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ARTICLE

The role of topical nano-based drug delivery systems for acne treatment: A systematic review and translational insights

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Acne vulgaris predominantly affects sebaceous gland-rich areas, including the face, neck, upper chest, shoulders, and back. Its pathogenesis involves increased sebum production, abnormal follicular keratinization, *Cutibacterium acnes*-mediated inflammation, and immune responses. Topical therapy—such as benzoyl peroxide, retinoids, and antimicrobials—remains the first-line treatment for mild-to-moderate acne due to localized action and reduced systemic effects. However, antibiotic resistance, skin irritation, and poor adherence are limiting. This systematic review critically analyzes clinical evidence on topical nano-based drug delivery systems for acne, assessing clinical performance, safety, and their potential to address unmet therapeutic needs. Following PRISMA guidelines, searches of four databases retrieved 1,303 records, of which 23 met inclusion criteria (2012–2025; 1,341 participants). Primary outcomes included lesion count reduction (inflammatory, non-inflammatory, total), acne severity, sebum production, and safety/tolerability. Mechanistic pathways of nanomedicines in acne pathogenesis and translational barriers were also evaluated. Nanocarriers—as solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, nanocrystals, liposomes, and nanoemulsions—loaded with active pharmaceutical ingredients (APIs) or natural compounds demonstrated superior lesion reduction and faster onset of action compared to conventional formulations. Benefits were linked to enhanced follicular targeting, controlled release, and anti-inflammatory or sebostatic effects. Formulations containing synthetic APIs (e.g., tretinoin, adapalene, clindamycin) and natural actives (e.g., quercetin, mangostin, syringic acid, linoleic acid) showed comparable efficacy, with some natural compounds offering superior safety and patient acceptability. Topical nanomedicines present promising clinical advantages in acne management, potentially improving adherence and outcomes. Further large-scale, head-to-head trials are needed to confirm their role alongside standard therapies and support regulatory adoption.

Keywords: Nanomedicine, Acne vulgaris, Nanoparticles, Transdermal drug delivery, Phytochemicals, Anti-inflammatory agents.

Introduction

Acne vulgaris is a chronic, multifactorial inflammatory skin disorder of the pilosebaceous unit, affecting approximately 85% of adolescents and a growing proportion of adults worldwide¹. With an estimated prevalence of 9.4% worldwide and an annual economic

burden exceeding 3 billion dollars in the United States alone, acne transcends mere cosmetic concerns, ranking among the top cutaneous diseases in terms of disability-adjusted life years^{2,3}. It is characterized by the formation of inflammatory and non-inflammatory lesions predominantly on the face and upper trunk, acne represents a chronic disorder of the pilosebaceous unit⁴. Generally, non-inflammatory lesions (open and closed comedones), inflammatory papules and pustules, nodules, and potential scarring occur.

Key pathogenesis driving acne development involves follicular hyperkeratinization, increased sebum production, *Cutibacterium acnes* (formerly *Propionibacterium acnes*) colonization, and inflammation⁵, within the pilosebaceous unit, collectively contributing to the severity and persistence of the condition⁶. While not life-threatening, acne significantly affects quality of life and mental health, often leading to psychological distress, including depression and anxiety³. The treatment strategies for acne vary based on the type and severity of lesions, with current guidelines advocating for topical agents as first-line therapy for mild to moderate cases^{7,8}. However, concerns regarding adverse effects,

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antibiotic resistance, and treatment costs underscore the need for alternative and complementary therapies⁹.

The clinical management of acne has evolved over decades, transitioning from sulfur and salicylic acid applications in the early 20th century to the introduction of topical antibiotics and retinoids in the 1970s and 1980s^{8,10}. More recently, concerns over bacterial resistance¹¹, drug tolerability, and treatment adherence¹² have spurred the search for advanced topical delivery systems capable of overcoming skin barrier limitations and enhancing site-specific drug delivery.

In this context, nanotechnology-based formulations have emerged as a transformative in dermatology, such as approach for acne management. Nanoformulations offer improved drug solubility, stability, controlled release, and better permeation through the stratum corneum while potentially reducing systemic exposure and adverse effects¹³. Among these, solid lipid nanoparticles (SLNs)¹⁴, nanostructured lipid carriers (NLCs)^{15,16}, nanoemulsions^{17–19}, liposomes²⁰, and niosomes²¹, nanogels have been extensively investigated to carrier common acne drugs (i.e., Clindamycin, Spironolactone, Benzoyl peroxide, Azelaic acid, and topical retinoids).

While several preclinical studies have demonstrated the benefits of nanocarriers in enhancing drug delivery through the skin, there remains a gap in systematically assessing their clinical effectiveness and safety in human trials. Moreover, as the field increasingly incorporates natural compounds with anti-inflammatory and antimicrobial activities (e.g., quercetin, alpha-mangostin, linoleic acid, syringic acid), evaluating their performance in nanostructured vehicles becomes essential to support evidence-based integration into dermatologic practice²². Some examples include tea tree oil, neem oil, mangosteen extract as main sources of bioactive compounds. Prior reviews have broadly described nano-delivery systems for acne^{23–27}, however a systematic synthesis of clinical trial data is lacking. Moreover, these reviews rarely compare synthetic versus natural active ingredients, or assess real-world tolerability and patient outcomes. This study fills this critical gap by focusing exclusively on human clinical trials and integrating quantitative outcomes such as total and inflammatory lesion count reduction, time to 50% improvement, porphyrin production, sebum levels, and patient satisfaction.

Therefore, this systematic review aims to synthesize and critically evaluate evidence of clinical trials regarding efficacy and safety of nanoformulated topical interventions for acne vulgaris, commenting gaps and emerging trends. Moreover, this review critically discusses translational challenges, integrating preclinical, regulatory, and market perspectives to propose a conceptual framework for clinical advancement. Finally, through a comprehensive synthesis of existing clinical evidence, this review seeks to inform clinical practice and guide future research endeavors to pursue optimized acne management strategies.

Search methods

Search strategy and eligibility criteria

A systematic search was conducted in four scientific databases (Science Direct, PubMed, Web of Science, and Scopus) from their inception to July 2025. The PubMed search strategy was used as a reference to develop search strategies for the other databases. English filtered the language of articles. The search terms included MeSH terms combined using Boolean operators to form the main search string, that was then adapted for each database style: (Nano OR Nanomedicine) AND (Acne OR "Acne vulgaris") AND (Topical OR "Topical acne agent") AND (Efficacy OR "Therapeutic efficacy") AND ("Clinical trials" OR "Randomized Clinical trial" OR "Double-blind clinical trial").

As inclusion criteria, studies were included if they were clinical trials evaluating the effectiveness of topical nanomedicine, with outcome measures including lesion count, time to reduce lesions by 50%, lesion area, sebum production, acne severity, porphyrin production, global clinical assessment, participant evaluation, and quality of life. Studies involving participants who used oral or mechanical therapies for acne vulgaris, those lacking a description of therapeutic composition or nano products, studies with participants having other dermatological conditions interfering with treatment evaluation, and studies conducted on animals were excluded.

Data extraction and synthesis

According to PRISMA methodology²⁸, two authors independently reviewed and extracted data using a predefined protocol. In cases of discrepancy, a third reviewer was consulted. Data extracted from each study included author details, publication year, study design and duration, study population, intervention details (Nano medicine, pharmaceutical form, dose/frequency, and administration route), controls, outcome measures, and adverse effects.

Beyond systematically reviewing clinical trials on nanomedicines for acne, we critically analyzed translational challenges and regulatory gaps identified across the included studies and complementary literature. This dual approach enables both evidence synthesis and contextual insight into barriers for clinical implementation.

Assessment of risk of bias

Two independent reviewers assessed the risk of bias in included randomized controlled trials (RCTs) using the Cochrane Guide for Review Authors on Assessing Study Quality using the Cochrane Collaboration tool. Studies were classified as having "low risk," "unclear risk," or "high risk" of bias based on criteria including random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias.

Included studies

Database searches yielded a total of 1,303 records up to July 2025. After removing duplicates, 1,253 records were screened



based on titles and abstracts, resulting in 115 articles selected for full-text reading. Of these, 92 articles did not meet

inclusion criteria, leaving 23 studies for inclusion in the systematic review (Figure 1).

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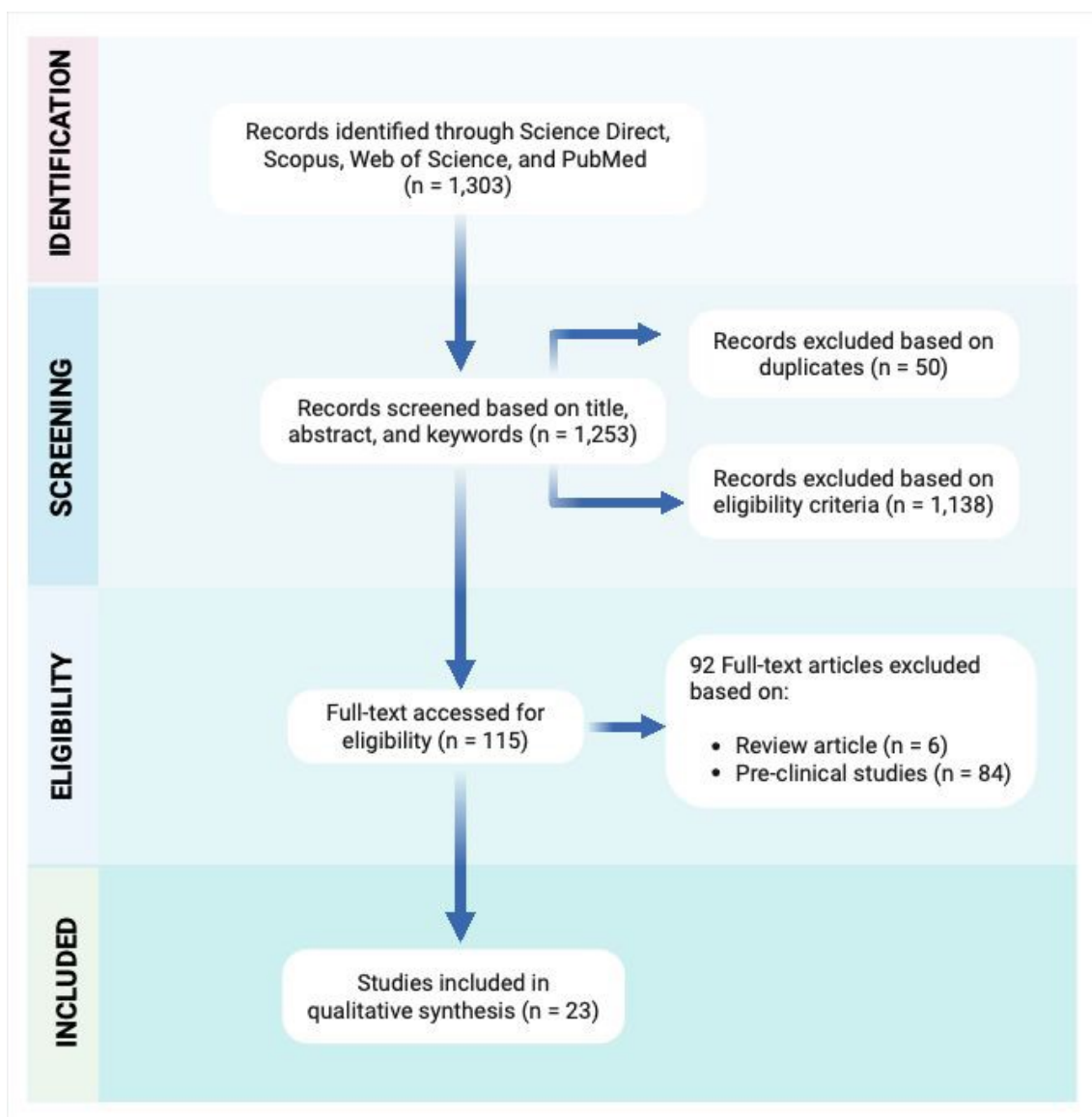


Figure 1 - PRISMA flow diagram of the database search, trial selection, and articles included in this systematic review.

Main findings and characteristics of the studies

The 23 included studies were summarized (Table 1). Among them, 11 were split-face studies, and 2 were before-and-after trials. Of all trials, 16 compared intervention with conventional treatment, 2 with another approved therapy, 3 with placebo, and 2 had no control. Study durations ranged from 4 to 12 weeks, involving 1,341 participants. Various acne severity

classifications were used, with lesion count being the most common. Interventions mostly included single nanomedicines or combinations of nanomedicine and antibiotic administered topically. Outcome measures included lesion count, time to reduce lesions by 50%, lesion area, sebum production, acne severity, porphyrin production, global clinical assessment, participant evaluation, and quality of life. Seventeen studies reported adverse effects.



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Table 1 - Main characteristics of the included studies in this systematic review.

Study design, duration	Participants N (intervention group/control group)	Acne classification (severity degree; classification system)	Intervention (Nano medicine; pharmaceutical form(s); dose/frequency; route(s) of administration)	Control	Outcomes	Adverse effects	Ref.
RCT--8 weeks	36/40	Mild to moderate acne vulgaris; GAGS	Spironolactone -NLC 1%; Gel	Spironolactone alcoholic gels 1%	Non-inflammatory, inflammatory, TLC, ASI	Dryness and itching most frequent symptoms in the control group	15
RCT-8 weeks	20/20	Mild to Moderate Acne; GAGS	Chitosan-coated spironolactone -NLC gel 1% + clindamycin 2% solution	Chitosan-coated NLC gel + clindamycin 2% solution	Non-inflammatory, inflammatory, TLC, ASI	NR	16
Before-After study-8 weeks	20	Mild to moderate acne vulgaris	Bergamot Essential Oil- Nano-Phytosomes- Spironolactone	-	Non-inflammatory, inflammatory, TLC	Without adverse effects in both groups	29
RCT-12 weeks	109/98	Mild, Moderate or severe; GAGS	Tretinoin Nanoemulsion; Gel:0.025% (Nioret® Nanogel™); cutaneous	Tretinoin 0.025% Gel (Retino-A® Gel)	Non-inflammatory, inflammatory, TLC, ASI	Dryness was the most common adverse event significantly less in the nano gel group	18
Split face study-6 weeks	10	mild-to-moderate acne vulgaris	Tretinoin-nano emulsion 0.05%	Tretinoin emulsion 0.05%	Non-inflammatory and inflammatory lesions	NR	30
Split face study-8 weeks	16	Mild to moderate facial acne vulgaris	Tretinoin-NLC emulgel 0.05%	Tretinoin cream 0.05%	Non-inflammatory and inflammatory lesions	NR	31
Split face study-4 weeks	6/6	Mild to moderate acne vulgaris	Tretinoin- liposomal 0.025% Gel	Tretinoin 0.025% Gel	Non-inflammatory, inflammatory, and Total Lesion Count	NR	20
Split face study-4 weeks	12	Facial acne vulgaris	Tretinoin- proniosomes 0.025% Gel	Acretin 0.025% Tretinoin	Non-inflammatory and inflammatory lesions	Very slight erythema (score $\frac{1}{4}$ 0.143 \pm 0.377) was observed for TRT proniosomal gel.	32
RCT-12 weeks	119/93	Mild, moderate, or severe acne vulgaris	Adapalene 0.1% and clindamycin 1% combination nano-emulsion gel (Adalene® Nanogel™)	Deriva-CMS® Gel	Non-inflammatory, inflammatory, TLC, ASI	Lower local irritation and erythema were recorded with the nano group	33
Before-After study-12 weeks	13	Mild to Moderate Acne	Adapalene-NLC 0.1%	No	Non-inflammatory, inflammatory, TLC, ASI	Local adverse effects (burning, scaling, and erythema) occurred in three	34
RCT -12 weeks	53/47	Mild to moderate acne vulgaris-NR	Tea tree oil nanoemulsion containing Adapalene 0.1%; Gel	Adapalene 0.1% Gel	Non-inflammatory, inflammatory, TLC, ASI	Dryness was the most common adverse effect in both groups	35



