QUALITY IN SPORT
eISSN 2450-3118 · Open Access · Peer-reviewed
apcz.umk.pl/QS Nicolaus Copernicus University in Toruń



WĄS, Łukasz, JOPEK, Jakub, BRZOSTOWSKI, Bartłomiej, KWOLEK, Klaudia, OŻGA, Sebastian and BIOLIK, Aleksandra. Zinc in the Pathophysiology and Treatment of Acne Vulgaris: Clinical Efficacy, Molecular Mechanisms, Safety Profile, and Future Therapeutic Perspectives – A Comprehensive Literature Review. Quality in Sport. 2026.79.76733. https://doi.org/10.12775/QS.2026.79.76733

ARTICLE TIMELINE
Received: 15.10.2026.
Accepted: 05.11.2026.
Published: 16.11.2026.

INDEXING & EVALUATION
MEiN points: 20 Unique ID: 201398
Disciplines: Economics & Finance; Management & Quality Sciences

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024 No. 32553. Unique Journal Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).

Punkty Ministerialne z 2019 — aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

© The Authors 2026. This article is published with open access under the License Open Journal Systems of Nicolaus Copernicus University in Toruń, Poland. Open Access: This article is distributed under the terms of the Creative Commons Attribution Non-commercial Share Alike License (http://creativecommons.org/licenses/by-nc-sa/4.0/), which permits unrestricted, non-commercial use, distribution, and reproduction in any medium, provided the work is properly cited. The authors declare no conflict of interest regarding the publication of this paper.

Zinc in the Pathophysiology and Treatment of Acne Vulgaris: Clinical Efficacy, Molecular Mechanisms, Safety Profile, and Future Therapeutic Perspectives – A Comprehensive Literature Review

1. Łukasz Wąs

Medical University of Silesia in Katowice, Poland

https://orcid.org/0009-0003-2962-5303

luuukasz.was@gmail.com

2. Jakub Jopek

Silesian Medical University in Katowice, Poniatowskiego 15 Street, 40-055 Katowice, Poland

https://orcid.org/0009-0005-4782-5231

jakubjjopek@gmail.com

3. Bartłomiej Brzostowski
Medical University of Silesia in Katowice, Katowice, Poland
https://orcid.org/0009-0008-3751-6613
bartlomiej.brzostowski@wp.pl

4. Klaudia Kwolek
Medical University of Silesia in Katowice, Katowice, Poland
https://orcid.org/0009-0003-2145-7528
kwolek.klaudia2@gmail.com

5. Sebastian Ożga
Medical University of Silesia in Katowice, Katowice, Poland
https://orcid.org/0009-0003-1337-7800
sebastian.ozga17@gmail.com

6. Aleksandra Biolik
Medical University of Silesia in Katowice, Katowice, Poland
https://orcid.org/0009-0009-6314-3897
aleksandra.biolik06@gmail.com

Abstract

Background: Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit involving sebum overproduction, follicular hyperkeratinization, Cutibacterium acnes colonization, and immune dysregulation. Zinc may reduce sebum, exert antibacterial and anti-inflammatory effects, and support wound healing.

Aim of the study: This review summarizes evidence on zinc in acne vulgaris, including its mechanisms, clinical effectiveness, safety, biomarker potential, effects on antibiotic resistance, scar healing and sebum production, and treatment costs.

Methods: PubMed was searched up to 2026. Clinical trials, meta-analyses, and mechanistic studies evaluating oral and topical zinc in acne were reviewed, with emphasis on serum zinc

levels, efficacy versus standard therapies, safety, antibiotic resistance, scarring, sebum and androgen modulation, zinc transporter genetics, and costs.

Results: Patients with acne often have lower serum zinc levels than healthy controls, particularly in severe disease, suggesting potential as a biomarker. Oral zinc modestly reduces inflammatory lesions but is less effective than tetracyclines and isotretinoin; topical zinc mainly provides adjunctive benefit. Both forms have favorable safety profiles. Zinc does not induce C. acnes antibiotic resistance and may reduce antibiotic use. It may support scar healing and decrease sebum partly through 5α-reductase inhibition. Evidence on zinc transporter genetics remains limited. Zinc is generally inexpensive, but robust cost-effectiveness data are lacking.

Conclusions: Zinc is a safe, accessible adjunctive option for acne vulgaris, particularly inflammatory lesions, but is less effective than established first-line therapies. Further standardized trials are needed to define optimal dosing, formulations, and patient selection.

Keywords: acne; acne vulgaris; zinc supplementation; zinc; zinc deficiency; topical treatment; retinoids; sebum production; acne scars management

1. Introduction

Acne vulgaris is one of the most prevalent dermatological disorders worldwide, affecting up to 85% of adolescents and a considerable proportion of adults. It is a chronic inflammatory disease of the pilosebaceous unit driven by several interrelated mechanisms, including increased sebum production, follicular hyperkeratinization, colonization by *Cutibacterium acnes*, and an exaggerated inflammatory response. These processes result in the formation of comedones, papules, pustules, and in more severe cases, nodules and scarring.[1][2][15][16]

Zinc has drawn growing attention as a potential adjunctive therapy in acne management. It is an essential trace element involved in numerous biological functions such as immune modulation, antioxidant defense, and wound healing. Experimental and clinical evidence indicates that zinc may decrease sebum production, inhibit *C. acnes* growth, reduce inflammatory cytokine levels (e.g., IL-1β, IL-17A), and support skin repair and scar remodeling. Moreover, zinc is relatively safe, inexpensive, and widely available in both oral and topical formulations.[3][4][9]

