biodegradable carriers, such as PLGA, chitosan, and polyvinyl alcohol (PVA), have been extensively explored as quercetin encapsulants. Amer et al. (2022) developed PVA/quercetin composite nanofibers fabricated by electrospinning, demonstrating a skin deposition percentage of 28.24% ± 0.012, significantly superior antibacterial activity against C. acnes compared to unformulated quercetin, and excellent cytocompatibility with skin fibroblasts in MTT assays [26]. In a subsequent clinical evaluation on acne patients, these nanofiber mats achieved reductions of 61.2%, 14.7%, and 52.9% in inflammatory, comedonal, and total acne lesion counts, respectively – a clinically meaningful outcome underscoring the therapeutic potential of nanostructured quercetin delivery [26].

Solid Lipid Nanoparticle (SLN) and Nanostructured Lipid Carrier (NLC) Gels

Lipid-based nanoparticulate systems – SLNs and NLCs – provide hydrophobic micro-compartments ideally suited to encapsulation of lipophilic quercetin. SLNs, composed of physiologically tolerated

solid lipids (e.g., glyceryl monostearate, cetyl palmitate), form stable colloidal suspensions that can be incorporated into gel matrices for topical application. NLCs, which combine solid and liquid lipid components to generate structural imperfections in the lipid matrix, typically afford higher drug loading and slower crystallisation-mediated drug expulsion than SLNs. When incorporated into carbopol or cellulose-derivative nanogels, SLN and NLC systems have demonstrated 2–4-fold improvements in quercetin dermal retention over conventional gel formulations in ex vivo porcine skin models [21]. A notable investigation by Bagde et al. combined quercetin (0.12%) with titanium dioxide (15%) in a nanogel that, in a UV-induced murine skin cancer model, downregulated COX-2, cyclin D1, PCNA, EP3, and EP4 expressions, demonstrating both anti-inflammatory and chemopreventive potential [21].

Nanoemulsion-Based Thermogels

Thermosensitive nanogel composites represent a more recent innovation, wherein drug-loaded nanoemulsions are incorporated into a temperature-sensitive poloxamer matrix that exists as a low-viscosity liquid at room temperature but transitions to a gel at skin temperature (~32–37 °C). This sol-to-gel phase transition upon skin application improves contact time and promotes controlled release at the site of action. A 2025 investigation by Chen et al. developed a tanshinone IIA and quercetin co-loaded nanoemulsion-thermogel (TQ hydrogel), employing oleic acid as the oil phase and poloxamer 407/188 as gelling agents [22]. The TQ hydrogel demonstrated mean particle sizes of ~60 nm, in vitro antimicrobial and antioxidant activities, and in vivo anti-acne efficacy in a rabbit ear model, establishing proof-of-concept for dual phytochemical delivery in thermosensitive nanogel systems.

Hydrogels Based on Natural Polysaccharides

Biopolymer-based nanogel matrices – employing sodium alginate (SA), methyl cellulose (MC), and carboxymethyl cellulose (CMC) – have gained interest owing to their biocompatibility, biodegradability, and processing ease. In a comparative study on quercetin hydrogels at 0.4% and 0.7% concentrations, MC-based gels exhibited the highest viscosity, adhesiveness, cohesiveness, and stickiness among formulation variants, and demonstrated superior quercetin retention in porcine ear skin ex vivo compared to SA- and CMC-based counterparts [28]. The study confirmed that polymer selection critically determines drug permeation behavior, with propylene glycol serving as an effective dermal permeation enhancer when incorporated into the gel matrix.

Characterization Parameters for Quercetin Nanogels

Robust physicochemical characterization is indispensable for quality assurance of quercetin nanogel formulations. Standard evaluation parameters encompass particle size and polydispersity index (PDI) by dynamic light scattering (DLS); zeta potential for colloidal stability assessment (typically ≥ ±30 mV); encapsulation efficiency (EE%) and drug loading capacity by HPLC; morphological evaluation by TEM or AFM; rheological profiling; in vitro drug release kinetics using Franz diffusion cells; and photostability testing under ICH Q1B conditions (Table 5) [9].

Table 5. Recommended characterization parameters, analytical methods, target specifications, and relevance to anti-acne application for quercetin-loaded nanogel formulations. These parameters collectively constitute a comprehensive preclinical quality-assurance framework [9, 26, 27].