RCT-8 weeks	15/15	Mild to Moderate facial Acne	Isotretinoin-SLN 0.05% Gel+clindamycin 2% solution	Isotrex® 0.05% Gel +clindamycin 2% solution	Non-inflammatory, inflammatory, TLC, ASI	No skin irritancy in intervention while three patients in the Isotrex® group were omitted	View Article Online DOI: 10.1039/D5BM00298B 14
Split face study-8 weeks	30	Mild (6%) to moderate (80%) facial acne vulgaris	Retinol Nano Liposomal Solution (Lipoceutical nanosome sesderma)	Topical retinoid cream	Number of total acne lesions, non-inflammatory, and inflammatory lesions	Local adverse events were significantly less in the nano formulation	36
Split face study-6 weeks	20	Mild to moderate acne facial acne vulgaris	Retinyl Palmitate-Ethosomal 0.05%; Gel;	Tretinoin cream (Acretin™ 0.05%)	Non-inflammatory, inflammatory, TLC	All patients had no, or slight skin irritation on the nano group	37
Split face study-4 weeks	23	mild to moderate acne	Retinaldehyde-loaded niosomes 0.05% Solution	-	Non-inflammatory lesions	Without adverse effects	38
RCT-12 weeks	100/100	Mild, moderate or severe facial acne vulgaris	Clindamycin Nano-emulsion Gel 1% (Zyclin® Nanogel™)	Clindamycin Gel 1% (Clindac-A® Gel)	Non-inflammatory, inflammatory, TLC, ASI	Local adverse events were less in the nano formulation	19
RCT-12 weeks	50/50	Mild to moderate acne vulgaris; GAGS	Niosomal Benzoyl Peroxide 1% and Clindamycin 1%; Lotion	Niosomal Clindamycin Lotion 1%	TLC; % reduction of acne lesions; lesions, ASI, GAGS	Without significant adverse effects, Pruritus at week 2 was higher in control group	39
RCT-8 weeks	33/35	mild to moderate facial acne	Azelaic Acid nanocrystal hydrogel 10%	Azelaic Acid cream 20% (Skinoren®)	Non-inflammatory, inflammatory, TLC	NR	40
RCT-8 weeks	32/32	Moderate severity of acne vulgaris	AgNP Gel 1% (ASAP®) +2.5% benzoyl peroxide	1% Clindamycin Gel+2.5% benzoyl peroxide	Non-inflammatory, inflammatory, TLC, ASI	No adverse effects in silver nanoparticle group-	41
Split-face study -8 weeks	20	Mild to moderate acne vulgaris; leeds system	Quercetin + EOs nanofibers	Placebo (Panthenol® Cream)	Non-inflammatory, inflammatory, TLC	Without adverse effects	42
Split-face study-8 weeks	20	Mild to moderate acne vulgaris; leeds system	Quercetin + EOs aspasomes thin film 1%;	Placebo (Panthenol® Cream)	Non-inflammatory, inflammatory, TLC	Without adverse effects	43
Split face-before-after study- 4 weeks	20	Mild to moderate;leeds system	Syringic acid loaded linoleic acid 1% transferosomes	Adapalene 0.1% Gel	Non-inflammatory, inflammatory, TLC	NR	44
Split-face study-12 weeks	28	Mild to moderate acne vulgaris; GAGS	Mangosteen extract nano gel 0.5%+ 2.5% benzoyl peroxide cream	1% clindamycin gel+ 2.5% benzoyl peroxide cream	Comedones, inflammatory lesions	No severe side effects in intervention group;	45

GAGS: Global Acne Grading System; EOs: essential oils; NLC: nanostructured lipid carriers; SLN: solid lipid nanocarriers; NR: not reported; ASI: acne severity index; TLC: total lesion count; RCT: randomized controlled trial; AgNP: silver nanoparticle.

Outcomes from clinical trials involving nano-based drug delivery systems for acne treatment

In the studies overviewed, a wide range of carriers were identified, including lipid-based vesicles (niosomes, liposomes, ethosomes, transferosomes), solid matrices (SLN, NLC), polymeric nanocarriers (electrospun fibers, polymeric nanoparticles), and hybrid systems such as phytosomes and aspasomes. This diversity reflects the tailored strategies adopted to improve solubility, penetration, and local

tolerability depending on the chemical nature of each active compound.

Efficacy by Lesion Type: Inflammatory, Non-Inflammatory, and Total Lesions

The number of non-inflammatory lesions was reduced from baseline in the intervention groups in all studies that used it as an outcome. Of these studies, only 15 reported that the reduction was statistically significant, 1 achieved considerable reduction, and 7 without significant reduction compared to control groups (Table 2).



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Table 2 - Reduction in the total, inflammatory and non-inflammatory acne lesion in the nano-formulation compared to the control group.

Intervention group	Inflammatory Lesions	Non-inflammatory Lesions	Total Lesions	Study design, duration	Ref.
adapalene 0.1% and clindamycin 1% combination nano-emulsion gel (Adalene® Nanogel™)	Significant reduction	Significant reduction	Significant reduction	split face study-8 weeks	Prasad et al., 2012 ³³
Clindamycin Nano-emulsion Gel 1% (Zyclin® Nanogel™)	Significant reduction	Significant reduction	Significant reduction	RCT-12 weeks	Bhavsar et al., 2013 ¹⁹
Isotretinoin-SLN 0.05% Gel+clindamycin 2% solution	Significant reduction	Significant reduction	-	RCT-8 weeks	Layegh et al., 2014 ¹⁴
Tretinoin Nanoemulsion; Gel:0.025% (Nioret® Nanogel™)	Significant reduction	Significant reduction	-	RCT-12 weeks	Chandrashekhar et al., 2015 ¹⁸
Tretinoin- proniosomes 0.025% Gel	Significant reduction	Significant reduction	Significant reduction	split face study-4 weeks	Rahman et al., 2015 ²⁰
Spiroinolactone -NLC 1%; Gel	Significant reduction	No significant	Significant reduction	RCT--8 weeks	Kelidari et al., 2016 ¹⁵
Tretinoin- liposomal 0.025% Gel	Significant superior efficacy	Significant superior efficacy	-	split face study-4 weeks	Rahman et al., 2016 ³²
Retinol Nano Liposomal Solution (Lipoceutical nanosome sesderma)	Significant reduction	Significant reduction	Significant reduction	split face study-8 weeks	El-Samahy et al., 2017 ³⁶
Silver Nanoparticle (AgNP) Gel 1% (ASAP®) +2.5% benzoyl peroxide	Slightly greater reduction	No significant difference	-	RCT-8 weeks	Jurairattanaporn et al., 2017 ⁴¹
Tretinoin-nano emulsion 0.05%	Significant reduction	Significant reduction	-	split face study-6 weeks	Sabouri et al., 2018 ³⁰
Mangosteen extract nano gel 0.5%+ 2.5% benzoyl peroxide cream	Significant reduction	Significant reduction	-	split-face study-12 weeks	Lueangarun et al., 2018 ⁴⁶
Niosomal Benzoyl Peroxide 1% and Clindamycin 1%; Lotion	No significant difference	No significant difference	No significant difference	RCT-12 weeks	Mohammadi et al., 2019 ³⁹
Quercetin-Tea tree oil aspasomes thin film 1%;	Significant reduction	No Significant reduction	Significant reduction	split-face study-8 weeks	Sherif Amer et al., 2020 ⁴³
Azelaic Acid Nanocrystal hydrogel 10%	Significant reduction	Significant reduction	Significant reduction	RCT-8 weeks	Tomic et al., 2021 ⁴⁰
Retinyl Palmitate-Ethosomal 0.05%; Gel;	Significant reduction	Significant reduction	Significant reduction	split face study-6 weeks	Salem et al., 2021 ⁴⁷
retinaldehyde-loaded niosomes 0.05%	Significant reduction	No significant difference	-	split face study-4 weeks	Kim et al., 2021 ³⁸
Tea tree oil nanoemulsion containing Adapalene 0.1%; Gel	Significant reduction	No Significant reduction	Significant reduction	RCT -12 weeks	Najafi et al., 2022 ³⁵
Tretinoin-NLC emulgel 0.05%	Significant reduction	Significant reduction	significantly higher	split face study-8 weeks	Samadi et al., 2022 ³¹
Quercetin+Tea tree oil-nanofibers; patch	Significant reduction	No significant difference	Significant reduction	split-face study -8 weeks	Sherif Amer et al., 2022 ⁴²



chitosan-coated spironolactone -NLC gel 1% + clindamycin 2% solution	No significant between groups	Significant reduction	Significant reduction	RCT-8 weeks	View Article Online Saeedi et al., 2023 ¹⁶ DOI: 10.1039/C3TB02988B
Bergamot Essential Oil- Nano-Phytosomes- Spironolactone	Significant reduction	Significant reduction	Significant reduction	Before-After study-8 weeks	Albash et al., 2023 ²⁹
syringic acid loaded linoleic acid 1% transferosomes	Considerable reduction	Significant reduction	Significant reduction	split face-before-after study- 4 weeks	Abd-allah et al., 2023 ⁴⁴

The studies reviewed used conventional synthetic drugs commonly used in acne treatment - such as tretinoin, adapalene, isotretinoin, clindamycin, and spironolactone - and naturally derived bioactives like quercetin, linoleic acid, syringic acid, and α -mangostin. These natural compounds have attracted increasing attention in dermatological nanomedicine due to their biocompatibility, anti-inflammatory and antioxidant properties, and lower potential for irritation⁴⁸. However, inherent limitations such as poor water solubility, chemical instability, and limited skin permeation have prompted the use of nanocarriers - such as transferosomes, nanofibers, lipid nanocrystals, phytosomes, and aspasomes - to enhance their delivery and therapeutic performance.

The presence of these bioactives reflects a current trend in nanomedicine: the pursuit of safer, more effective, and sustainable therapeutic alternatives, often combining anti-inflammatory, bacteriostatic, and skin-repair mechanisms⁴⁹. Thus, Figure 2 summarizes the variety of nanoscale strategies available for acne management but also highlights the chemical and functional diversity of the active ingredients, offering a more integrated perspective between traditional pharmacology and nature-inspired innovation.

Comparative efficacy by active ingredient delivered via nano-based drug delivery systems

Spironolactone

Spironolactone (SP) is an anti-androgenic agent categorized as a Biopharmaceutical Classification System (BCS) class II compound, characterized by high permeability and low solubility⁵⁰. As observed in various clinical studies, its use in acne management is linked to its capacity to reduce sebum production⁵¹. Despite its efficacy, the oral form of spironolactone is limited by low and variable bioavailability and endocrine side effects, which restrict its systemic use⁵². Topical formulations have been investigated as an alternative to enhance local drug delivery, minimize systemic exposure, and improve patient compliance⁵³.

In this sense, stood out NLCs, composed of a blend of solid and liquid lipids, offer enhanced drug loading efficiency and controlled release profiles. Their biocompatible lipid composition makes them particularly suitable for application on inflamed or sensitive skin⁵⁴. For example, literature reports the sebostatic activity NLCs for spironolactone in the management of alopecia, mediated by androgen receptor blockade. This

mechanism involves the reduction of sebum production in sebaceous glands and the inhibition of androgen receptors in the dermal papillae⁵⁵.

NLCs for spironolactone allows for intimate contact with the stratum corneum, promoting greater skin absorption of the encapsulated spironolactone through the formation of a uniform film on the skin surface after application^{15,56}. In a randomized clinical trial conducted by Kelidari et al. (2016) evaluated a NLC gel containing 1% spironolactone in comparison with a 5% alcoholic spironolactone gel. Both groups demonstrated a significant reduction in non-inflammatory and inflammatory lesions after 8 weeks, although the difference between the formulations was not statistically significant. The NLC formulation reduced non-inflammatory lesions by approximately 47.6% and inflammatory lesions by 29.7%, while the alcoholic gel achieved reductions of 52.3% and 22.7%, respectively. Both treatments significantly lowered the total lesion count from baseline ($P < 0.001$).

Similarly, Saeedi et al. (2023) assessed a chitosan-coated spironolactone NLC gel combined with 2% clindamycin solution in comparison to a placebo formulation. The combination therapy led to a notable reduction in non-inflammatory lesions (from 26.45 ± 6.66 to 10.00 ± 3.9) compared to placebo (from 28.15 ± 6.97 to 20.25 ± 6.29) after 8 weeks ($P < 0.0001$). The total lesion counts also decreased more markedly in the intervention group.

In a before-and-after study, Albash et al. (2023) investigated spironolactone-loaded nanophytosomes combined with bergamot (*Citrus medica* L.) essential oil (BEO). After 8 weeks of topical treatment, comedonal lesions were reduced by 100%, with substantial improvements in inflammatory lesions and total lesion count (reductions above 90%).

These outcomes suggest that the combined phytosome system may enhance therapeutic efficacy through a potential antibacterial and anti-inflammatory synergy between BEO and spironolactone. This effect can be attributed to two proposed antiacne mechanisms of BEO reported in the literature⁵⁷: (i) modulation of sebaceous gland activity by reducing gland proliferation, limiting triglyceride accumulation, and decreasing the release of pro-inflammatory cytokines such as IL-1 α ; and (ii) induction of apoptosis in sebaceous glands coupled with antibacterial activity against *C. acnes*, both contributing to the attenuation of inflammatory responses in acne lesions.

Although the topical nanoformulations containing spironolactone — such as NLCs, phytosomes, and chitosan-coated carriers — demonstrated favorable outcomes in



reducing acne lesion counts and minimizing adverse effects, the clinical significance of these differences remains uncertain. In some cases, the magnitude of improvement between formulations (e.g., phytosomes vs. NLCs) was modest and statistically overlapping, raising the question of whether these differences translate into meaningful clinical benefits for patients. Moreover, most studies reviewed were conducted with small sample sizes (ranging from 20 to 40 participants), which may limit the generalizability and statistical power to

detect nuanced efficacy or safety differences. Another critical gap is the lack of long-term follow-up to assess sustained effectiveness and the safety of chronic use, especially given spironolactone's known systemic hormonal effects. Future clinical trials with larger cohorts, standardized protocols, and extended monitoring periods are warranted to validate these findings and to support regulatory and clinical adoption of topical spironolactone nanocarriers in acne management.