Despite these promising properties, the role of zinc in acne therapy remains incompletely defined. Clinical studies vary in design, dosing, and zinc formulations, producing inconsistent results regarding its efficacy compared to standard treatments such as antibiotics, retinoids, and chemical peels. Furthermore, there is growing interest in its influence on antibiotic resistance, genetics of zinc transporters, and potential as a biochemical marker of disease severity.[5][7][25][26][27]

Given the multifactorial nature of acne vulgaris and the limitations of current therapies, it is essential to clarify the contribution of zinc as both a therapeutic and biological factor. This review aims to synthesize the available evidence regarding zinc's mechanisms of action, clinical effectiveness, safety profile, and emerging roles in modern acne management.[11][13][27][30]

2. Research materials and methods

This article is structured as a narrative review of the current literature on zinc in acne vulgaris. The review integrates data from clinical trials, systematic reviews and meta-analyses, observational studies, and mechanistic research addressing zinc's role in acne pathophysiology, treatment, safety, genetics, and economics.

Eligible studies included human research on patients with acne vulgaris evaluating oral or topical zinc preparations, analyses of serum or tissue zinc concentrations in acne, trials comparing zinc with standard therapies, and studies on zinc-related mechanisms such as sebum modulation, inflammatory pathways, C. acnes resistance, wound healing, and genetic determinants of zinc transport. Publications focusing on costs and health-economic aspects of zinc versus antibiotics and retinoids were also considered when available.

3. Literature Review

3.1 The pathophysiology of acne and potential targets for zinc

The classic pillars of acne pathogenesis are: sebum overproduction driven by androgenic stimulation of sebaceous glands, hyperkeratinization of follicular outlets leading to microcomedone formation, Cutibacterium acnes colonization of the follicle, and chronic inflammation involving both innate and adaptive immune responses.[1,15].

These mechanisms interact to produce the clinical spectrum of acne lesions, from comedones to inflammatory papules and nodules.[2][16]

Zinc is of interest as an adjunctive therapy, because theoretically it modulates several of these pathogenic pathways. Zinc can decrease sebum production, exert antibacterial effects against C. acnes, attenuate inflammatory responses, including the reduction of pro-inflammatory cytokines such as IL-1β and IL-17A. Additionally, zinc may promote wound healing and skin repair.[3][4][9]

Clinical studies have shown that oral and topical zinc formulations can reduce lesion counts and inflammation, though efficacy varies by dose and formulation.[4][9]

The multifaceted actions of zinc on sebum, bacterial growth, inflammation, healing provide a mechanistic rationale for its adjunctive use in acne management.[3][4][9]

3.2 Zinc concentrations in patients with acne vulgaris

Zinc concentrations in patients with acne vulgaris are generally lower than in healthy controls. Meta-analytic data confirm a statistically significant reduction in mean serum zinc levels among acne patients compared to controls, although the absolute difference is modest and may not reach statistical significance in all individual studies.[5][7][26]

For example, one study found mean serum zinc levels of 81.31 ± 17.63 μg/dL in acne patients versus 82.63 ± 17.49 μg/dL in controls, with no significant difference overall, but a trend toward lower zinc in more severe cases.[5]

The reduction in serum zinc is most pronounced in males with severe acne.[26]

These findings support the use of serum zinc as a potential biochemical marker in acne vulgaris, with lower levels correlating with increased disease severity.[5][7][26][27]

3.3 Oral zinc treatment - effectiveness

Oral zinc treatment is modestly effective in patients with acne vulgaris, particularly for reducing inflammatory lesion counts, but is less effective than oral antibiotics such as minocycline. A systematic review and meta-analysis found that oral zinc preparations, including zinc sulfate and zinc gluconate, significantly decrease the number of inflammatory papules compared to placebo, with no significant increase in adverse effects [7].

In a multicenter randomized controlled trial, zinc gluconate (30 mg elemental zinc daily) achieved a clinical success rate of 31.2% (defined as >2/3 reduction in inflammatory lesions) after 3 months, compared to 63.4% for minocycline (100 mg daily), confirming that zinc is effective but inferior to oral antibiotics for inflammatory acne.[8]

Network meta-analysis data indicate, that oral zinc is not among the most effective oral pharmacological treatments for moderate to severe acne, oral tetracyclines and oral isotretinoin showing superior efficacy.[9]

However, oral zinc may be considered as an adjunct or alternative in patients who cannot tolerate antibiotics or have contraindications. In summary, oral zinc is effective for reducing inflammatory lesions in acne vulgaris, but efficacy is lower than that of oral antibiotics and other first-line pharmacological treatments.[7][8][9]

3.4 The comparative effectiveness, safety, and tolerability of zinc (oral and topical) versus other established acne treatments

Table 1.

Treatment Modality	**Efficacy**	**Safety**	**Tolerability**	**Key References**
Oral Zinc	Modest efficacy for inflammatory lesions; inferior to oral antibiotics.	Generally safe; mild GI side effects.	Well tolerated; low dropout rates.	[7][8][9]
Topical Zinc	Modest efficacy; mainly adjunctive, not first-line.	Safe; minimal adverse effects.	Well tolerated.	[7][10][11]
Topical Pharmacological Combinations (Retinoids + Benzoyl Peroxide)	High efficacy for mild to moderate acne.	Dryness, irritation, rare allergic reactions.	Moderate tolerability; irritation may limit use.	[12][13][14]
Oral Antibiotics	Moderate to high efficacy, for inflammatory acne.	Gastrointestinal upset, photosensitivity, resistance risk.	Moderate tolerability; some discontinuation	[12][15][16]

			due to side effects.	
Oral Isotretinoin	Highest efficacy for severe/refractory acne.	Mucocutaneous, musculoskeletal, ophthalmic side effects; teratogenicity.	Lower tolerability; frequent minor side effects, rare serious events.	[12][13][17]
Chemical Peels	Effective for mild to moderate acne; tailored by acid type.	Safe side effects depend on acid/concentration.	Good tolerability; individualized.	[12,][18][19]
Phototherapy	Variable efficacy; some benefit in mild to moderate acne.	Generally safe; rare blistering/scarring.	Tolerability varies; evidence quality low.	[12][20]