Parameter	Analytical method	Target specification	Relevance to anti-acne application
Particle size & PDI	Dynamic Light Scattering (DLS)	<200 nm; PDI <0.3	Follicular penetration; colloidal stability.
Zeta potential	Electrophoretic mobility (DLS)	≥ ±30 mV	Prevents aggregation; predicts shelf-life stability.
Encapsulation efficiency	RP-HPLC (370 nm detection)	>75%	Drug payload adequacy for therapeutic concentration.
Drug release kinetics	Franz diffusion cell (synthetic/porcine membrane)	Sustained over 8–24 h	Prolonged follicular drug exposure; reduced dosing frequency.

Morphology	TEM / AFM	Spherical; uniform; non-aggregated	Confirms nanostructure integrity pre-application.
Rheology	Rotational viscometry	1000–8000 mPa·s (semi-solid)	Spreadability; skin contact time; patient acceptability.
Antimicrobial activity	MIC / MBC / Disc diffusion (C. acnes)	MIC ≤ quercetin solution reference	Direct anti-acne efficacy validation.
Photostability	ICH Q1B fluorescent/UV light exposure	≤5% degradation at 6 months	Shelf-life adequacy for commercial product.
Skin permeation (ex vivo)	Franz cell with porcine ear / human skin	Follicular deposition > interfollicular	Pilosebaceous targeting; dermal bioavailability.
Cytotoxicity	MTT assay (HaCaT, fibroblasts)	IC_{50} > 50 μM	Safety at topical concentrations.

BIOAVAILABILITY ENHANCEMENT THROUGH NANOFORMULATION

The biopharmaceutical advantages of nanoscale encapsulation for quercetin delivery are well-documented. Nanosizing to sub-200 nm diameters dramatically increases the surface area available for dissolution, enhancing apparent solubility through curvature-driven reduction in interfacial free energy. Polymeric and lipid matrices confer additional protection from oxidative and hydrolytic degradation, effectively prolonging the functional half-life of quercetin in topical formulations stored under ambient conditions [23].

Dermal bioavailability in the context of acne treatment is best conceptualized as drug deposition within the follicular infundibulum and upper dermis – the anatomical loci of C. acnes colonization and immune-inflammatory cascades. Confocal laser scanning microscopy (CLSM) studies employing fluorescently labelled quercetin nanocarriers have confirmed preferential accumulation in hair follicles compared to the interfollicular epidermis, a phenomenon attributed to the "reservoir effect" of the follicular orifice and facilitated diffusion along the concentration gradient into the sebum-rich follicular canal [27]. This follicular targeting translates directly to higher drug concentrations at the site of acne pathogenesis, potentially reducing total drug dose required for therapeutic effect [24].

SAFETY PROFILE AND TOXICOLOGICAL CONSIDERATIONS

Quercetin possesses a well-established favorable safety profile at therapeutically relevant topical concentrations. The molecule is classified as Generally Recognized as Safe (GRAS) by the FDA for dietary applications, and extensive preclinical and Phase I clinical data demonstrate good tolerability via dermal routes. Cytotoxicity assays on human dermal fibroblasts, HaCaT keratinocytes, and sebocyte cell lines consistently report no significant cytotoxic effects below 50 μM – concentrations substantially exceeding those achievable in topical formulations under physiological skin contact conditions [26].

Nanotechnology-based excipients introduce additional safety dimensions warranting case-by-case assessment. Silver nanoparticles, while potently antimicrobial, raise concerns regarding potential transdermal absorption and systemic silver accumulation (argyria) with long-term use. PLGA and PLA polymers are well-established biocompatible excipients with extensive FDA regulatory precedent. Poloxamers and carbopol are regarded as non-irritant, non-comedogenic skin excipients at standard concentrations. Overall, quercetin nanogel formulations for anti-acne applications present a favorable therapeutic index; however, formal dermal sensitization testing (OECD guideline 429), repeat-dose dermal toxicity studies, and genotoxicity assessments remain prerequisite for regulatory approval of novel formulations [14].

CLINICAL AND PRECLINICAL EVIDENCE

Preclinical evidence for quercetin's anti-acne activity spans diverse in vitro and in vivo models. In vitro studies employing C. acnes-stimulated keratinocyte (HaCaT), monocyte (THP-1), and macrophage (RAW264.7) cell lines have collectively established quercetin's capacity to suppress key

inflammatory mediators – IL-1β, IL-6, IL-8, TNF-α – while concurrently inhibiting bacterial growth [8]. The murine ear model of C. acnes-induced skin inflammation has demonstrated significant reductions in erythema and oedema following both topical and intradermal quercetin treatment, providing in vivo proof-of-concept for anti-inflammatory and anti-acne efficacy [3].