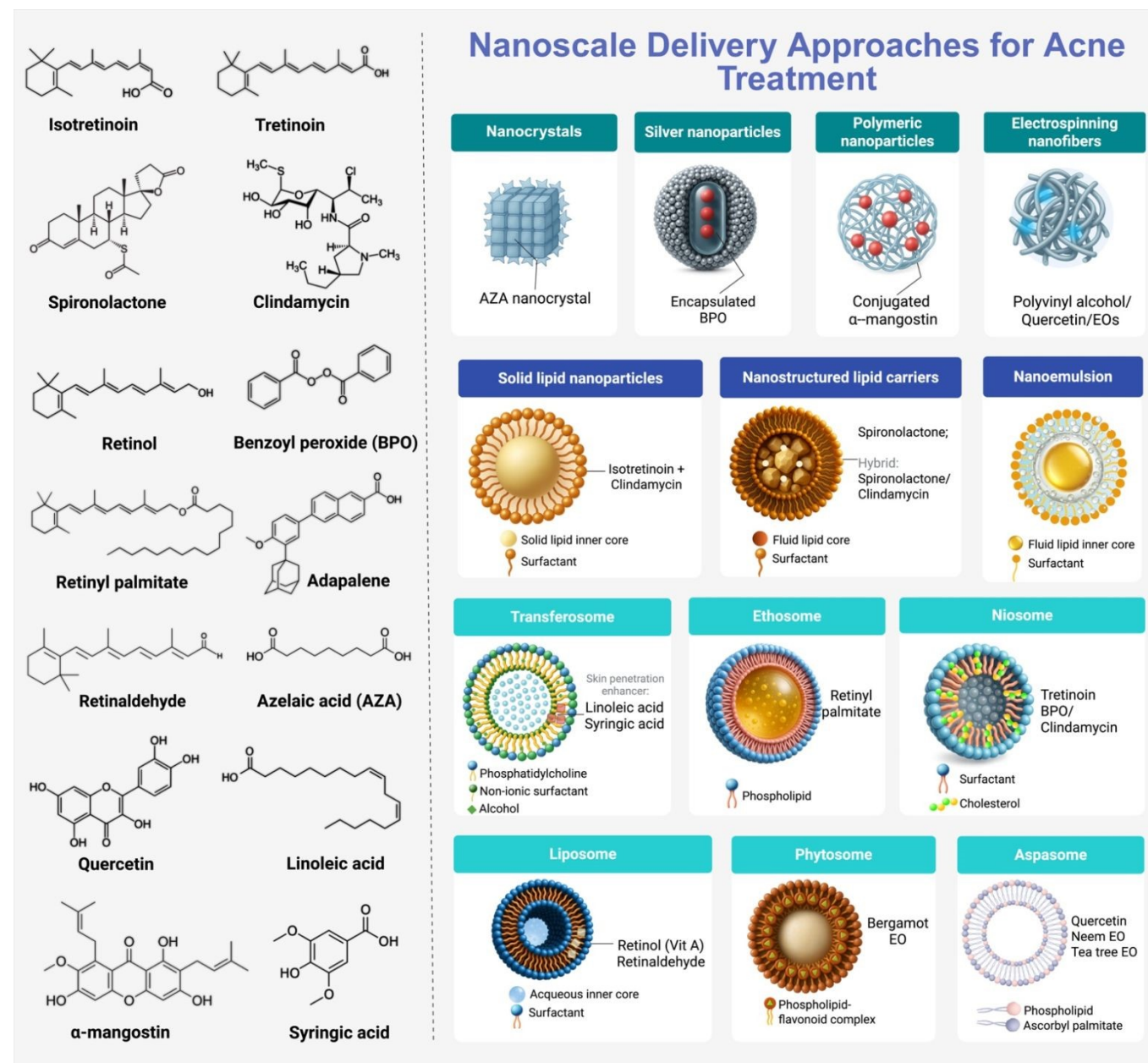


Figure 2- Main active pharmaceutical ingredients (APIs) used in topical nanomedicine formulated at the nanoscale for improved dermal delivery and anti-acne performance.

Topical retinoids (tretinoin, adapalene, isotretinoin)

Topical retinoids represent the first-line treatment for mild to moderate forms of acne vulgaris. Their use aims to normalize the proliferation and differentiation of follicular keratinocytes,

thereby reducing microcomedone formation and supporting proper desquamation within the pilosebaceous unit. By doing so, these agents help prevent the creation of an environment that favors the growth of *Cutibacterium acnes* (formerly



Propionibacterium acnes). Although effective, topical retinoids are frequently associated with local adverse effects, including erythema, peeling, dryness, burning, and pruritus. These side effects can contribute to reduced treatment adherence. Moreover, retinoid use may increase cutaneous sensitivity to ultraviolet radiation, necessitating concurrent photoprotection measures (Vasam et al., 2023).

Among retinoids, adapalene is generally considered more stable and better tolerated due to its selective affinity for retinoic acid receptors, whereas tretinoin and isotretinoin are more photosensitive and often more irritating. Recent advances in nanotechnology have sought to overcome these limitations. Nanocarrier-based delivery systems—such as SLNs, nanoemulsions, and liposomes—have been explored to enhance drug stability, reduce irritation, and improve dermal penetration. These systems offer the potential to maintain therapeutic efficacy while mitigating adverse effects, thereby improving patient compliance.

Tretinoin

Tretinoin, a derivative of vitamin A, is widely used as a first-line topical therapy for various forms of acne vulgaris^{9,12}. Its mechanism of action involves binding to nuclear retinoic acid receptors, which helps normalize follicular keratinization. This process reduces microcomedone formation by modulating keratinocyte proliferation and differentiation within the stratum corneum, thus decreasing the number of non-inflammatory lesions^{9,12}. Additionally, tretinoin has been reported to exert anti-inflammatory effects, potentially through toll-like receptor inhibition, contributing to the reduction of inflammatory lesions¹².

Beyond its action on keratinocytes, tretinoin may stimulate collagen synthesis and influence sebaceous gland activity, although the clinical relevance of these effects in acne remains under investigation¹⁶. The drug is associated with local adverse effects such as dryness, peeling, burning, and itching, which can lead to reduced patient adherence or discontinuation of therapy¹⁶. Tretinoin's low aqueous solubility and instability when exposed to air, light, or heat necessitate higher concentrations or more frequent application, potentially exacerbating these side effects^{29,58}. Its irritation potential is known to depend on both concentration and formulation vehicle²⁹.

Conventional topical delivery (e.g., creams, gels, lotions) often faces challenges such as poor skin penetration and stability, as the active compound is susceptible to degradation by ultraviolet light and environmental exposure⁵⁹. Nanotechnology-based delivery systems—including liposomes, niosomes, SLNs, and NLCs—have been investigated to improve tretinoin's stability, penetration, and therapeutic index^{12,18,29,30}. In a randomized clinical trial involving 207 patients, Chandrashekar et al. (2015) demonstrated that both tretinoin nanoemulsion gel (0.025%) and conventional tretinoin gel (0.025%) significantly reduced inflammatory and non-inflammatory lesions over 12 weeks. The nanoemulsion group showed a greater reduction in inflammatory lesions (78.1% ±

25.2%) compared to the conventional gel (66.9% ± 35.2%, $p = 0.02$), while the difference for non-inflammatory lesions was not statistically significant ($p = 0.1$).

A split-face study by Sabouri et al. (2018) reported that a 0.05% tretinoin nanoemulsion resulted in significant reductions in blackheads, whiteheads, and papules at 6 weeks, whereas conventional tretinoin emulsion did not achieve significant changes. Similarly, Samadi et al. (2022) found that a 0.05% tretinoin NLC emulgel led to significantly greater reductions in blackheads and whiteheads than conventional tretinoin cream at both 4 and 8 weeks ($p < 0.001$ for both lesions).

Rahman et al. (2016) conducted a split-face study with 12 patients comparing tretinoin liposomal 0.025% gel with conventional 0.025% gel, showing significantly greater reduction in total lesion count with the nano-formulation. In an earlier study, Rahman et al. (2015) also observed superior performance of a tretinoin proniosomal gel over marketed tretinoin formulations in improving various acne lesion types throughout the treatment period.

Although the clinical data reviewed suggest improved lesion reduction with tretinoin-loaded nanocarriers—particularly nanoemulsions, NLCs, liposomes, and proniosomes—comparative effectiveness varies among formulations. Differences in carrier composition, skin penetration depth, and drug-release profiles may explain the heterogeneity of clinical outcomes.

Importantly, although some trials indicate enhanced tolerability of tretinoin nanoformulations, this is not consistently reported across studies, and direct comparisons often lack standardized scoring systems for adverse effects. The presence of side effects such as erythema, peeling, and dryness remains a concern in both conventional and nano-based formulations.

Overall, while nanoformulations appear to offer improved pharmacokinetic profiles and moderate clinical advantages over conventional tretinoin gels—particularly in inflammatory lesion reduction—the clinical relevance of these differences remains to be fully established. Future randomized trials with larger sample sizes, longer follow-up periods, and harmonized reporting of both efficacy and tolerability outcomes are needed to better position tretinoin-based nanomedicine in acne therapy.

Adapalene

Adapalene is a third-generation synthetic retinoid that has been widely used in acne therapy for approximately three decades^{15,16,29}. Compared to earlier retinoids, adapalene presents distinct physicochemical characteristics, including greater chemical and photostability, increased molecular rigidity, and enhanced lipophilicity. However, like other retinoids, it suffers from poor aqueous solubility, which can limit its bioavailability in conventional formulations²⁹.

To overcome these limitations, various nanocarrier systems—such as nanoemulsions and NLCs—have been explored for adapalene delivery. These platforms offer potential advantages, including improved solubility, targeted delivery, controlled release, and enhanced stability^{12,15}.



In a randomized clinical trial involving 212 participants, Prasad et al. (2012) compared a nanoemulsion gel containing adapalene 0.1% and clindamycin 1% (Adalene® Nanogel™) to a conventional gel formulation (Deriva-CMS® Gel). The nanoemulsion group demonstrated significantly greater reductions in total, inflammatory, and non-inflammatory lesions at week 12 ($P < 0.001$ for all endpoints). These improvements were already apparent by week 4 and persisted throughout the study duration.

Similarly, Najafi-Taher et al. (2022) conducted a randomized trial with 100 patients (53 in the nanoemulsion group and 47 controls), evaluating a tea tree oil nanoemulsion combined with adapalene 0.1% versus a standard adapalene 0.1% gel. The nanoemulsion formulation achieved superior reductions in total, inflammatory, and non-inflammatory lesion counts across all time points ($P < 0.001$ for all). The nanoemulsion group showed pronounced decreases in inflammatory lesions ($\beta = -3.282 \pm 0.5989$) and non-inflammatory lesions ($\beta = -5.473 \pm 1.1429$) after 12 weeks compared to controls. The overall difference in total lesion reduction between groups was statistically significant ($\beta = -8.832 \pm 1.5189$; $P < 0.001$).

While both studies show statistically significant reductions in lesion counts with nanoemulsion-based adapalene formulations, the contribution of adjunct compounds—clindamycin in Prasad et al. (2012) and tea tree oil in Najafi-Taher et al. (2022)—should be considered when interpreting efficacy outcomes. These actives possess known antibacterial and anti-inflammatory effects that may independently contribute to lesion reduction. Therefore, the enhanced results cannot be solely attributed to the nanocarrier or to adapalene alone. Additionally, while statistical differences were significant, the magnitude of lesion reduction should be evaluated in the context of clinical relevance—i.e., whether these changes translate to perceptible patient improvement or higher adherence. Future studies employing head-to-head designs with monotherapy nanoformulations would help clarify the specific role of nanocarriers in enhancing adapalene efficacy.

Isotretinoin

Isotretinoin, a derivative of 13-cis-retinoic acid, belongs to the first generation of retinoids and has been explored for both systemic and topical acne therapies. Although effective, the topical formulations of isotretinoin available on the market (e.g., creams and gels) are associated with limitations, including unwanted systemic absorption and local skin irritation¹⁴. Moreover, isotretinoin is known to be photosensitive, undergoing degradation upon exposure to ultraviolet light, which further compromises its stability and efficacy¹⁴.

To address these challenges, the use of nanocarriers such as SLNs has been investigated to enhance cutaneous delivery, improve photostability, and reduce both systemic exposure and irritation¹⁴.

In a randomized clinical trial involving 30 participants, Layegh et al. (2013) compared a formulation containing isotretinoin 0.05% SLN gel combined with clindamycin 2% solution to a

conventional isotretinoin 0.05% gel (Isotrex®) plus clindamycin. After 8 weeks of treatment, the SLN formulation demonstrated significantly greater improvements in both non-inflammatory and inflammatory lesions. Specifically, the recovery rate for non-inflammatory lesions at week 4 was $41.49\% \pm 6.24\%$ in the SLN group compared to $32.25\% \pm 6.61\%$ in the control group. By week 8, these rates increased to $77.05\% \pm 4.79\%$ and $53.69\% \pm 7.34\%$, respectively ($P < 0.01$). Similarly, inflammatory lesion recovery was higher in the SLN group at week 8 ($83.59\% \pm 3.79\%$) compared to controls ($61.15\% \pm 5.34\%$; $P < 0.01$).

The trial by Layegh et al. (2013) demonstrates statistically significant improvements in both inflammatory and non-inflammatory lesions with the SLN-based isotretinoin formulation. However, the overcome of some limitations must be considered. The study included a small sample size ($n = 30$), which may affect the generalizability of the findings. Furthermore, while lesion count reductions were notable, it remains unclear whether these translate into meaningful clinical benefits—such as improved patient satisfaction, long-term remission, or reduced relapse rates. Additionally, the combined use of clindamycin in both groups complicates the attribution of therapeutic efficacy solely to the nanocarrier system. Further large-scale, controlled trials could validate these results and assess the long-term safety, tolerability, and pharmacokinetic profile of topical SLN-based isotretinoin formulations.

Regarding the anti-acne mechanism, isotretinoin (13-cis-retinoic acid) exhibits a unique sebo-suppressive effect that distinguishes it from other retinoids. This activity has been linked to its ability to competitively inhibit the oxidative 3α -hydroxysteroid dehydrogenase (3α -HSD) function of retinol dehydrogenase-4 (RoDH-4), an enzyme expressed in both human liver and skin. RoDH-4 catalyzes the oxidation of steroid precursors such as 3α -androstenediol and androsterone into the potent androgens dihydrotestosterone (DHT) and androstenedione, which stimulate sebum production⁶⁰. Isotretinoin, as well as 3,4-didehydroretinoic acid, significantly inhibits this conversion in vitro, thereby reducing local androgenic stimulation of sebaceous glands. In contrast, other retinoids such as all-trans-retinoic acid, acitretin, and adapalene do not inhibit this pathway. These findings suggest that isotretinoin's inhibition of RoDH-4 may underlie its superior ability to suppress sebum secretion in acne therapy.

3.1.2.4 Retinyl palmitate, retinol, and retinaldehyde Retinyl palmitate (RP), recognized as one of the most stable derivatives of retinoic acid, has gained attention for its potential in acne management when incorporated into nanocarrier systems. These formulations aim to improve RP's stability and enhance its cutaneous penetration, offering a promising alternative to conventional topical therapies³⁷.

In a split-face study involving 20 patients, Salem et al. (2021) compared a retinyl palmitate ethosomal hydrogel (0.05%) to a marketed tretinoin cream (Acretin™ 0.05%) over six weeks. Both treatments resulted in significant reductions in total, inflammatory, and non-inflammatory lesion counts from baseline ($P < 0.001$ for both formulations). However, the RP ethosomal hydrogel was associated with a significantly greater



reduction in non-inflammatory lesions ($P = 0.008$) and total lesion count ($P = 0.016$) at week 6 compared to the tretinoin cream. Importantly, the RP formulation also demonstrated superior tolerability, with minimal reports of skin irritation relative to the tretinoin-treated side.