Oral zinc (typically zinc sulfate 600 mg/day or zinc gluconate 200 mg/day) demonstrates modest efficacy in reducing inflammatory lesions, but is consistently less effective than oral antibiotics such as minocycline.[7][8][9]

Safety is favorable, with mild gastrointestinal symptoms as the most common adverse effect and low rates of treatment discontinuation.[7][8]

Topical zinc preparations show modest benefit, mainly as adjuncts, and are not recommended as first-line monotherapy; they are safe and well tolerated, with minimal adverse effects.[8][10][11]

Topical pharmacological combinations (retinoids plus benzoyl peroxide) are the most effective first-line treatments for mild-to-moderate acne, achieving substantial reductions in both inflammatory and noninflammatory lesions.[12][13]

These combinations are associated with local irritation and dryness, which may limit tolerability in some patients.[13][14]

Oral antibiotics (primarily tetracyclines) are highly effective for moderate to severe inflammatory acne, but carry risks of gastrointestinal upset, photosensitivity, and antibiotic resistance; tolerability is moderate, with some discontinuation due to side effects.[15][16]

Oral isotretinoin is the most effective therapy for severe or refractory acne, targeting all pathogenic mechanisms.[12][13][17]

However, it is associated with frequent minor side effects (dry skin, cheilitis) and rare but serious adverse events (teratogenicity, hepatotoxicity), necessitating careful monitoring and patient selection.[13][17]

Chemical peels (e.g., salicylic, glycolic, azelaic, pyruvic acids) are effective and safe for mild to moderate acne, with side effects and tolerability dependent on acid type and concentration; these can be tailored to individual patient needs.[18][19]

Phototherapy (including blue/red light and photodynamic therapy) offers variable efficacy, with some benefit in mild-to-moderate acne, but the quality of evidence is low and long-term safety data are limited.[20]

3.5 Results of treatment with topical zinc preparations in acne vulgaris

Topical zinc preparations in patients with acne vulgaris result in a modest reduction in inflammatory lesion counts, primarily due to their antibacterial and anti-inflammatory properties, and may decrease sebum production. [7][10]

The clinical evidence supporting topical zinc is of limited quality and inconsistent, with a SORT strength of recommendation B, indicating that while topical zinc can be beneficial, it is not considered a first-line monotherapy and should be viewed as adjunctive to standard treatments. [10]

Novel formulations, such as hyaluronic acid-stabilized zinc oxide nanoparticles, have demonstrated enhanced efficacy in reducing acne lesions and erythema, outperforming topical antibiotics in preclinical and early clinical studies, with a favorable safety profile and no significant toxicity observed.[3]

Overall, topical zinc is well tolerated, with minimal adverse effects reported, and may be considered for patients seeking alternatives to conventional topical agents or as part of combination therapy.[4][7][10]

3.6 Comparison with other nutraceutical approaches: nicotinamide, omega-3 fatty acids, vitamin D, and probiotics

Comparative Mechanisms of Action

Nicotinamide (vitamin B3) is primarily anti-inflammatory and may reduce androgen synthesis, thereby decreasing sebum output.[31][32]

Omega-3 fatty acids exert anti-inflammatory effects by modulating eicosanoid pathways and reducing pro-inflammatory cytokines.[9]

Vitamin D modulates immune responses, suppresses pro-inflammatory cytokines, and may restore skin barrier integrity.[9][33]

Probiotics influence the gut-skin axis, modulate systemic and local cytokine production, and may improve insulin sensitivity and reduce lipogenesis.[9][34]

Efficacy in Clinical Trials

Nicotinamide (topical 4% gel or oral supplement) has shown significant reduction in acne lesion counts in several studies, performing similarly to standard topical antibiotics, but the evidence is limited and inconsistent, with a need for larger trials.[31][32]

Omega-3 fatty acids (eicosapentaenoic acid and/or docosahexaenoic acid, 2000 mg/day) and omega-6 fatty acids (γ-linoleic acid, 400 mg/day) have demonstrated significant reductions in both inflammatory and noninflammatory lesions in small randomized trials, with improvement in mean acne grade.[9]

Vitamin D supplementation (1000 IU/day cholecalciferol) in vitamin D-deficient patients leads to a greater reduction in inflammatory lesions compared to placebo, but does not significantly affect noninflammatory or total lesion counts.[9][33]

Probiotics (various strains, including Lactobacillus plantarum, L. rhamnosus, L. acidophilus, Bifidobacterium lactis) have shown improvement in lesion counts and severity in multiple small randomized trials, both as monotherapy and adjunctive therapy, with some studies demonstrating statistically significant improvements in global acne severity and lesion reduction.[9][34]

Safety Profiles

Nicotinamide is safe, with no major adverse effects reported in clinical trials.[31][32]

Omega-3 fatty acids are well tolerated, with limited adverse effects, typically mild gastrointestinal symptoms.[9]

Vitamin D is safe at recommended doses, with no adverse events reported in clinical trials.[9][33]

Probiotics are well tolerated, with adverse event rates similar to placebo; no serious safety concerns have been identified.[9][34]

3.7 The role of zinc in scar healing and skin remodeling in acne vulgaris

Zinc plays a direct role in scar healing and skin remodeling during and after acne vulgaris by modulating inflammation, promoting antioxidant activity, and supporting cellular processes essential for tissue repair. Zinc supplementation reduces pro-inflammatory cytokines (such as IL-1β and IL-17A), matrix metalloproteinase-9 (MMP9), and oxidative stress markers, which are elevated in acne lesions and contribute to tissue damage and impaired healing.[3]