Clinical data on quercetin in acne remain limited but preliminary outcomes are encouraging. The clinical evaluation of quercetin-loaded PVA nanofibers by Amer et al. (2022) in acne patients reported reductions of 61.2% in inflammatory lesions, 14.7% in comedones, and 52.9% in total lesion count over the treatment period – results comparing favorably with those reported for conventional topical agents in similarly designed pilot trials [26]. However, randomized, double-blind, vehicle-controlled, adequately powered Phase II/III clinical trials comparing quercetin nanogel formulations against established first-line topical agents (e.g., adapalene 0.1% gel, clindamycin 1% gel) are notably absent from the literature. This constitutes the most critical evidence gap impeding clinical adoption of quercetin-based therapeutics in acne management.

FUTURE PERSPECTIVES AND RESEARCH ROADMAP

Several strategic priorities emerge from critical synthesis of the existing literature. First, rigorous head-to-head comparative studies between quercetin nanogels and established first-line topical anti-acne agents – employing validated lesion-counting protocols (IGA, ISGA) and patient-reported outcome measures (DLQI) – are urgently required to establish clinical positioning. Second, surface modification of quercetin nanocarriers with follicle-targeting moieties – such as positively charged chitosan coatings that adsorb preferentially to the negatively charged follicular surface – merits systematic exploration for enhanced pilosebaceous delivery [25].

Third, combination nanogel formulations co-loading quercetin with complementary anti-acne bioactives – resveratrol (anti-inflammatory), tanshinone IIA (sebostatic), niacinamide (barrier repair), or zinc pyrithione (antimicrobial) – present multi-target therapeutic opportunities aligned with the multifactorial aetiology of acne [22]. Fourth, green and sustainable extraction protocols for quercetin from *B. purpurea* using deep eutectic solvents (DES) or supercritical fluid extraction (SFE) should be developed to meet evolving demands for environmentally responsible pharmaceutical manufacturing [11].

Fifth, the microbiome modulation potential of quercetin nanogels warrants investigation, particularly regarding selective suppression of C. acnes without adversely disrupting beneficial commensals, such as *Staphylococcus epidermidis* – a concern conventional broad-spectrum antibiotics have failed to address. Sixth, regulatory clarity regarding the categorization of quercetin nanogel products – as cosmetics, cosmeceuticals, or over-the-counter drugs – carries significant implications for clinical trial design, safety dossier requirements, and market approval timelines, and would facilitate the orderly progression of investigational formulations through the approval pipeline [7].

CONCLUSION

The present review has assembled and critically synthesized evidence establishing quercetin, as isolated from *Bauhinia purpurea*, as a mechanistically diverse, multi-target candidate for the management of acne vulgaris and associated cutaneous inflammation. The molecule's documented capacities to suppress NF-κB-driven and MAPK-mediated inflammatory cascades, inhibit Cutibacterium acnes growth, modulate sebaceous gland activity, and restore redox homeostasis collectively provide a robust pharmacological rationale for its anti-acne application.

The formulation of quercetin within advanced nanogel delivery systems – encompassing carbopol-based nanoparticulate gels, SLN/NLC nanogels, polymeric nanogel composites, and thermosensitive nanoemulgels – has demonstrably addressed the molecule's intrinsic biopharmaceutical limitations of poor solubility, photolability, and limited dermal permeation. Available in vitro, ex vivo, and early clinical data indicate that these nanoformulations enhance follicular drug deposition, improve antibacterial efficacy, and achieve meaningful clinical lesion reductions.

Notwithstanding these advances, the field stands at a pivotal juncture: the absence of large-scale, rigorous clinical trials remains the most consequential bottleneck separating scientific promise from therapeutic reality. Structured progression through well-designed clinical development – guided by the mechanistic clarity and pharmacological rationale reviewed herein – holds genuine potential to establish quercetin-loaded nanogels as a clinically validated, safe, and effective addition to the anti-acne therapeutic armamentarium. The convergence of traditional phytomedicinal wisdom with contemporary nanotechnology, exemplified in this quercetin–*Bauhinia purpurea* platform, embodies the productive intersection of ethnopharmacology and translational pharmaceutical science.

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Conflict of Interest Statement

The authors declare no conflict of interest in relation to the contents of this manuscript.

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