El-Samahy et al. (2017) conducted an eight-week split-face study with 30 participants, comparing a retinol nano-liposomal solution (Lipoceutical Nanosome Sesderma) to a conventional topical retinoid cream. The nano-liposomal formulation achieved significantly greater reductions in total and inflammatory lesion counts compared to the conventional treatment ($P < 0.001$). While both formulations improved non-inflammatory lesions, the difference between them was not statistically significant. Notably, the nano-liposomal retinol formulation was more effective in reducing inflammatory lesions ($P < 0.001$)³⁶.

In another split-face study, Kim et al. (2021) evaluated a retinaldehyde-loaded niosomal solution (0.05%) in 23 patients with facial acne. The treatment resulted in significant reductions in both closed and open comedones compared to baseline, with closed comedones decreasing by 8.58% at week 2 ($P = 0.036$) and by 24.01% at week 4 ($P < 0.001$).³⁸

The use of nanocarriers—such as ethosomes, liposomes, and niosomes—has shown promise in enhancing the cutaneous delivery, stability, and tolerability of vitamin A derivatives. However, their incremental clinical benefit over standard formulations remains to be fully established. Although several studies report superior reduction of lesions (particularly non-inflammatory or comedonal types) and improved tolerability, the cost-effectiveness and scalability of these advanced systems must be critically weighed. Additionally, variations in study design, small sample sizes, and short treatment durations may limit the generalizability of the findings. Further large-scale, head-to-head clinical trials are needed to determine whether these nanocarrier-based formulations offer meaningful advantages that justify their added formulation complexity and cost in real-world clinical settings.

Topical retinoids, including retinol derivatives, play a central role in acne treatment by targeting several key mechanisms of the disease. Once applied to the skin, retinol undergoes enzymatic conversion to retinoic acid, which exerts its biological activity by binding to nuclear retinoic acid receptors (RARs)⁶¹. This interaction leads to the regulation of gene transcription pathways involved in keratinocyte proliferation, differentiation, inflammation, and immune response⁶². Among the three RAR subtypes (α , β , and γ), the γ isoform is predominant in the epidermis, and receptor selectivity may influence clinical outcomes⁶¹. Retinoids promote normalization of desquamation within the follicular epithelium, reducing microcomedone formation, and they modulate inflammatory processes at the genetic level. Recent transcriptomic analyses have revealed that certain retinoids, such as trifarotene, can uniquely regulate gene networks associated with immune activation, cell migration, and extracellular matrix remodeling in acne lesions, offering mechanistic insights into their therapeutic effects⁶³.

Azelaic acid

Azelaic acid (AZA) is a saturated dicarboxylic acid naturally produced by *Malassezia furfur*. It is known for its multifaceted action, combining antibacterial effects against *Cutibacterium acnes* (formerly *Propionibacterium acnes*), anti-inflammatory properties, and keratolytic activity. Additionally, AZA inhibits tyrosinase, as well as DNA synthesis and mitochondrial enzyme function, making it effective not only for mild to moderate acne vulgaris but also for addressing post-inflammatory hyperpigmentation⁴⁰.

Its topical formulations typically require twice-daily application due to an approximate half-life of 12 hours. AZA is generally well tolerated, with a favorable safety profile and low potential for causing irritation⁴⁰.

Tomic et al. (2021) conducted a randomized, double-blind clinical trial involving 70 patients (35 per group) to compare a 10% azelaic acid nanocrystal hydrogel (AZA-NC) with a 20% azelaic acid cream (Skinoren®). Both treatments demonstrated significant reductions in inflammatory and non-inflammatory lesions by week 8, with noticeable improvements already observed at week 4. At week 8, the AZA-NC hydrogel achieved a 39.15% reduction in inflammatory lesions and a 34.58% reduction in non-inflammatory lesions (both $P < 0.001$), while the conventional cream produced reductions of 33.76% and 27.96%, respectively ($P < 0.001$ for both)⁴⁰. The hydrogel formulation appeared to offer slightly greater efficacy, particularly for non-inflammatory lesions, and showed high effect sizes (partial η^2 values of 0.794 for inflammatory, 0.848 for non-inflammatory, and 0.846 for total lesion reduction). Although both treatments were effective, these results suggest that the nanocrystal hydrogel may provide an incremental benefit in lesion reduction and skin tolerability over standard AZA cream⁴⁰. Further studies with larger sample sizes and longer follow-up periods may be needed to determine whether the nanocrystal formulation offers tangible benefits in real-world settings beyond improved cosmetic acceptability.

AZA exerts its anti-acne effects through multiple complementary mechanisms. It displays potent bacteriostatic activity against *P. acnes* by penetrating bacterial cells via ion transporters, disrupting cytoplasmic pH balance, and inhibiting thioredoxin reductase, a key enzyme in redox regulation⁶⁴. AZA also attenuates follicular hyperkeratinization by reversibly inhibiting keratinocyte proliferation and altering terminal differentiation, leading to reduced microcomedone formation⁶⁵. Its anti-inflammatory effects are mediated through the downregulation of the TLR2–KLK5–LL37 pathway and suppression of pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α) via NF- κ B and MAPK signaling inhibition⁶⁶. Additionally, AZA reduces oxidative stress by limiting NADPH oxidase activity and enhancing peroxisome proliferator-activated receptor gamma (PPAR- γ) expression⁶⁷. Clinically, it has been shown to decrease sebum secretion and improve post-inflammatory hyperpigmentation and erythema, contributing to overall acne improvement and skin tone normalization⁶⁸.

Benzoyl peroxide



Benzoyl peroxide (BPO) is a lipophilic compound that facilitates penetration through the stratum corneum and exerts both keratolytic and bactericidal actions against *C. acnes*. Unlike antibiotics, BPO is directly toxic to bacterial cell components, which prevents the development of bacterial resistance. This property makes BPO particularly valuable in combination therapies, where it has been shown to suppress the emergence of antibiotic-resistant *C. acnes* strains. Additionally, clinical trials indicate that BPO may reduce the burden of already resistant bacteria, contributing to improved outcomes.

When used in conjunction with clindamycin⁶⁹ or topical retinoids such as tretinoin⁷⁰, BPO enhances anti-inflammatory effects and lesion reduction without significantly increasing local irritation. Although it does not possess intrinsic anti-inflammatory properties, its ability to reduce bacterial load indirectly contributes to the mitigation of inflammation⁷¹. On the other hand, this combination often increases the risk of local adverse effects—including irritation, peeling, dryness, and burning—which tend to be dose-dependent³⁹.

When encapsulated in niosomes, BPO exhibits a controlled release profile that enhances its antibacterial and keratolytic activity. This delivery system improves BPO's stability and cutaneous penetration while minimizing irritation³⁹. The sustained release facilitates prolonged action against *C. acnes* colonization and reduces local inflammation, making it a promising strategy for enhancing efficacy and tolerability in acne treatment.

In a 12-week randomized clinical trial involving 100 patients, Mohammadi et al. (2019) compared a niosomal formulation containing benzoyl peroxide 1% combined with clindamycin 1% lotion to a niosomal clindamycin 1% lotion without BPO. The group receiving the BPO combination showed a greater mean reduction in acne lesions (64.21%) compared to the clindamycin-only group (59.04%). Nonetheless, this difference was not statistically significant. Baseline total lesion counts were similar between groups (28.16 ± 2.15 in the BPO group and 30.56 ± 2.76 in the control group; *P* = 0.49), and at the end of the study, both groups had comparable lesion counts (11.42 ± 0.91 vs. 10.36 ± 1.03; *P* = 0.44). The study suggests a numerical improvement with the addition of BPO, however, the lack of statistical significance invites further exploration into factors such as BPO concentration, vehicle, and duration of treatment. Future research may help elucidate whether nanoencapsulation strategies can optimize BPO's efficacy-tolerability balance and enhance clinical relevance in acne management.

Clindamycin

Clindamycin is a lincosamide antibiotic that exerts its antibacterial effect by inhibiting bacterial protein synthesis⁷². In the context of acne management, clindamycin also reduces the production of free fatty acids through the inhibition of lipase and suppresses leukocyte chemotaxis and the release of pro-inflammatory cytokines, contributing to its therapeutic efficacy⁷². However, the use of clindamycin as monotherapy for periods longer than three months is discouraged due to the risk of

inducing bacterial resistance. This risk is particularly relevant in maintenance therapy¹⁹. DOI: 10.1039/D5PM00298B

The concentration of clindamycin that reaches the pilosebaceous ducts plays a critical role in its effectiveness, as insufficient or variable drug levels are associated with reduced efficacy and a higher likelihood of resistance development. Consequently, advanced delivery systems, as nanoemulsions, designed to improve penetration into the pilosebaceous unit, allowing more efficient delivery, and may enhance both therapeutic outcomes and resistance prevention¹⁹. Clindamycin inhibits bacterial protein synthesis and downregulates pro-inflammatory cytokines, leading to a reduction in papules and pustules. When delivered via nanoemulsion, the formulation enhances skin penetration and may help mitigate bacterial resistance by maintaining effective local drug concentrations¹⁹.

A randomized clinical trial by Bhavsar et al. (2014), involving 200 participants, compared a clindamycin 1% nano-emulsion gel (Zyclin® Nanogel™) with a conventional clindamycin 1% gel (Clindac-A® Gel). The nano-emulsion gel demonstrated significantly greater reductions in total acne lesions (69.3% vs. 51.9%; *P* < 0.001), inflammatory lesions (73.4% vs. 60.6%; *P* < 0.005), and non-inflammatory lesions (65.1% vs. 43.7%; *P* < 0.001). These differences were apparent as early as week 4 and persisted throughout the 12-week study. The nano-emulsion formulation also showed a trend toward improved tolerability compared to the conventional gel. These findings suggest that nano-emulsion formulations may offer meaningful clinical advantages in terms of both efficacy and tolerability. Future studies could explore their utility in broader patient populations and assess cost-effectiveness to inform decisions about their adoption in routine practice.

Silver nanoparticles

Silver has long been recognized for its antimicrobial properties, with silver sulfadiazine historically used in the treatment of burn wounds⁴¹. Its bactericidal action is attributed to its ability to disrupt bacterial cell walls and promote the generation of reactive oxygen species (ROS) within microbial cells⁷³. Although rare, topical silver use has been associated with argyria—a bluish-gray skin discoloration—typically seen only at high systemic or topical exposures.

The advent of nanotechnology has enabled the development of silver nanoparticles (AgNPs), which offer improved antimicrobial efficacy due to enhanced skin penetration and increased surface area contacts with bacterial cell walls⁷³. Importantly, these nanoparticles require lower concentrations to achieve bactericidal effects, reducing the risk of side effects compared to conventional silver preparations.

In vitro studies have demonstrated that silver nanoparticles can inhibit *C. acnes* growth and may also provide anti-inflammatory benefits⁴¹. In a randomized controlled trial with 64 participants, Jurairattanaporn et al. (2017) compared a 1% silver nanoparticle gel combined with 2.5% benzoyl peroxide (ASAP®) to 1% clindamycin gel plus 2.5% benzoyl peroxide over 8 weeks. Both groups showed substantial reductions in inflammatory and



non-inflammatory lesion counts. By week 8, the reduction in inflammatory lesions was slightly greater in the AgNP group (79.7%) compared to the clindamycin group (72.6%), though the difference was not statistically significant ($P = 0.18$). Similarly, non-inflammatory lesion reduction was comparable between the groups (61.1% for AgNP vs. 66.8% for clindamycin; $P = 0.22$). Total lesion counts decreased in both groups by approximately 69–71%, again without significant differences ($P = 0.71$).

Silver nanoparticles exhibit promising antimicrobial and anti-inflammatory properties. It is crucial to mention that their clinical advantage over conventional antibiotics like clindamycin remains unclear based on current data. Further studies exploring long-term safety, formulation cost, and comparative tolerability could help clarify the potential role of AgNP-based treatments in routine acne management.

Inclusion of natural compounds

In recent years, there has been increasing scientific interest in the use of naturally derived compounds in acne management^{22,74}, particularly those incorporated into nanocarrier systems^{75,76}. These bioactive compounds, often extracted from plants, fruits, or essential oils, offer a wide spectrum of therapeutic properties—including antioxidant, anti-inflammatory^{77,78}, antimicrobial, and sebum-regulating effects—making them attractive alternatives or complements to conventional synthetic drugs⁴⁹.

However, the clinical use of many natural actives is limited by intrinsic challenges such as poor aqueous solubility, instability under physiological conditions, and limited penetration across the stratum corneum⁷⁶. Nanotechnology-based delivery platforms, including NLC⁷⁹, liposomes²³, transferosomes⁴⁴, nanoparticles⁴⁶, nanofibers⁴², and phytosomes²⁹, have been employed to overcome these limitations and to optimize the dermal bioavailability and therapeutic outcomes of natural compounds.

This section explores the clinical application of nanoformulations containing natural active ingredients evaluated in human trials. Key phytochemicals reviewed include quercetin, syringic acid, α -mangostin, and tea tree oil—each studied in combination with advanced nanostructured delivery systems. The available evidence highlights promising efficacy, particularly in the reduction of inflammatory lesions, and favorable tolerability profiles, reinforcing the potential of these agents in modern acne therapeutics.

Quercetin

Quercetin (QC) is a natural flavonoid that has attracted growing interest in dermatological research due to its antioxidant⁷⁸, anti-inflammatory^{79,80}, antibacterial⁸¹, and even anticancer properties⁸². Its potential for acne treatment is mainly linked to its anti-inflammatory action, which helps reduce lesion-associated inflammation⁸³. Quercetin has demonstrated bacteriostatic effects against *C. acnes* and has been associated with improvements in various acne lesion types⁸¹. Mechanistically, quercetin is known to inhibit tumor necrosis factor- α (TNF- α) and other pro-inflammatory mediators, contributing to its anti-inflammatory efficacy^{78,79}.

Despite these promising properties, direct topical application of quercetin is limited by its poor water solubility, instability, and low epidermal permeability, which hinder its bioavailability and clinical effectiveness. As a result, nano-formulations have been developed to enhance its cutaneous delivery. Sherif Amer et al. (2022) evaluated a quercetin and tea tree oil nanofiber patch in a split-face study involving 20 patients with mild to moderate acne vulgaris. After 8 weeks, the nanofiber patch achieved significant reductions in inflammatory lesions ($61.2\% \pm 10.2$) and total lesion count ($52.9\% \pm 9.9$), compared to a Panthenol® cream placebo ($12.5\% \pm 15.2$ and $15.3\% \pm 10.7$, respectively; $P < 0.05$). However, the reduction in comedonal lesions was not significant ($14.7\% \pm 16.5$ vs. $22.5\% \pm 19.9$; $P > 0.05$). In a similar split-face study, Amer et al. (2020) investigated a 1% quercetin-tea tree oil aspasome thin film in 20 acne patients. The aspasome formulation led to significant reductions in inflammatory lesions ($77.9\% \pm$ value not specified) and total lesion count ($55.3\% \pm$ value not specified) compared to the placebo side (6.7% for inflammatory lesions and 10.1% for total lesions; $P < 0.05$). The reduction in comedones was minimal (11.8% vs. 19.1%; $P > 0.05$). These results suggest that quercetin-based nanoformulations are more effective against inflammatory lesions than comedonal lesions.

These findings suggest that quercetin-loaded nanoformulations may be especially effective in targeting inflammatory components of acne. While encouraging, further studies with larger sample sizes are needed to confirm the generalizability of these results. Additionally, the inclusion of tea tree oil—a compound with its own anti-inflammatory and antimicrobial effects—certainly contributed for outcomes observed.