Zinc also enhances glutathione peroxidase (GSH-Px) activity, supporting antioxidant defenses and reducing lipid peroxidation, thereby protecting skin cells from further injury.[1]

Zinc is a cofactor for numerous metalloenzymes involved in cell proliferation, migration, and extracellular matrix remodeling, all of which are critical for effective wound healing and scar formation.[22]

Zinc deficiency impairs these processes, leading to delayed re-epithelialization and abnormal scar formation.[22][23]

Topical zinc formulations, such as hyaluronic acid-stabilized zinc oxide nanoparticles, have demonstrated the ability to promote cell proliferation and migration, reduce sebum secretion, and exert anti-inflammatory effects, supporting scar-free repair and preventing recurrence of acne lesions.[4]

Zinc transporters are essential for maintaining zinc homeostasis within the skin, and their proper function is necessary for optimal wound healing and remodeling.[24]

Overall, zinc supplementation and topical application can improve the quality of post-acne healing by attenuating inflammation, enhancing antioxidant capacity, and facilitating the cellular events required for scar resolution and skin remodeling.[3][4][22][23][24]

3.8 The role of zinc in C. acnes antibiotic resistance

Zinc does not induce Cutibacterium acnes antibiotic resistance and may modulate or reduce resistance to certain antibiotics in patients with acne vulgaris. Zinc salts possess direct bacteriostatic activity against C. acnes and exert anti-inflammatory effects, but unlike antibiotics, they do not select for resistant strains through genetic mutation or horizontal gene transfer.[10]

The indiscriminate use of antibiotics in acne therapy has fueled the development of antimicrobial resistance in C. acnes, which can be transferred to other skin flora and body sites, complicating management. Alternatives to antibiotics, including oral zinc, are advocated to mitigate this risk.[25]

Zinc's antibacterial action is not associated with the development of resistance, and its use may help preserve skin microbiome homeostasis and reduce the need for antibiotics.[10][25]

No clinical evidence suggests that zinc supplementation or topical zinc promotes antibiotic resistance in C. acnes. Instead, zinc may be beneficial in antibiotic stewardship strategies for acne management, especially in the context of rising resistance to tetracyclines and macrolides.[25]

3.9 Zinc as a biochemical marker in acne vulgaris

Zinc is a potential biochemical marker in patients with acne vulgaris, as lower serum zinc levels are frequently observed in this population compared to healthy controls, and these levels may correlate with acne severity and lesion type. Measurement of serum zinc can provide auxiliary information about disease activity and may help identify patients who could benefit from zinc supplementation, especially in cases of moderate to severe acne where deficiency is more pronounced.[5][7][26]

However, the clinical utility of zinc as a routine biomarker is limited by inconsistent findings across studies and lack of standardized thresholds for deficiency in the context of acne.[5][27]

Zinc determination in serum or hair may serve as an adjunctive test in dermatological assessment, but further research is needed to establish its prognostic value and guide supplementation strategies.[27]

3.10 The effect of zinc on sebum and the androgen component of acne vulgaris

Zinc decreases sebum production, which is a key pathogenic factor in acne vulgaris, and may modulate androgen-related mechanisms involved in sebaceous gland activity. Zinc's effect on

sebum is supported by clinical studies showing improvement in acne severity and lesion counts with oral zinc supplementation, particularly at higher doses (e.g., zinc sulfate 600 mg/day), which is associated with a reduction in inflammatory lesions and overall acne scores compared to placebo.[7][9]

The mechanism is thought to involve inhibition of 5α-reductase, the enzyme responsible for converting testosterone to dihydrotestosterone (DHT), thereby reducing androgen-driven stimulation of sebaceous glands and subsequent sebum production.[10][23]

Additionally, zinc exerts anti-inflammatory and antioxidant effects, further attenuating the androgen-mediated inflammatory cascade in acne pathogenesis. While the exact molecular pathways remain incompletely defined, the preponderance of evidence indicates that zinc supplementation can reduce sebum output and may partially counteract androgenic stimulation of sebaceous glands, contributing to its therapeutic benefit in acne vulgaris. [3][4]

3.11 Safety profile and adverse effects of zinc use in acne vulgaris

The safety profile of zinc in the treatment of acne vulgaris is generally favorable, with most adverse effects being mild and self-limited. For oral zinc preparations, the most commonly reported adverse effects are gastrointestinal symptoms, including nausea, vomiting, abdominal pain, and indigestion. These effects occur at similar rates to oral antibiotics when used for acne, and rarely lead to treatment discontinuation. Higher doses of oral zinc (e.g., zinc sulfate 600 mg/day) are associated with increased rates of gastrointestinal complaints, but serious adverse events are uncommon.[8,9]

No significant differences in overall side effect incidence have been observed between zinc and comparators in meta-analyses.[7]

Topical zinc preparations are well tolerated, with minimal adverse effects reported. Occasional mild local irritation or dryness may occur, but serious or systemic toxicity is not observed, even with advanced formulations such as hyaluronic acid-stabilized zinc oxide nanoparticles.[4]

No significant safety concerns have been identified in clinical trials of topical zinc for acne.[4][7]

There are no reports of severe or long-term toxicity associated with either oral or topical zinc in the context of acne treatment in the current medical literature. Zinc is considered a safe adjunct or alternative, especially for patients who cannot tolerate standard therapies.[4][7][9]

3.12 Genetics and zinc pathways in acne vulgaris

Genetic factors influence zinc metabolic pathways in the pathogenesis and treatment of acne vulgaris primarily through the regulation of zinc transporter proteins, which are essential for maintaining zinc homeostasis in the skin. Mutations or dysregulation in genes encoding zinc transporters (such as the SLC39A/ZIP and ZnT families) can impair zinc uptake, distribution, and cellular availability, leading to local or systemic zinc deficiency and increased susceptibility to inflammatory skin disorders, including acne vulgaris. For example, acrodermatitis enteropathica is caused by mutations in ZIP4, resulting in severe zinc deficiency and characteristic skin lesions.[24][28][29]

Zinc transporters are critical for epidermal and dermal function, modulating processes such as keratinocyte proliferation, immune response and wound healing. Genetic variation in these transporters may affect individual responses to zinc supplementation and the efficacy of zinc-based therapies in acne.[24][28]

Zinc deficiency, whether genetically determined or acquired, exacerbates inflammation and oxidative stress in acne lesions, restoration of zinc levels - either through oral or topical supplementation, can mitigate these effects and improve clinical outcomes.[3][7][23]

Current evidence supports the role of zinc as both a therapeutic agent and a marker of disease severity in acne, but the impact of specific genetic variants on zinc metabolism and treatment response remains incompletely characterized. Further research is needed to clarify how genetic differences in zinc transporter function influence acne pathogenesis and the effectiveness of zinc interventions.[24][28][29]

3.13 The costs of treatment with zinc preparations vs. antibiotics/retinoids in acne vulgaris

Data on the costs of treatment with zinc preparations compared to antibiotics and retinoids for patients with acne vulgaris are limited, but available literature consistently indicates that zinc preparations (both oral and topical) are substantially less expensive than oral antibiotics and topical retinoids. Zinc is described as a low-cost alternative for acne management, with minimal systemic side effects, making it attractive for patients seeking affordable options.[11]

In contrast, oral antibiotics (such as tetracyclines and minocycline) and topical retinoids (such as tretinoin, adapalene, and tazarotene) are prescription medications that generally incur higher direct costs, especially in the United States, and may also be associated with additional costs related to monitoring and management of adverse effects.[13][30]

Cost-effectiveness analyses from the National Health Service in England show that topical treatment combinations and oral antibiotics are among the most cost-effective options for mild-to-moderate and moderate-to-severe acne, but do not specifically include zinc preparations in their models, reflecting a lack of robust cost-effectiveness data for zinc.[30]

The American Academy of Dermatology guidelines recommend topical retinoids and oral antibiotics as first-line therapies, but do not address zinc due to limited high-quality comparative data.[13]

In summary, zinc preparations are less costly than antibiotics and retinoids, but there is a lack of high-quality, direct comparative cost-effectiveness data in the medical literature. Zinc may be considered when cost is a major concern, but its efficacy is generally lower than that of standard first-line therapies.[11][13][30]

3.14 Limitations of available studies and knowledge gaps on zinc treatment in acne vulgaris

The limitations of available studies and the current knowledge gaps regarding the use of zinc as a treatment for acne vulgaris include inconsistent study quality, heterogeneity in dosing and formulations, lack of standardized outcome measures, and insufficient understanding of zinc's mechanisms of action in acne.[7][9][10][21]

Most clinical trials evaluating zinc for acne are small, short-term, and of poor or fair methodological quality, with only a minority meeting high standards for randomization, blinding, and risk of bias assessment.There is substantial variability in the type (sulfate, gluconate, oxide), dose (ranging from 200 mg to 600 mg daily), and route (oral vs topical) of zinc used, making direct comparisons and meta-analyses challenging.[9][10][21]

Outcome measures are not standardized, with studies reporting different endpoints (e.g., lesion counts, severity scores, subjective improvement), further limiting comparability.[9][21]

The precise mechanisms by which zinc exerts anti-acne effects, whether through sebum reduction, anti-inflammatory activity, or antibacterial action, remain incompletely elucidated.[3][7][9][10]

There is a lack of long-term safety data and insufficient evidence regarding optimal dosing, duration, and patient selection for zinc therapy.[9][10][21]

Few studies directly compare zinc to established first-line treatments, and there is limited data on its efficacy in combination regimens or in specific subpopulations (e.g., severe acne, antibiotic-resistant cases).[8][9]

Overall, further large, well-designed randomized controlled trials with standardized protocols and mechanistic studies are needed to clarify the role of zinc in acne management.[9][10][21]

4. Discussion

4.1 Effectiveness vs. Standard Treatment

Hierarchy of Effectiveness

Zinc occupies an intermediate position in acne therapeutics, showing efficacy superior to placebo but generally not surpassing first-line treatments. When oral zinc sulfate (600 mg/d) was compared to oxytetracycline, lesion reduction was comparable (58.2% vs 63.3%, $P > .05$), suggesting high-dose zinc may approach antibiotic efficacy without achieving superiority.[9]

For topical formulations, zinc combined with antibiotics demonstrated advantages over antibiotics alone, with zinc acetate contributing significantly to erythromycin/zinc antimicrobial action. However, topical zinc/clindamycin showed no significant difference versus clindamycin monotherapy in lesion reduction ($P = 0.769$).[17]

A systematic review revealed only slightly more than half of studies demonstrated zinc effectiveness, underscoring its variable performance compared to more consistently effective standard treatments.[9]

Dosing Issues

Zinc efficacy exhibits a clear dose-response relationship with significant formulation-dependent variability. Lower doses of zinc sulfate (440 mg/d) failed to demonstrate superiority over placebo (47.1% vs 38.9%, $P > .05$), while higher doses (600 mg/d) showed significant improvements in lesion counts ($P = .03$) and acne scores ($P = .01$). Zinc gluconate at 200 mg/d demonstrated robust efficacy with clinician-reported improvement in 75% versus 23.5% with placebo ($P < .001$). Interestingly, loading dose strategies (400 mg/d for 3 weeks) proved no more effective than conventional 200 mg/d dosing ($P = .74$). The critical challenge is that effective doses often exceed recommended daily allowances many-fold, substantially

increasing gastrointestinal adverse effects including nausea, vomiting, and abdominal pain at rates similar to antibiotic comparators.[9]