Syringic acid

Syringic acid (SA) is a natural phenolic acid (hydroxybenzoic acid) derived as a secondary metabolite of plant tissues. It is recognized for its diverse biological properties, including anti-inflammatory, antimicrobial, antioxidant, anticancer, and immunomodulatory effects⁸⁴. Despite these promising characteristics, SA presents poor aqueous solubility, limiting its bioavailability. The incorporation of SA into nanocarrier systems has been proposed as a strategy to overcome these limitations and enhance its therapeutic potential⁸⁵.

Linoleic acid (LA), an omega-6 essential fatty acid obtained from dietary sources, was selected as a complementary component in nanoplatforms due to its antimicrobial action against *C. acnes*⁸⁶. LA not only exhibits antibacterial activity but also helps correct essential fatty acid imbalances in sebum that contribute to follicular plugging and acne progression⁸⁷. Furthermore, LA is known to enhance the skin penetration of nanocarriers, potentially boosting the therapeutic efficacy of encapsulated agents⁸⁸. Studies have also suggested that unsaturated fatty acid-based polymeric micelles can exert a synergistic effect when combined with active compounds, improving treatment outcomes⁸⁹.

In a split-face, before-and-after study, Abd-Allah et al. (2023) evaluated the efficacy of syringic acid-loaded linoleic acid 1% transferosomes compared to adapalene 0.1% gel. After one month of treatment, the side treated with syringic acid transferosomes exhibited a substantial reduction in total acne



lesions ($79.5\% \pm 7$), whereas the adapalene-treated side showed only an $18.7\% \pm 6.1$ reduction ($P < 0.001$). The nanocarrier formulation also appeared to provide superior anti-inflammatory benefits, as reflected in the greater overall lesion reduction. These results are promising, particularly in terms of rapid lesion reduction. Since they are derived from a single short-duration trial, larger and longer-term studies could confirm the durability and generalizability of these effects. Additionally, linoleic acid itself exhibits anti-acne properties, adding a synergistic contribution to the observed therapeutic outcomes.

Mangosteen extract

Mangosteen extract, derived from the fruit rind of *Garcinia mangostana* Linn., has been traditionally used in the treatment of wounds, skin infections, eczema, and acne. Its primary active compound, alpha-mangostin, has demonstrated a wide range of pharmacological activities, including antioxidant, anti-inflammatory, antibacterial (notably against *C. acnes*), antifungal, anti-allergic, and even anti-skin cancer properties⁴⁵. In a split-face study involving 28 participants with mild to moderate acne vulgaris, Lueangarun et al. (2019) compared the efficacy of a 0.5% mangosteen extract nano gel combined with 2.5% benzoyl peroxide cream (MNLG) to that of a 1% clindamycin gel plus 2.5% benzoyl peroxide cream. Both treatments resulted in significant reductions in comedone counts from baseline by week 12: 66.86% reduction on the MNLG-treated side and 55.33% on the clindamycin-treated side. Although the MNLG formulation achieved a greater mean reduction in comedones, the difference between groups was not statistically significant. Regarding inflammatory lesions, both groups showed substantial improvement from baseline to week 12. The MNLG side achieved reductions of 18.32 ± 13.45 to 6.8 ± 6.34 ($P < 0.001$), and the clindamycin side showed reductions of 17.5 ± 12.87 to 8.04 ± 9.52 ($P < 0.001$), with no significant difference between treatments. These findings highlight the potential of mangosteen-based nano gels as a promising alternative or adjunct in acne treatment, particularly for patients seeking phytotherapeutic options. While the current evidence shows comparable efficacy to standard antibiotic-based regimens, larger and longer-term trials are warranted to clarify their role in acne management and to evaluate sustained benefits and safety profiles.

Mechanisms of action of nanoformulated actives in acne treatment

Beyond the individual outcomes observed across nanoformulated actives, several overlapping biological mechanisms contribute to the therapeutic effects of nanomedicines in acne treatment. These include antimicrobial activity against *C. acnes*, modulation of inflammation, regulation of sebum production, and normalization of follicular keratinization. The main mechanisms vary depending on the

active compound and nanocarrier employed, as summarized in Figure 3.

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Among the various mechanisms investigated in nanoformulated antiacne therapies, the modulation of inflammatory pathways via PPAR γ activation by AZA emerges as particularly promising. Unlike other strategies focused primarily on sebostatic effects or keratinization normalization, the activation of PPAR γ integrates multiple therapeutic benefits: suppression of NF- κ B and p38 MAPK pathways, reduction of pro-inflammatory cytokine release, control of keratinocyte proliferation, and potential modulation of lipid metabolism in the skin. These effects position AZA not only as an anti-inflammatory agent but also as a modulator of cutaneous homeostasis. Considering that PPAR γ is also implicated in the regulation of the skin barrier and microbiota, leveraging this pathway may open avenues for combined or adjunctive therapies, especially when paired with antioxidants or other PPAR γ agonists. Thus, PPAR γ -targeted interventions could extend benefits beyond lesion reduction to broader improvements in skin health and resilience.

Both isotretinoin and spironolactone exhibit distinct yet complementary mechanisms in acne management, each with translational relevance enhanced by nanotechnology. Isotretinoin, particularly in nanoformulations, induces sebaceous gland regression through sebocyte apoptosis and differentiation, alongside normalization of follicular keratinization and anti-inflammatory effects. This multimodal action results in a profound and often sustained therapeutic response, especially in severe or recalcitrant acne. In contrast, spironolactone operates via androgen receptor blockade, specifically mitigating hormonally driven sebum production with minimal systemic absorption when applied topically in NLCs. While isotretinoin offers a broad, systemic reset of acne pathophysiology, spironolactone provides a targeted, safer option for hormonal acne and isotretinoin-intolerant patients. These complementary mechanisms underscore the potential for personalized and combined therapeutic strategies, optimizing acne treatment through mechanistic precision.

Quercetin, a flavonoid widely distributed in various fruits and vegetables, demonstrates significant potential in acne management due to its antioxidant, anti-inflammatory, and antimicrobial properties. Its ability to scavenge reactive oxygen species (ROS) contributes to the reduction of oxidative stress, a key factor in acne pathophysiology. Additionally, quercetin modulates the NF- κ B signaling pathway, leading to decreased production of pro-inflammatory cytokines such as TNF- α and IL-6. Importantly, quercetin also exhibits antibacterial effects against *C. acnes* and has been associated with the inhibition of porphyrin production, which further attenuates inflammation mediated by bacterial activity. When incorporated into nanocarrier systems, quercetin enhances the efficacy of conventional acne treatments by complementing their mechanisms of action, particularly in formulations that do not directly address oxidative stress. Moreover, its inclusion may improve cutaneous tolerability, reducing the irritation commonly associated with synthetic APIs, thereby contributing to better patient compliance and therapeutic outcomes.



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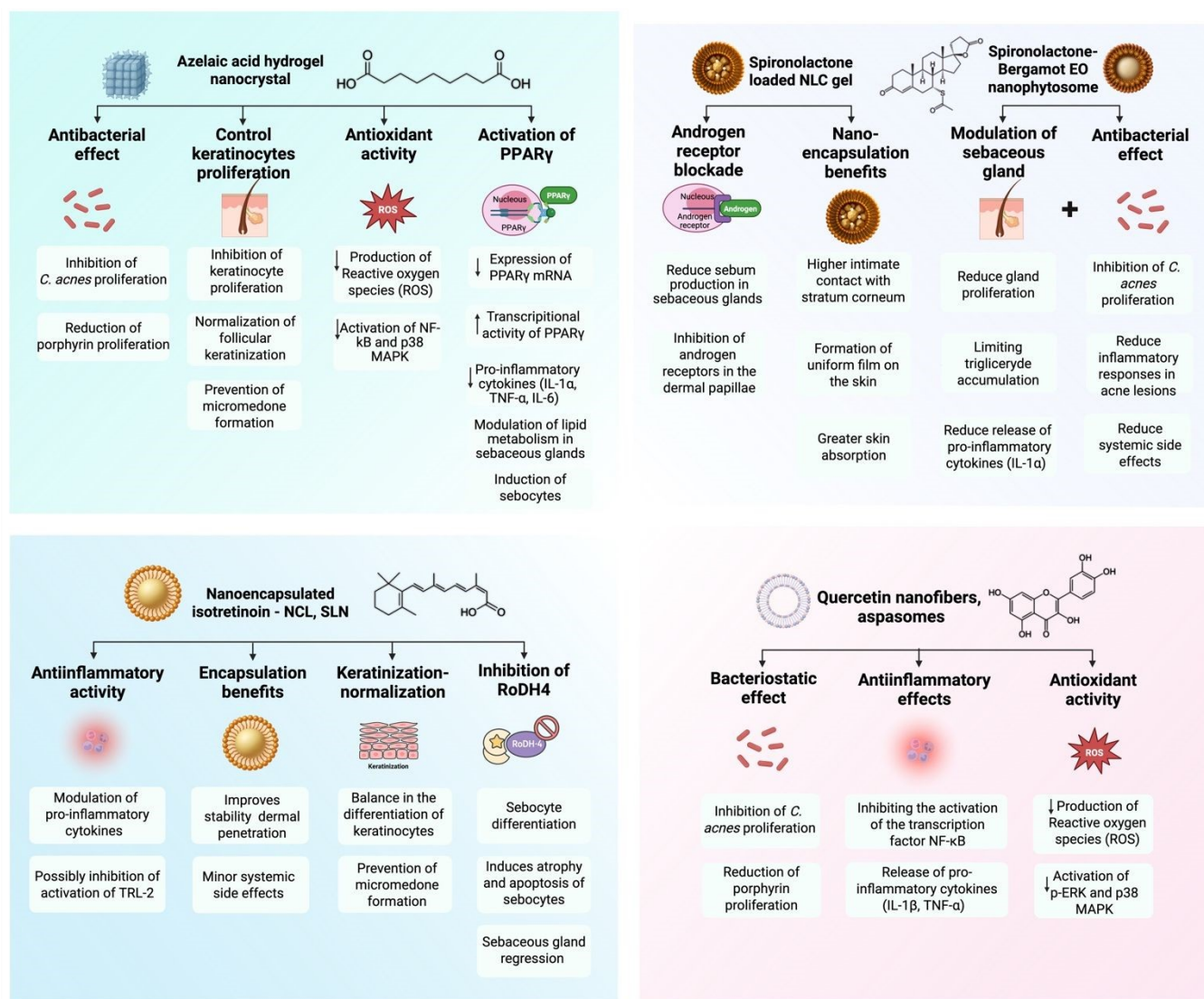


Figure 3 - Integrated mechanisms of action of nano-based drug delivery in acne treatment. Nanoformulations enhance therapeutic efficacy by combining antimicrobial activity against *Cutibacterium acnes*, anti-inflammatory effects, sebum production regulation, and correction of follicular keratinization.

Furthermore, the incorporation of natural natural bioactive compounds into nanomedicines alongside conventional APIs offers a promising complementary strategy for sustainable and innovative in acne treatment. Natural compounds such as quercetin, α -mangostin, and syringic acid contribute multifunctional mechanisms—including antioxidant, anti-inflammatory, and antibacterial effects—that can synergize with the targeted actions of synthetic drugs. This synergy not only enhances therapeutic efficacy but may also mitigate

adverse effects commonly associated with conventional APIs, such as irritation or antibiotic resistance. Moreover, natural actives can modulate pathways not typically addressed by standard treatments, such as oxidative stress or skin microbiota balance, thus offering a more holistic approach to acne pathophysiology. A comprehensive overview of the multiple mechanisms by which nanoformulated actives exert therapeutic effects on acne is illustrated in Figure 4.



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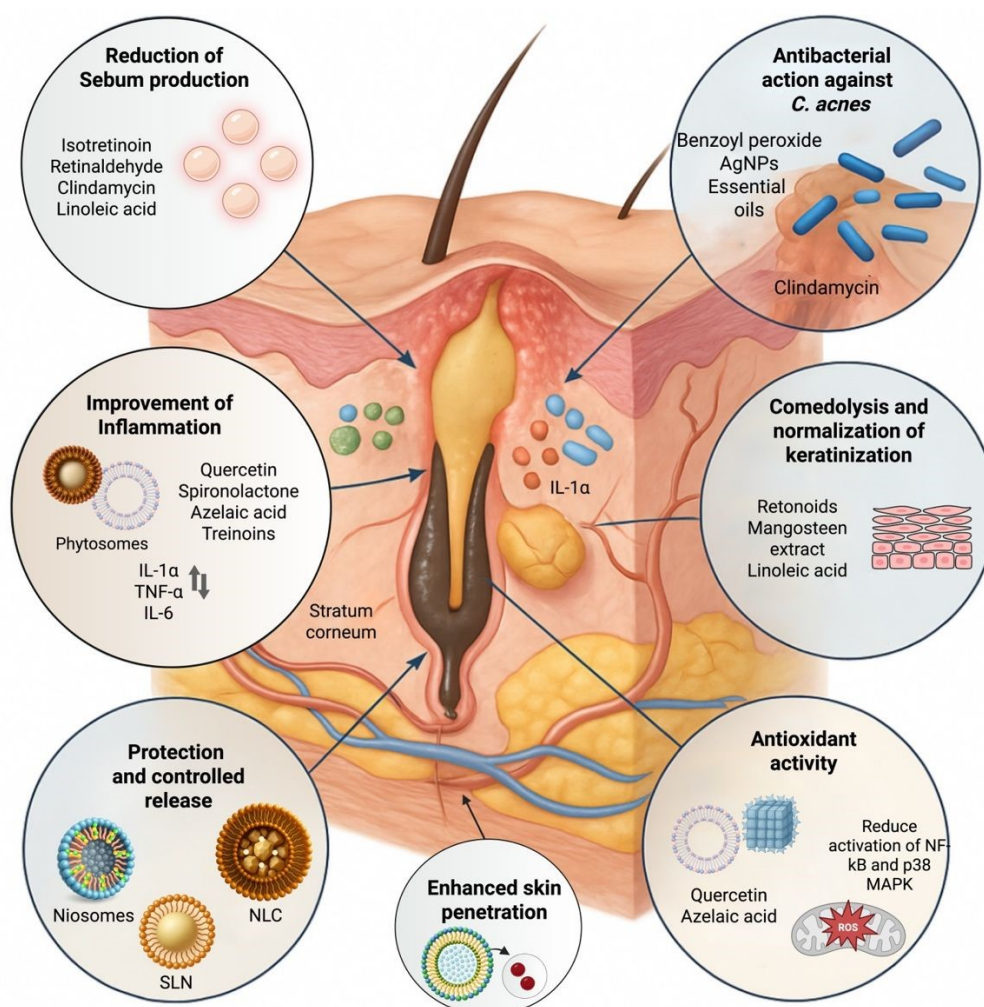


Figure 4 - Schematic representation of the mechanisms of action of nanoformulated actives for acne treatment.

Clinical Severity Outcomes (ASI and GAS)

Acne Severity Index (ASI)

To evaluate the effectiveness of nanomedicine in acne vulgaris treatment, 10 studies comprising 1,042 participants assessed changes in acne severity using the Acne Severity Index (ASI). In a randomized clinical trial involving 212 participants, Prasad et al. (2012) compared a nanoemulsion gel containing adapalene 0.1% and clindamycin 1% (Adalene® Nanogel™) with a conventional adapalene-clindamycin gel (Deriva-CMS®). The nanoemulsion group exhibited a greater mean reduction in ASI (1.9 ± 0.9 [95% CI: 1.71–2.02]) compared to the control group

(1.4 ± 1.0 [95% CI: 1.17–1.58]; $P < 0.001$). This significant improvement in the nano group was observed as early as 4 weeks and persisted throughout the study ($P < 0.05$ at all assessments). Ahmad Nasrollahi et al. (2021) conducted a before–after study with 13 patients, applying adapalene 0.1% NLC gel to one side of the face. After 12 weeks, the acne severity grade decreased significantly from 2.31 at baseline to 1.38 ($P = 0.02$), with 77% of patients achieving "clear" or "almost clear" status.