Zinc vs. Isotretinoin

Direct comparative trials between zinc and isotretinoin are notably absent from the literature. While isotretinoin remains the gold standard for severe acne with robust evidence and standardized protocols, zinc lacks comparable data for severe disease. [9]

Isotretinoin achieves profound remission through sebum suppression and follicular normalization, whereas zinc demonstrates more modest effects primarily on inflammatory lesions.[7]

Safety profiles differ markedly-isotretinoin carries risks of teratogenicity, neuropsychiatric effects, and mucocutaneous adverse effects requiring strict monitoring, while zinc's adverse effects are predominantly gastrointestinal without systemic toxicity concerns. [9][11]

This positions zinc as a potential alternative for patients with isotretinoin contraindications, but not as an equivalent substitute for severe disease where isotretinoin's superior efficacy remains preferable.[9]

4.2 Zinc as a "Weapon" in the Fight Against Antibiotic Resistance

Alternative to Antibiotics

Zinc represents a viable non-antibiotic alternative for acne in the context of rising antimicrobial resistance. Oral zinc and retinoids can help reduce dependence on antibiotics and prevent resistance development. [35]

When compared directly to oxytetracycline, high-dose zinc sulfate (600 mg/d) achieved comparable lesion reduction (58.2% vs 63.3%, $P > .05$), demonstrating that zinc can approach antibiotic efficacy without contributing to resistance.[9].

Recent reviews advocate for a gradual shift from antibiotics to alternatives including oral zinc, particularly given that antibiotic efficacy in acne is attributed primarily to anti-inflammatory action rather than antimicrobial action.[25]

Synergy

Zinc demonstrates synergistic effects when combined with antibiotics, potentially mitigating resistance development. The combination of zinc with antibiotics is more advantageous than

antibiotics alone, with zinc acetate contributing significantly to erythromycin/zinc antimicrobial action. [36]

In vitro, zinc salts reduced *Propionibacterium acnes* resistance to erythromycin, and at concentrations of 300 μg/ml, zinc prevented growth of erythromycin-resistant cells entirely. [37-38]

In vivo, zinc gluconate (30 mg/d) reduced inflammatory lesions regardless of whether erythromycin-resistant *P. acnes* was present, suggesting zinc maintains efficacy even in resistant populations.[37]

The combination of erythromycin and zinc inhibits both sensitive and resistant strains, making systemic zinc combined with topical erythromycin attractive given increasing erythromycin resistance. [37-38]

4.3 Genetics and Personalization: Zinc Transporters (ZIP/ZnT)

Zinc homeostasis in the skin is rigorously controlled by two transporter families: SLC39/ZIP (importers) and SLC30/ZnT (exporters), which regulate intracellular zinc levels critical for keratinocyte function.[39]

The skin contains the third highest zinc abundance in the body, with epidermal concentrations exceeding dermal levels due to the zinc requirement for active keratinocyte proliferation and differentiation.[40]

Several ZIP transporters demonstrate tissue-specific expression patterns relevant to acne pathophysiology: ZIP2 is specifically expressed in differentiating keratinocytes and is essential for normal epidermal formation-knockdown decreases intracellular zinc and inhibits keratinocyte differentiation. [39]

ZIP4, mutated in acrodermatitis enteropathica, regulates epidermal homeostasis through zinc-dependent ΔNp63 transcriptional activity, and its knockdown dysregulates differentiation with proliferating keratinocytes appearing in uppermost skin layers.[41]

ZIP10 is expressed in the interfollicular epidermis, epidermal appendages, and hair follicles, where it epigenetically regulates epidermal homeostasis by modulating histone acetyltransferase (HAT) activity-ZIP10 depletion causes epidermal malformations that are restored by zinc supplementation.[42-43]

Despite this mechanistic understanding, no zinc transporter polymorphisms have been directly associated with acne susceptibility in genome-wide association studies. Large GWAS meta-analyses identifying 46–50 acne risk loci have implicated pathways involving hair follicle structure, Wnt/MAPK signaling, lipid biosynthesis (FADS2, FASN), and inflammatory responses (TNF, IL families), but not zinc transport genes. [43-44]

Candidate gene studies have similarly focused on TNF, CYP17A1, and FST variants rather than ZIP/ZnT polymorphisms.[45]

4.4 Healing and Aesthetics (Post-Acne Scarring):

Role in skin remodeling

Zinc participates in all phases of cutaneous wound healing and scar remodeling through its function as a cofactor in numerous transcription factors and zinc-dependent matrix metalloproteinases (MMPs) that augment autodebridement and keratinocyte migration during wound repair. [46] In the proliferative phase, zinc is required for DNA and protein synthesis, cell division, collagen synthesis, and granulation tissue generation. [47]

A randomized double-blind trial demonstrated that topical zinc treatment enhances MMP-1 expression beneath the neoepidermis via paracrine mechanisms, promoting keratinocyte migration essential for re-epithelialization, while also upregulating metallothionein expression that may contribute to anti-inflammatory activities. [48]

The relationship between zinc and MMPs is particularly relevant to scar formation. MMPs are zinc-dependent endopeptidases that can degrade essentially all extracellular matrix components, and disturbance in the balance between ECM production and degradation leads to either chronic ulcers (excessive degradation) or hypertrophic scars and keloids (excessive ECM accumulation). [49]

Zinc confers resistance to epithelial apoptosis through cytoprotection against reactive oxygen species and bacterial toxins, possibly through antioxidant activity of cysteine-rich metallothioneins. [46]

Additionally, mast cells release zinc through the ZnT2 transporter, activating the GPR39/IL-6 signaling axis to promote wound healing-mice lacking IL-6 or GPR39 demonstrate impaired wound healing. [50]

Innovations

Emerging nanotechnology platforms are advancing zinc delivery for acne-related skin repair. Hyaluronic acid-stabilized zinc oxide nanoparticles (HA-ZnO) demonstrate selective antibacterial activity against *C. acnes* with killing efficacy more than 16 times greater than against commensal *S. epidermidis*. The sustained release of Zn^{2+} promotes cell proliferation and migration, reduces sebum secretion, and exerts anti-inflammatory effects supporting "scar-free acne repair." Clinical trials confirm efficacy in reducing acne lesions with high safety profiles. [4]

Microneedle-based delivery systems represent another innovation. Dissolving microneedles containing ZnO nanoparticles dispersed in ionic liquids demonstrate synergistic antibacterial properties and accelerate wound healing when applied to infected wounds.[51] Microneedle technology penetrates the stratum corneum minimally to form temporary micro-channels, enabling efficient delivery of nanoparticles and photosensitizers, with applications in acne and scar treatment. [52-53]

Hyaluronic acid and zinc oxide composite microneedles combine enhanced drug permeation, improved skin hydration, high mechanical durability, and antimicrobial properties. [54]

However, direct clinical evidence linking zinc supplementation to improved post-acne scarring outcomes remains limited. While systematic reviews confirm zinc's efficacy in treating active acne lesions, no studies have specifically evaluated zinc-enhanced interventions for scar prevention or treatment. [21]

4.5 Diagnostics and Biomarkers

Zinc as an Indicator of Disease Severity

Multiple studies have established an inverse correlation between serum zinc levels and acne severity. A systematic review and meta-analysis confirmed that subjects with acne have significantly lower serum zinc levels compared to controls, and that zinc treatment leads to significant improvement in inflammatory papule counts. [7]

One study of 100 acne patients and 100 controls using atomic absorption spectrophotometry found a correlation between serum zinc levels and both severity and type of acne lesions, with lower zinc levels associated with more severe presentations-suggesting zinc may serve as a potential biomarker for disease activity. [5]

This pattern extends to other immune-mediated inflammatory skin diseases (IMSDs): a comprehensive meta-analysis of 113 studies involving 7,014 patients demonstrated that serum zinc levels are significantly decreased in patients with vitiligo, psoriasis, and alopecia areata compared to healthy controls. [55]

In atopic dermatitis, pooled analyses show significantly lower serum, hair, and erythrocyte zinc levels in affected patients, with heightened CXCL10 expression in AD skin lesions correlating with reduced serum zinc levels.[56-57]

Lack of Standardization

Despite these associations, significant methodological heterogeneity limits the clinical utility of zinc as a diagnostic biomarker. Pre-analytical variables substantially influence zinc measurement: capillary samples yield zinc concentrations 8% higher than venous blood from the same donors, serum samples measure 5% higher than plasma, and samples processed 4–24 hours after collection show 5–12% higher zinc content than immediately processed samples. Holding temperatures further confound results, with samples held at 20°C or 37°C showing 0.5–7% higher zinc content than refrigerated samples. [58]

The Biomarkers of Nutrition for Development (BOND) Zinc Expert Panel acknowledges that while plasma zinc concentration responds to severe dietary restriction and supplementation, there is considerable interindividual variability, and concentrations are influenced by recent meal consumption, time of day, inflammation, and certain drugs and hormones.[59]

Furthermore, systematic reviews of zinc in acne and atopic dermatitis consistently note that included studies are of low or moderate quality, making interpretation problematic and highlighting the need for standardized protocols. [56]

4.6 Economics and Accessibility

Cost-Effectiveness

Zinc represents a potentially cost-effective alternative to conventional acne therapies, though direct comparative economic analyses remain limited. A review of published reports on comparative effectiveness and costs concluded that isotretinoin is more cost-effective than long-term antibiotic therapy mainly because of its greater efficacy and long-term cost savings-while initial costs are higher, substantial savings accrue in subsequent years. [60]

However, this analysis did not include zinc as a comparator. Zinc supplementation has been characterized as a "relatively easily implemented and inexpensive intervention" for addressing

zinc deficiency, with various formulations available including liquid solutions, syrups, pills, tablets, capsules, and powders. In low- and middle-income countries, zinc supplementation as part of a package of interventions to reduce undernutrition has been described as "among the most cost-effective interventions for advancing human welfare."[7]

The economic advantage of zinc extends beyond direct medication costs. Isotretinoin requires mandatory participation in the FDA-mandated iPLEDGE risk management program, which necessitates clinician and patient registration, signed consent, monthly clinical evaluation and counseling, and for individuals of childbearing potential, monthly pregnancy tests and confirmation of two forms of contraception. [16]

Laboratory monitoring during isotretinoin treatment should include liver function tests and fasting lipid panels at baseline and peak dose. [61]

Supplements vs. Medications

The regulatory distinction between zinc supplements and prescription acne medications creates important accessibility differences. Zinc is described as "a promising alternative to other acne treatments owing to its low cost, efficacy, and lack of systemic side effects." Unlike isotretinoin, which is FDA-approved only for severe recalcitrant nodular acne and requires extensive monitoring, zinc supplements are available over-the-counter and can be self-administered. [13]