Similarly, Najafi-Taher et al. (2022) evaluated a tea tree oil nanoemulsion with adapalene 0.1% against a marketed adapalene 0.1% gel in 100 patients. The nanoemulsion group demonstrated significantly greater reductions in ASI over 12



weeks ($P < 0.001$). The trend analysis confirmed a larger decrease in the nano group ($\beta = -5.79 \pm 1.02$; $P < 0.001$), with 71.69% of participants reaching successful outcomes (clear or almost clear), compared to 6.38% in the control group. Notably, no worsening of acne severity was reported in either group. Bhavsar et al. (2013) reported similar findings in a 12-week randomized trial of 200 patients, comparing a clindamycin 1% nano-emulsion gel (Zyclin® Nanogel™) to conventional clindamycin 1% gel (Clindac-A®). The nano formulation led to a significantly greater reduction in acne severity (mean change: -1.6 ± 0.9 vs. -1.0 ± 0.8 ; $P < 0.001$). Approximately 55% of patients in the nano group achieved a two-grade improvement in severity, compared to 27% in the conventional group ($P < 0.001$).

These findings consistently demonstrate a statistically significant reduction in acne severity following treatment with various nanoformulations. ASI provides a useful objective metric for quantifying lesion improvement; it may be valuable to further contextualize these changes in terms of their clinical relevance. Future studies should explore whether the observed ASI reductions translate into perceptible benefits for patients—such as improved quality of life, self-esteem, or adherence to treatment. Incorporating patient-reported outcome measures (PROMs) alongside ASI would help bridge this gap and provide a more holistic assessment of treatment success.

The Gauge of Acne Severity (GAS)

To assess the effectiveness of nanomedicine in reducing acne severity, 10 studies involving 1,042 participants evaluated changes in acne severity grades during treatment.

In a randomized clinical trial with 212 participants, Prasad et al. (2012) compared a nano-emulsion gel combining adapalene 0.1% and clindamycin 1% (Adalene® Nanogel™) with a conventional adapalene-clindamycin formulation (Deriva-CMS® Gel). The nano-emulsion group showed a greater mean reduction in acne severity score (1.9 ± 0.9 [95% CI: 1.71–2.02]) than the control group (1.4 ± 1.0 [95% CI: 1.17–1.58]; $P < 0.001$). Notably, this significant improvement in severity was evident by week 4 and persisted throughout the treatment period ($P < 0.05$ at all time points).

Similarly, Ahmad Nasrollahi et al. (2021) conducted a before–after study with 13 patients, applying adapalene 0.1% NLC gel to one side of the face (right side), with the other side left untreated. After 12 weeks, the treated side showed a significant reduction in acne severity grade, decreasing from 2.31 at baseline to 1.38 ($P = 0.02$). Approximately 77% of participants achieved outcomes categorized as "clear" or "almost clear."

These studies suggest that nanocarrier-based formulations may offer more rapid and sustained improvements in clinical acne severity. Most available data are derived from small sample sizes or split-face designs, which may limit generalizability. Future research involving larger, multicenter trials may help to determine whether these GAS outcomes translate into consistent and meaningful clinical benefits across broader and more diverse patient populations.

Time to 50% lesion reduction

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Three studies involving a total of 61 participants reported on the time required to achieve a 50% reduction in acne lesion counts. In a before–after study by Ahmad Nasrollahi et al. (2021), 13 patients with mild to moderate acne were treated with adapalene 0.1% NLC gel. After 12 weeks, significant reductions were observed in blackheads, whiteheads, and papules compared to baseline ($P = 0.01$, 0.03, and 0.04, respectively). The percentage reduction rates at 12 weeks were 40% for overall acne grading, 72% for papules, 64% for whiteheads, and 49% for blackheads. Salem et al. (2021) conducted a split-face trial with 20 participants, comparing a 0.05% retinyl palmitate ethosomal hydrogel to a 0.05% tretinoin cream (Acretin™) in mild to moderate facial acne. By week 6, the nano-formulation side showed greater mean reductions in lesion counts: 46.69% for non-inflammatory lesions, 39.32% for inflammatory lesions, and 39.95% for total lesions, versus 34.32%, 28.35%, and 28.49% for the tretinoin-treated side. These differences, however, did not reach statistical significance ($P = 0.071$, 0.432, and 0.179, respectively).

In a split-face study by Lueangarun et al. (2018) involving 28 patients, a 0.5% mangosteen extract nano gel combined with 2.5% benzoyl peroxide cream was compared to a combination of 1% clindamycin gel and 2.5% benzoyl peroxide cream. The percent reduction in inflammatory lesions at week 12 was similar between groups (67.05% for the nano gel vs. 64.16% for the clindamycin group). However, clinical severity assessments by an expert panel showed a significantly greater improvement in the nano-treated side, with median severity grading improving from 2.33 to 1.33 ($P < 0.001$), compared to 2.33 to 1.67 ($P < 0.001$) for the clindamycin side. Furthermore, the final expert grading at week 12 favored the nano gel group (1.33 vs. 1.67; $P = 0.004$).

These findings suggest that certain nanoformulations—such as adapalene-NLC, retinyl palmitate ethosomes, and mangosteen extract nano gels—may accelerate lesion reduction when compared to conventional formulations. However, given the small sample sizes and split-face designs of these studies, it remains unclear whether these timeframes for achieving a 50% reduction in lesion counts can be generalized to broader clinical settings. Larger randomized trials with standardized endpoints are warranted to confirm these preliminary outcomes and inform evidence-based recommendations for acne management using nanocarriers.

Figure 5 provides a comparative overview of the clinical performance of various nanoformulations in acne vulgaris, integrating both lesion reduction rates and time to achieve ~50% reduction. Notably, adapalene-NLC and mangosteen nano gel achieved some of the highest reductions in inflammatory lesions (72% and 67%, respectively), yet differed substantially in their time to response (12 weeks for both). On the other hand, tretinoin nanoemulsion and retinyl palmitate ethosomal gel showed moderate efficacy (50% and 39% inflammatory lesion reduction, respectively) but reached this improvement more rapidly, in around 6 weeks. This dual-panel visualization underscores a key trend: while certain formulations



demonstrate high efficacy, their onset of action may be slower, and vice versa. The comparison also highlights the relative consistency between inflammatory and non-inflammatory lesion responses within most nanoformulations, suggesting that these systems may offer balanced therapeutic benefits. Such insights are critical when selecting topical nanocarriers, as they

enable clinicians to balance rapid clinical improvement against overall lesion clearance. The heterogeneity observed across formulations and lesion types also points to the need for further head-to-head trials and standardized outcome reporting in future clinical studies.

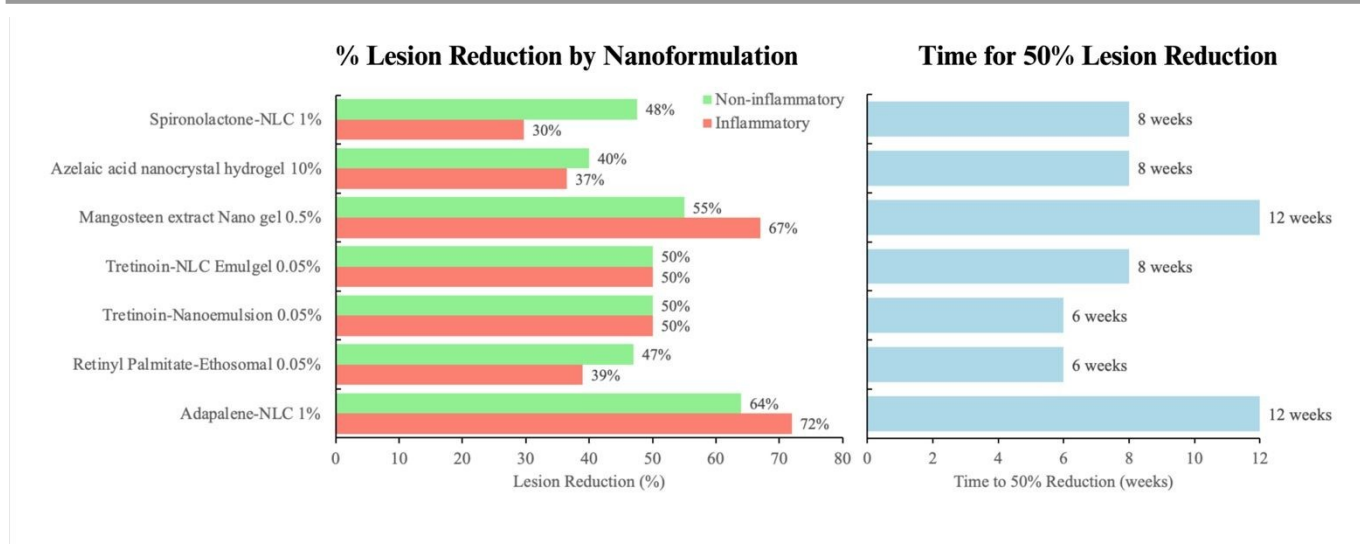


Figure 5 - Comparison of lesion reduction and time to achieve ~50% reduction across nanoformulations for acne vulgaris. Left: inflammatory (red bars) and non-inflammatory (green bars) lesion reduction. Right: time to ~50% reduction (weeks). Data are based on reported clinical trial outcomes. Abbreviations: NLC = nanostructured lipid carrier.

Porphyrin production as a biomarker

Porphyrin production, an indirect marker of *C. acnes* presence in the skin, was evaluated as an outcome in four studies involving a total of 67 participants. Different methodologies were employed for its quantification, including Wood's lamp examination, UV photography image analysis, e VISIA® system assessments.

In a split-face study with 10 patients, Sabouri et al. (2018) found that treatment with a 0.05% tretinoin nanoemulsion significantly reduced porphyrin-related parameters (size and quantity of fluorescent spots) in pilosebaceous follicles, whereas no significant change was observed with a conventional 0.05% tretinoin emulsion. Although both formulations reduced inflammatory and non-inflammatory lesion counts, the difference between treatments was not statistically significant, likely due to the small sample size. The nanoemulsion group demonstrated significantly greater reductions in porphyrin production compared to the conventional emulsion side. Samadi et al. (2022), in a split-face study of 16 patients with mild to moderate acne, reported that tretinoin 0.05% NLC emulgel significantly decreased both the size and intensity of porphyrin fluorescence after 8 weeks of treatment ($P = 0.007$ and $P = 0.006$, respectively). No significant reductions were seen with conventional tretinoin cream. Similarly, Ahmad Nasrollahi et al. (2021) observed significant reductions in porphyrin size and intensity ($P = 0.03$) after 12 weeks of applying adapalene 0.1% NLC gel in a before-after study with 13 patients. Finally, Lueangarun et al. (2018), in a

split-face trial with 28 patients, reported significant reductions in porphyrin severity scores as assessed by Wood's lamp, in both the mangosteen extract nano gel combined with 2.5% benzoyl peroxide cream group and the 1% clindamycin gel plus 2.5% benzoyl peroxide cream group. Both treatments significantly improved porphyrin grading scores from baseline to week 12, with no statistically significant difference between groups ($P < 0.001$ for both). While promising as a biomarker, evaluating the reliability of porphyrin suppression as a surrogate outcome could enhance the interpretability of acne treatment trials and support its integration into routine dermatological assessments.

Sebum production and desquamation

Sebum production was evaluated as an outcome in a single split-face study involving 23 participants²¹. The trial investigated the effects of a 0.05% retinaldehyde-loaded niosomal solution on cutaneous sebum levels. Sebum secretion was measured using a Sebumeter®, showing a significant reduction over the treatment period. The mean baseline sebum level was $327.95 \pm 90.20 \mu\text{g}/\text{cm}^2$, which decreased to $282.60 \pm 99.70 \mu\text{g}/\text{cm}^2$ at week 2 and $250.65 \pm 97.60 \mu\text{g}/\text{cm}^2$ at week 4 ($P < 0.001$). In addition to sebum levels, desquamation was assessed to evaluate improvement in pilosebaceous hyperkeratosis, using Visioscan® imaging. The desquamation index (DI) showed a significant decline from 10.99 ± 1.69 at baseline to 9.81 ± 1.10 at week 2 and 8.89 ± 1.32 at week 4 ($P <$



0.001). Thus, the reductions in sebum secretion and desquamation are statistically significant.

Global clinical evaluation

Global clinical evaluations offer a comprehensive perspective on treatment response and tolerability. In the studies reviewed, global clinical evaluation was used as an outcome measure in three studies involving a total of 337 participants. Treatment response was categorized by specialist assessments based on study-specific scales. In general, "excellent" indicated complete or near-complete resolution of lesions; "good" indicated significant improvement; "fair" reflected partial improvement; and "poor" referred to no improvement or worsening of lesions. Tolerability was similarly graded according to the severity of adverse events, ranging from mild (minimal discomfort) to severe (interfering with daily activities).

In a 12-week randomized trial with 207 participants, Chandrashekhar et al. (2015) reported that a tretinoin nano gel was significantly better tolerated than a conventional tretinoin gel ($P = 0.003$). In the nano gel group, 86.7% of patients were rated as having "excellent" tolerability, 7.6% as "good," and 5.7% as "fair," with no "poor" ratings. In contrast, in the conventional gel group, 75.3% were rated as "excellent," 6.2% as "good," 14.4% as "fair," and 4.1% as "poor." El-Samahy et al. (2017) conducted an 8-week split-face study involving 30 patients with predominantly moderate acne. Regarding lesion count reduction, eight patients were rated as having an "excellent" response, 12 as "good," and 10 as "fair." In terms of tolerability, the nano retinol formulation was significantly better tolerated, with 90% of patients rated as "excellent" and 10% as "good." None of the patients in the nano group were rated as having "poor" tolerability. In comparison, the conventional retinoid group had 6.7% rated as "good" and 93.7% as "fair," with no "excellent" ratings. In a 12-week randomized trial with 100 patients, Mohammadi et al. (2019) found that 80% of participants in the niosomal benzoyl peroxide 1% plus clindamycin 1% group achieved "excellent" or "good" outcomes, compared to 76.1% in the niosomal clindamycin-only group ($P = 0.377$). Final ratings in the BPO-clindamycin group were 18% "excellent," 62% "good," 20% "fair," and 0% "poor." In the control group, 28.3% were rated as "excellent," 47.8% as "good," 21.7% as "fair," and 2.2% as "poor" ($P = 0.37$).

Participants' evaluation

Participants' perspectives on treatment efficacy and formulation characteristics were reported in 12 studies, involving a total of 1,011 patients (six split-face studies and six randomized controlled trials). Overall, patient satisfaction with nanoformulations appears consistently high.

Saeedi et al. (2023), in an 8-week RCT with 40 patients with mild to moderate acne, reported high satisfaction with product attributes such as smell, appearance, spreadability, and consistency. Similarly, Albash et al. (2023), in an 8-week before–after study with 20 patients, noted that their bergamot

essential oil–spironolactone nano-phytosome formulation had good skin adherence and was generally well accepted.

Chandrashekhar et al. (2015), in a 12-week RCT with 207 participants, reported a treatment success rate of 57.6% in the tretinoin nanoemulsion group compared to 44.4% in the conventional gel group ($P = 0.07$). Significantly more patients achieved complete lesion clearance in the nano group (9% vs. 1.1%; $P = 0.01$). Samadi et al. (2022), in an 8-week split-face study, found higher satisfaction scores for the tretinoin NLC emulgel side (mean VAS scores of 7 and 7.4 at weeks 4 and 8) than for the conventional cream side (5.94 and 6.00; $P = 0.016$ and 0.001). Most patients reported improved skin smoothness and lesion reduction on the NLC side.

Prasad et al. (2012) found a significantly higher treatment success rate in the nano-adapalene-clindamycin group (58.5%) compared to the control group (26.4%; $P < 0.001$). Ahmad Nasrollahi et al. (2021) reported that 92% of patients felt their skin looked clearer and lesion counts had decreased following adapalene NLC use. Salem et al. (2021) observed visible clinical improvement with retinyl palmitate ethosomal gel. Kim et al. (2021) noted that 85% of participants were "very satisfied" or "satisfied," and 80% perceived better skin texture with retinaldehyde-loaded niosomes. Bhavsar et al. (2013) reported a significantly higher success rate in the clindamycin nano-emulsion group (53%) compared to the conventional group (28%; $P < 0.001$). Mohammadi et al. (2019) found higher improvement rates with niosomal BPO-clindamycin (64.21% vs. 59.04%), although this was not statistically significant. Tomic et al. (2021) observed a success rate of 36.5% for azelaic acid nanocrystal hydrogel compared to 30.4% for azelaic acid cream ($P < 0.001$). Jurairattanaporn et al. (2017) found better satisfaction at week 6 for silver nanoparticles compared to clindamycin ($P = 0.01$), though this difference was not maintained by week 8. Finally, Lueangarun et al. (2018) reported high satisfaction in both the mangosteen nano gel and clindamycin groups, with significant score improvements over time, but no significant difference between the two treatments.

Adverse effects and tolerability

Across the studies reviewed, nanomedicine-based formulations generally demonstrated favorable safety profiles with fewer or milder adverse effects compared to conventional treatments.

Kelidari et al. (2016), in an 8-week RCT with 76 patients with mild to moderate acne, reported no serious adverse events related to treatment. Dryness and itching were the most common symptoms, occurring in 2.7% of patients using spironolactone-NLC 1% gel and 15% of those using alcoholic spironolactone gel. Saeedi et al. (2023) found no significant differences in adverse reactions between groups in an 8-week trial of 40 patients. The chitosan-coated spironolactone NLC gel plus clindamycin 2% solution did not cause notable redness, itching, burning, or inflammation compared to placebo. Albash et al. (2023), in a before–after study with 20 patients, reported no cases of irritation or erythema during the use of bergamot essential oil–spironolactone nano-phytosomes over 2 months.



Chandrashekhar et al. (2015), in a 12-week RCT with 207 patients, observed significantly fewer adverse events in the tretinoin nano group (13.3%) compared to the conventional gel group (24.7%; $P = 0.04$). Dryness was the most frequent event in both groups, but peeling, burning, and photosensitivity occurred only in the conventional group. Most adverse events were mild in the nano group, while moderate events predominated in the control group. Prasad et al. (2012) reported no serious adverse events in either group during a 12-week RCT with 212 patients. Adverse event rates were significantly lower in the adapalene 0.1% and clindamycin 1% nanoemulsion group (13.6%) compared to the control group (36.3%; $P < 0.001$), with fewer cases of irritation and erythema ($P = 0.025$ and 0.045). Layegh et al. (2014) found no reports of irritation in the isotretinoin-SLN group, whereas three patients in the Isotrex® group discontinued due to local side effects. Salem et al. (2021), in a 6-week split-face study, noted that local reactions were more frequent and severe with tretinoin cream compared to retinyl palmitate ethosomal gel, which was better tolerated. El-Samahy et al. (2017) also reported significantly fewer local side effects with a retinol nano-liposomal solution compared to a conventional retinoid cream. Kim et al. (2021), in a 4-week split-face study with 23 patients, found retinaldehyde-loaded niosomes were well tolerated, with no significant irritation or adverse events. Bhavsar et al. (2013) observed a trend toward better tolerability with clindamycin nano-emulsion gel versus conventional gel in a 12-week RCT ($p = 0.12$). All events in the nano group were mild, while a third of control group events were moderate.

A comparative analysis of adverse effects associated with topical nanoformulations in acne treatment reveals a clear distinction between formulations containing synthetic and natural actives. As shown in Figure 6, the majority of natural-based nanoformulations were well tolerated, with no adverse events reported in most studies. In contrast, synthetic-based nanoformulations were more frequently associated with mild inflammatory properties and linoleic acid's antimicrobial and barrier-restorative effects may underpin these outcomes, though larger and longer-term studies are needed.

α -Mangostin, derived from mangosteen extract, was investigated in a nano gel formulation combined with benzoyl peroxide⁴⁶. In a split-face trial, the mangosteen nano gel achieved comparable comedone and inflammatory lesion reductions to clindamycin-based therapies, with a trend toward superior tolerability.

Tea Tree Oil, with known antimicrobial effects against *C. acnes*, was incorporated into a nanoemulsion with adapalene³⁵. This combination achieved significant lesion reductions compared to adapalene alone, though disentangling the specific contribution of the essential oil versus the carrier remains challenging.

Collectively, these findings underscore that nanoformulations of natural compounds can enhance bioavailability, skin penetration, and clinical efficacy, while often exhibiting improved safety profiles compared to synthetic counterparts. However, the evidence base is still emergent, with studies typically limited by small sample sizes, short durations, and

to moderate effects, including erythema, dryness, peeling, and local irritation. Notably, only one formulation containing natural actives (tea tree oil combined with adapalene) led to a high severity adverse reaction, same as for control group. These findings suggest that nanoformulations based on natural compounds may offer a safer tolerability profile, potentially enhancing patient adherence and comfort during acne therapy.

Natural bioactives in nano-based drug delivery systems for acne: clinical insights

The incorporation of naturally derived bioactive compounds in nanomedicine formulations for acne reflects a growing interest in leveraging phytochemicals' anti-inflammatory, antimicrobial, and antioxidant properties. Clinical evidence on nanoformulated natural actives remains limited compared to synthetic drugs, yet preliminary trials suggest promising efficacy, particularly in reducing inflammatory lesions with favorable tolerability profiles.

Among the phytocompounds evaluated in this review, Quercetin, a flavonoid with potent anti-inflammatory and antibacterial activities, was evaluated in two split-face studies using nanofiber patches⁴² and aspasome thin films⁴³, both combined with tea tree oil. These studies reported significant reductions in inflammatory and total lesion counts compared to placebo, although effects on comedonal lesions were modest. Quercetin's mechanism likely involves TNF- α inhibition and oxidative stress reduction, but poor solubility and low permeability necessitate nanoencapsulation for therapeutic viability.

Syringic Acid, a phenolic compound, was tested in a linoleic acid-loaded transferosome system⁴⁴. A clinical trial demonstrated a remarkable ~80% reduction in total lesion counts within just one month of treatment, outperforming adapalene gel. The synergism between syringic acid's anti-combination with other actives, which complicates efficacy attribution.

Future clinical research should:

- Explore head-to-head comparisons between nanoformulated natural and synthetic actives.
- Investigate the mechanistic pathways of natural compounds within nanocarriers, particularly their influence on skin microbiota and inflammatory mediators.
- Address pharmacokinetic profiling of natural bioactives delivered via nanocarriers.
- This growing domain suggests that natural-synthetic hybrid strategies, particularly within smart nanocarrier systems, may represent a sustainable and patient-preferred pathway in acne therapeutics.

Integrated framework to overcome translational barriers in nano-based drug delivery for acne



Although this review focuses on clinical trials, the clinical success of nano-based drug delivery systems relies on robust preclinical design and manufacturing reproducibility. Many limitations in efficacy or safety observed in trials can be traced to formulation or characterization gaps.

Therefore, an integrated pharmaceutical framework is proposed, encompassing key stages of translation—from formulation design and predictive modeling to preclinical validation and adaptive clinical evaluation.

Technological and manufacturing innovations

Nanocarrier development for dermatological applications faces scalability challenges, batch-to-batch variability, and limitations in characterization. Implementing Design of Experiments (DoE) and Quality by Design (QbD) approaches can systematically optimize formulation parameters to ensure robustness and reproducibility⁹⁰. This is particularly relevant to acne clinical trials, where inconsistent formulation properties have been associated with variability in therapeutic outcomes and reduced reproducibility across studies.

QbD paradigm is a systematic approach that links lifecycle stages to predefined quality targets while enabling control of critical attributes and process parameters⁹¹. The implementation of QbD goes beyond formulation optimization, enabling the identification of critical quality attributes (CQAs) such as particle size, zeta potential, and drug release kinetics, and their linkage to critical process parameters (CPPs)⁹². This systematic approach facilitates regulatory alignment and enhances reproducibility across manufacturing scales. In this

context, DoE serves as a key operational tool within QbD, allowing multivariate evaluation of formulation variables (e.g., surfactant concentration, lipid composition, homogenization conditions) and their interactions⁹³. This reduces empirical trial-and-error approaches and supports robust process design. Although the implementation of QbD may require substantial initial investment, its capacity to enhance reproducibility and reduce long-term manufacturing costs supports its economic viability. Furthermore, when integrated with real-time analytical tools (Process Analytical Technology, PAT), QbD enables real-time monitoring of critical quality attributes, allowing early detection of deviations, minimizing process variability, accelerating scale-up, and reducing the risk of costly batch failures or recalls⁹⁴.

The superiority of integrating QbD principles with nanotechnology in drug development to ensure product quality, consistency, and efficiency was recently highlighted by Maheshwari et al., 2026⁹⁵. This paradigm aligns with current regulatory expectations for advanced drug delivery systems, reinforcing the role of QbD as a bridge between laboratory innovation and industrial translation⁹¹.

Furthermore, advanced analytical techniques, such as asymmetric flow field-flow fractionation (AF4-MALS)⁹⁶ and cryo-TEM⁹⁷, provide critical insights into particle morphology, size distribution, and stability. Computational predictive models, leveraging machine learning, can be employed to forecast formulation behavior, predict stability profiles, and optimize process parameters for scale-up manufacturing⁹⁸.



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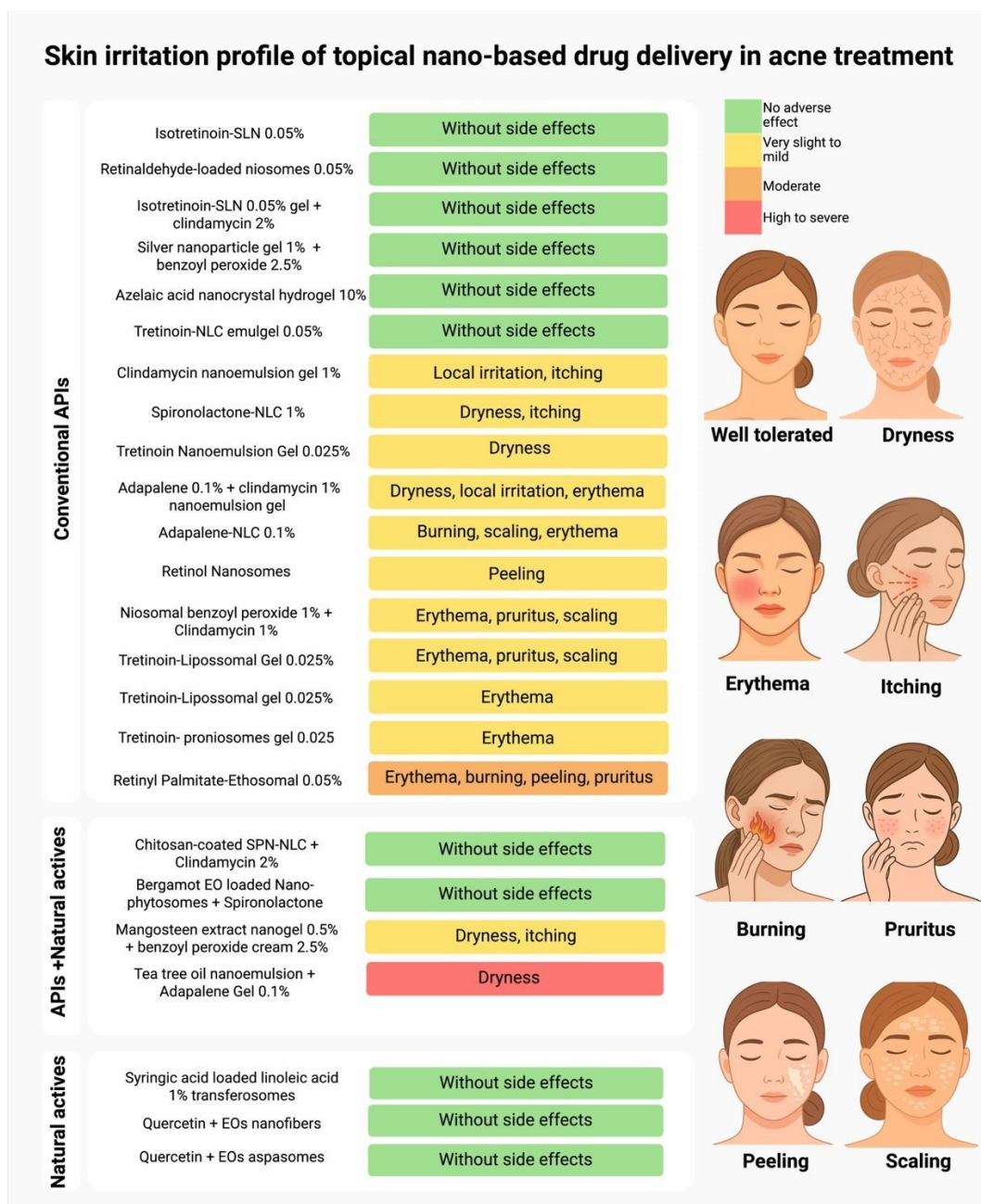


Figure 6- Tolerability profile of topical nanoformulations in acne treatment – comparing adverse effects of conventional active pharmaceutical ingredients (APIs) and natural compounds.

Advanced preclinical models

Conventional animal models inadequately reproduce human skin physiology and pathology, limiting the predictability of preclinical outcomes. Emerging *in vitro* and *ex vivo* systems—

such as 3D human skin equivalents, organ-on-chip models, and *in silico* simulations of follicular targeting—offer improved human relevance and mechanistic understanding. This limitation is reflected in the weak correlation often observed between preclinical efficacy and clinical performance in acne



studies, highlighting the need for more predictive human-relevant models.

Advanced 3D human skin equivalents have emerged as highly relevant preclinical platforms to bridge the translational gap between conventional *in vitro* assays and clinical outcomes. Unlike traditional monolayer cell cultures or animal models, these systems better recapitulate the structural, biochemical, and barrier properties of human skin, including stratified epidermal layers, functional lipid organization, and follicular architecture⁹⁹. As demonstrated in recent studies, 3D reconstructed skin models enable more accurate assessment of nanocarrier penetration, retention, and follicular targeting, as well as local toxicity and inflammatory responses under physiologically relevant conditions⁹⁹. Moreover, these platforms allow the evaluation of formulation performance in diseased-like environments, including acne-associated alterations such as sebaceous activity and microbial interactions¹⁰⁰. Consequently, the integration of 3D human skin equivalents into preclinical pipelines enhances the predictive power of efficacy and safety data, reducing the reliance on animal testing and improving the likelihood of successful clinical translation of topical nanomedicines.

Therefore, recent advances in organ-on-a-chip technology have enabled the development of skin-on-a-chip platforms that better reproduce the physiological complexity of human skin. Most current models focus on integrating microvascular channels into full-thickness skin constructs¹⁰¹, comprising both epidermal and dermal layers, or on co-culturing skin with other organ models to simulate inter-organ interactions. Unlike static *in vitro* systems, skin-on-a-chip platforms incorporate dynamic fluid flow, enabling the simulation of blood circulation, nutrient transport, and waste removal. These features allow more realistic evaluation of nanocarrier behavior, including permeation kinetics, distribution profiles, and time-dependent cellular responses under physiologically relevant conditions. In the context of acne, these systems offer unique opportunities to model key pathophysiological aspects, such as sebaceous gland activity, microbial colonization by *C. acnes*, and localized inflammatory responses¹⁰². The ability to control microenvironmental conditions in real time makes these platforms particularly suitable for investigating nano-based therapeutic strategies targeting complex skin disorders.

In silico approaches have also been applied to identify bioactive compounds targeting acne-related pathways. For instance, molecular docking studies have demonstrated that phytochemicals derived from *Ocimum sanctum* exhibit potential anti-inflammatory activity through inhibition of the c-Jun N-terminal kinase (JNK) pathway, with favorable binding energies and interaction profiles comparable to reference ligands. Moreover, the incorporation of *in silico*-identified compounds into nanocarriers designed for follicular targeting may further enhance therapeutic efficacy by ensuring localized delivery at the primary site of acne pathogenesis.

In parallel, adopting standardized *Core Outcome Sets (COS)*, such as those from the Acne Core Outcomes Research Network (ACORN), promotes harmonization between preclinical and clinical data collection and enhances reproducibility¹⁰³. ACORN emphasizes the importance of integrating multiple outcome domains, including clinical severity, patient-reported outcomes, long-term disease control, and safety profiles¹⁰⁴. This is particularly relevant for nano-based systems, where improved physicochemical performance must ultimately translate into clinically meaningful benefits captured by standardized outcome measures.

Adaptive clinical trial designs

Clinical trials investigating acne nano-drug delivery systems often face heterogeneous endpoints, small sample sizes, and limited stratification. Such limitations have been evident in the analysed trials, where heterogeneous endpoints and insufficient stratification contributed to inconclusive or modest efficacy results. Adaptive clinical designs—allowing interim data analysis and protocol adjustment—can improve trial efficiency and data quality¹⁰⁵.

Adaptive clinical trial designs have emerged as a flexible alternative to conventional RCTs, allowing for prospectively planned modifications to key study parameters based on interim analyses of accumulating data. These modifications may include adjustments to sample size, treatment arms, patient population, or endpoint selection, while maintaining control of statistical error rates. Several adaptive strategies have been described in dermatology, including group sequential designs enabling early stopping, response-adaptive randomization to favor more effective treatments, and seamless phase 2/3 designs that integrate dose-finding and confirmatory phases within a single protocol¹⁰⁶. Such approaches can improve trial efficiency, reduce development time, and minimize patient exposure to ineffective or potentially harmful treatments.

This flexibility is particularly relevant for nanomedicine-based therapies, where multiple formulation variables—such as particle size, surface properties, and drug release profiles—may influence clinical outcomes. Adaptive trial designs allow real-time optimization of these parameters at the clinical level, facilitating a more efficient translation of nanoformulations into clinically effective treatments.

Stratified trial designs involve the classification of patients into predefined subgroups based on baseline characteristics, allowing for more precise evaluation of treatment effects within clinically relevant populations¹⁰⁷. Stratified trial designs represent a key strategy to address interpatient variability by categorizing participants into clinically or biologically relevant subgroups. In dermatology, such stratification may consider factors such as disease severity, lesion type, skin microbiome composition, or inflammatory status¹⁰⁸. When integrated within adaptive trial frameworks, stratified designs can be implemented as adaptive enrichment strategies, in which interim analyses guide the selection or restriction of patient subpopulations more likely to benefit from the intervention¹⁰⁹.



This not only could improve statistical efficiency but also facilitates a more personalized approach to treatment evaluation. Perhaps this is particularly relevant for nanomedicine-based therapies, as the performance of nanoformulations may vary significantly depending on patient-specific factors such as sebum production, follicular density, and skin barrier integrity. Stratified and enrichment-based designs therefore provide a valuable framework to align formulation performance with patient-specific responses¹⁰⁸.

Regulatory and science alignment

The absence of harmonized regulatory guidelines for topical nanomedicines remains a critical translational bottleneck. Differences in regulatory expectations between agencies, particularly regarding physicochemical characterization and safety assessment, complicate the development and approval process. In this context, early alignment with regulatory science principles, including the identification of critical quality attributes (CQAs), such as particle size, surface charge, encapsulation efficiency, and release behavior—can be essential to ensure reproducibility and product consistency for regulatory approval¹¹⁰.

Furthermore, the lack of standardized and validated analytical methodologies for nanomaterial characterization continues to hinder comparability across studies and limits regulatory confidence. Addressing these challenges requires integrated efforts combining robust analytical validation, standardized outcome measures, and translationally relevant models to bridge the gap between preclinical development and clinical application. Collaboration among academic, industrial, and regulatory partners can accelerate the development of standardized frameworks for safety and efficacy evaluation of dermatological nanomedicines.

An integrated pathway for pharmaceutical translation

Despite significant advances in nano-based drug delivery systems for acne treatment, the successful clinical translation of these technologies remains limited by fragmentation across the development pipeline. This review highlights the need for integrated frameworks that connect early-stage discovery, formulation optimization, preclinical validation, and clinical evaluation.

Approaches such as *in silico* screening, advanced *in vitro* models (e.g., 3D human skin equivalents and organ-on-a-chip systems), and adaptive and stratified clinical trial designs collectively contribute to a more predictive and efficient development process. In particular, the incorporation of standardized outcome measures, such as those proposed by ACORN, and the QbD principles enable alignment between formulation performance and clinically meaningful endpoints.

However, regulatory and scientific misalignment remains a critical bottleneck, especially due to the lack of harmonized

guidelines for topical nanomedicines and the absence of standardized analytical methodologies. Addressing these challenges requires early integration of regulatory science principles, including the identification of critical quality attributes and the adoption of validated characterization strategies.

Moving forward, the convergence of nanotechnology, regulatory science, and translational methodologies is essential to enable the development of more effective, reproducible, and patient-centered therapies. Such integration may ultimately support the emergence of precision nanomedicine approaches tailored to the complex and heterogeneous nature of acne.

Figure 7 outlines the proposed integrated pharmaceutical framework, linking formulation design, preclinical validation, and adaptive clinical assessment into a cohesive translational continuum. This approach emphasizes predictive modelling and quality-by-design principles to strengthen the connection between formulation performance and clinical outcomes. By embedding these stages into a unified process, the framework supports the rational development and clinical translation of nanomedicines for acne therapy.

Conclusions and Outlook

Topical nanoformulations for acne treatment have demonstrated promising therapeutic outcomes, particularly in reducing total, inflammatory, and non-inflammatory lesion counts while improving tolerability and patient satisfaction. Across the 23 included clinical trials, lipid-based nanocarriers – such as SLNs, NLCs, and nanoemulsions – proved especially effective for enhancing drug stability, skin penetration, and local bioavailability. Formulations containing both synthetic actives (e.g., tretinoin, adapalene, clindamycin) and natural compounds (e.g., quercetin, mangostin, syringic acid, linoleic acid) showed comparable clinical performance, with some natural-based systems offering superior safety profiles and patient acceptability.

However, the heterogeneity of clinical endpoints, variation in outcome reporting, and limited standardization of evaluation tools (e.g., lesion counts, tolerability scales, porphyrin levels) hamper cross-study comparisons were main gaps to be filled. Moreover, most trials have small sample sizes and short durations, restricting the generalizability and long-term assessment of safety and efficacy. Emerging trends include the integration of biocompatible and stimuli-responsive nanocarriers, the co-delivery of multiple actives, and the development of hybrid formulations (e.g., chitosan-coated lipid carriers, phytosomes) that aim to enhance therapeutic synergy while minimizing adverse effects. The use of nanotechnology also aligns with the growing demand for plant-based and sustainable actives, offering an alternative to conventional retinoids and antibiotics, particularly in the context of rising antimicrobial resistance. Future research should focus on optimizing these combinatorial formulations to harness the full potential of natural-synthetic interactions within nanocarriers. This combinatorial strategy aligns with emerging trends in



dermatology that seek holistic, safer, and more patient-centered solutions.

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Integrated framework to overcome translational gaps in nano-based drug delivery systems for acne treatment

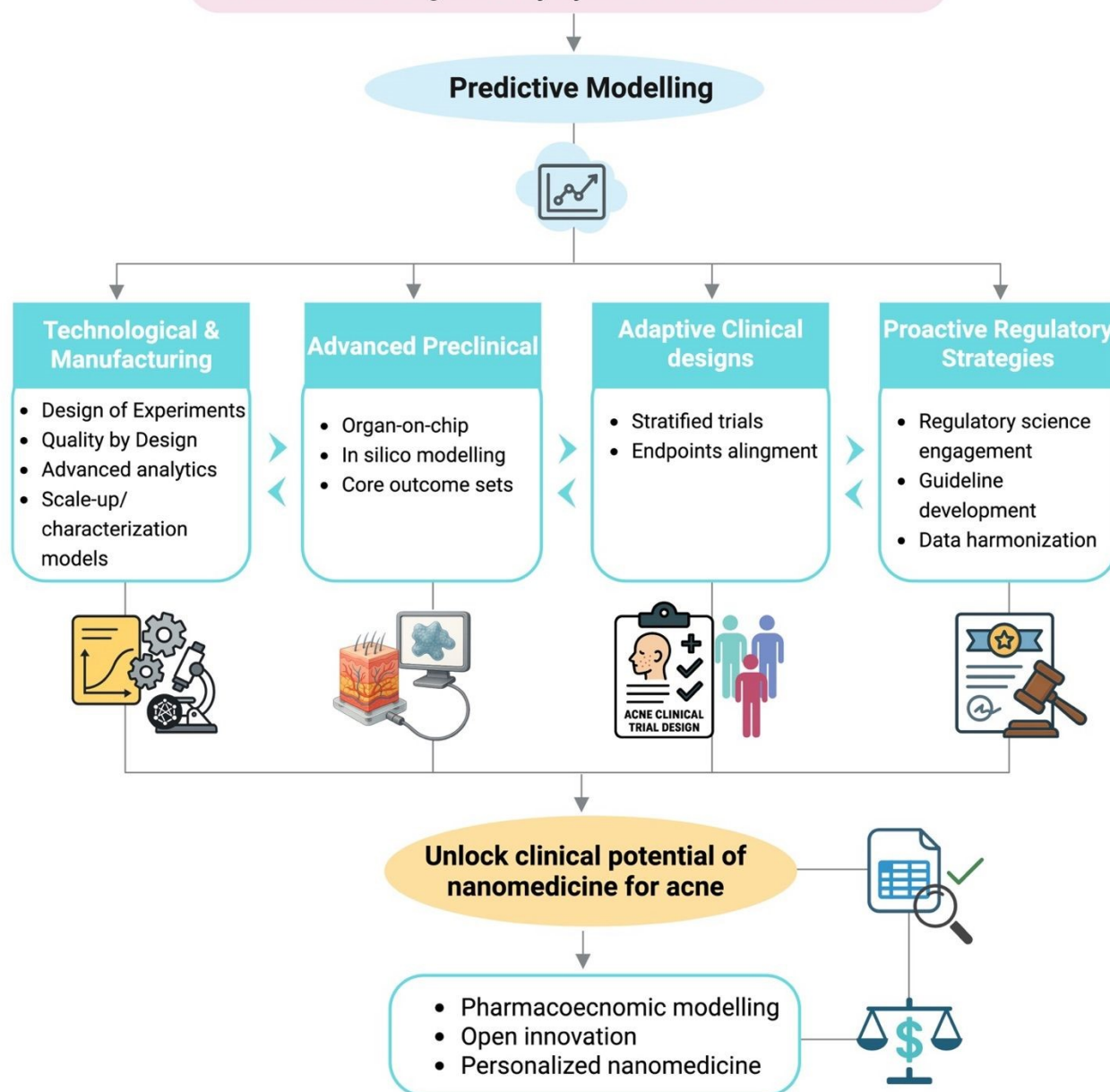


Figure 7 - Conceptual flowchart illustrating an integrated framework to overcome translational barriers in nanomedicines for acne treatment, aiming to accelerate the transition from research to clinical practice and market adoption.

Moreover, this review identified critical translational barriers that hinder the broader clinical adoption of acne nanomedicines, including challenges in scalable manufacturing, limited predictability of preclinical models, heterogeneous clinical endpoints, and persistent regulatory uncertainties. Addressing regulatory and scientific alignment emerges as a central requirement to overcome these barriers. The absence of harmonized regulatory guidelines and standardized characterization methodologies compromises reproducibility

and regulatory confidence. In this context, early integration of regulatory science principles—such as the identification and control of critical quality attributes (CQAs), including particle size, surface charge, encapsulation efficiency, and release kinetics—can provide a structured pathway to ensure product consistency, safety, and efficacy. Coupled with validated analytical methods and standardized clinical endpoints, this approach may facilitate more robust evidence generation and streamline the regulatory approval process.



Importantly, regulatory alignment should be complemented by advances in clinical trial design. Adaptive and stratified clinical approaches offer a powerful framework to address interpatient variability and optimize therapeutic evaluation. By enabling interim analyses, population enrichment, and subgroup-specific assessments, these strategies can improve statistical efficiency. To advance the clinical impact of acne nanomedicines, future research must prioritize: i. well-powered, multicenter randomized controlled trials with standardized outcomes; ii. long-term follow-up to assess sustained efficacy, relapse, and safety; iii. Comparative studies benchmarking nanoformulations against standard therapies and among different nanocarriers.; iv. mechanistic studies elucidating nanoparticle–skin and nanoparticle–microbiome interactions; and v. early regulatory dialogue and economic modelling to support clinical translation.

Altogether, this review highlights the evolving potential of nanomedicine in dermatology, not only as a scientific innovation but as a viable clinical and commercial strategy. Strategic translational efforts will be essential to move beyond laboratory success and establish nanoformulations as a standard-of-care in acne management.

Author contributions

Hamidreza Kelidari: Conceptualization; Methodology; Data curation; Formal analysis; Investigation; Methodology; Writing - original draft; Validation; Anna Paula Azevedo de Carvalho: Formal analysis; Investigation; Methodology; Writing - original draft; Carlos Adam Conte-Junior: Resources; Writing - review & editing; Funding acquisition; Supervision.

Conflicts of interest

There are no conflicts to declare.

Data availability

There are no data to report; all information enclosed is in the public domain.

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reduce development timelines, and support more personalized treatment paradigms—particularly relevant for nanomedicine systems whose performance depends on patient-specific factors such as skin barrier integrity, sebum production, and microbiome composition.

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Data availability statement

There are no data to report; all information enclosed is in the public domain