However, this accessibility comes with trade-offs: zinc was the most studied nutraceutical for acne, yet most studies were of poor quality with substantial heterogeneity in results, and zinc was often dosed at many times the recommended daily allowance, which may increase adverse effect risk. Gastrointestinal adverse effects (nausea, vomiting, abdominal pain) were the most commonly reported side effects with zinc, occurring at rates similar to antibiotics in comparative studies. The lack of standardized dosing protocols for zinc in acne represents a barrier to clinical implementation. Studies have used varying formulations (zinc sulfate, zinc gluconate) at doses ranging from 200 to 600 mg daily, with higher doses more often demonstrating efficacy. [9]

This contrasts with isotretinoin's well-established dosing paradigm of 0.5–1.0 mg/kg/day with a cumulative target of 120–150 mg/kg. [16]

5. Conclusions

Zinc plays a multifaceted and biologically plausible role in the pathogenesis and management of acne vulgaris, targeting several key mechanisms including sebum production, inflammation, *Cutibacterium acnes* proliferation, and wound healing. The overall body of evidence supports zinc as a modestly effective therapeutic option, particularly for inflammatory lesions, with additional benefits in skin repair and potential relevance in reducing post-acne sequelae.

Clinical data consistently demonstrate that both oral and topical zinc formulations can improve acne severity; however, their efficacy remains inferior to established first-line treatments, such as oral antibiotics, topical retinoid combinations, and isotretinoin. Zinc therefore occupies an intermediate position in the therapeutic hierarchy, making it most suitable as an adjunctive therapy or an alternative in patients who cannot tolerate standard treatments or in whom antibiotic use is undesirable.

Importantly, zinc offers several advantages, including a favorable safety profile, low cost, and lack of contribution to antibiotic resistance. Its potential role in antibiotic stewardship is particularly relevant in the context of increasing antimicrobial resistance in acne management. Additionally, zinc may exert synergistic effects when combined with conventional therapies, further supporting its adjunctive use.

Emerging evidence suggests that zinc may also serve as a biochemical marker of disease severity, although its clinical utility is limited by methodological variability and lack of standardized reference values. Advances in zinc-based formulations, including nanoparticle and microneedle delivery systems, represent promising future directions, particularly in enhancing efficacy and targeting skin remodeling processes.

Despite these encouraging findings, the current literature is limited by heterogeneity in study design, dosing regimens, formulations, and outcome measures, as well as a lack of high-quality, long-term randomized controlled trials. Furthermore, the influence of genetic factors on zinc metabolism and treatment response remains insufficiently understood.

In conclusion, zinc should be regarded as a safe, accessible, and biologically relevant adjunct in acne therapy, with particular value in mild-to-moderate inflammatory acne and in patients seeking alternatives to antibiotics. However, its role as a standalone or first-line treatment remains limited, and further well-designed studies are required to define optimal dosing strategies, identify responsive patient populations, and clarify its place in evidence-based acne management

Disclosure

Author Contribution:

Conceptualization: Łukasz Wąs, Jakub Jopek,
Methodology: Łukasz Wąs, Jakub Jopek, Sebastian Ożga
Software: Bartłomiej Brzozowski, Klaudia Kwolek
Check: Łukasz Wąs, Jakub Jopek
Formal analysis: Łukasz Wąs, Bartłomiej Brzozowski, Klaudia Kwolek
Investigation: Jakub Jopek, Sebastian Ożga
Resources: Klaudia Kwolek, Aleksandra Biolik
Data curation: Bartłomiej Brzozowski, Klaudia Kwolek, Aleksandra Biolik
Writing-rough preparation: Łukasz Wąs, Jakub Jopek, Sebastian Ożga
Writing-review and editing: Łukasz Wąs, Jakub Jopek, Aleksandra Biolik
Visualization: Bartłomiej Brzozowski, Aleksandra Biolik
Supervision: Łukasz Wąs, Jakub Jopek
Project administration: Łukasz Wąs, Sebastian Ożga

All authors have read and agreed with the published version of the manuscript

Funding Statement:
Not applicable.

Institutional Review Board Statement:
Not applicable.

Informed Consent Statement:
Not applicable.

Data Availability Statement:
The authors confirm that the data supporting this study are available in the article's references.

Conflict of Interest:
Authors declare no conflict of interest.

In preparing this work, the authors used ChatGPT for the purpose of improving language and

readability, text formatting, and verification of bibliographic styles. After using this tool/service, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

REFERENCES:

[1] Williams, H. C., Dellavalle, R. P., & Garner, S. (2012). Acne vulgaris. *Lancet (London, England)*, *379*(9813), 361–372. https://doi.org/10.1016/S0140-6736(11)60321-8

[2] Cruz, S., Vecerek, N., & Elbuluk, N. (2023). Targeting Inflammation in Acne: Current Treatments and Future Prospects. *American journal of clinical dermatology*, *24*(5), 681–694. https://doi.org/10.1007/s40257-023-00789-1

[3]Gu, X., Wang, B., Zhang, T., Zhang, Q., Mao, B., Tang, X., Zhao, J., & Cui, S. (2025). Zinc-Enriched *Bifidobacterium longum* subsp. *longum* CCFM1195 Alleviates *Cutibacterium acnes*-Induced Skin Lesions in Mice by Mitigating Inflammatory Responses and Oxidative Stress. *Nutrients*, *17*(11), 1803. https://doi.org/10.3390/nu17111803

[4]Zhu, J., Wen, T., Ma, Y., Zeng, Q., Li, P., & Zhou, W. (2025). Biomimetic hyaluronic acid-stabilized zinc oxide nanoparticles in acne treatment: A preclinical and clinical approach. *Journal of controlled release : official journal of the Controlled Release Society*, *382*, 113754. https://doi.org/10.1016/j.jconrel.2025.113754

[5]Rostami Mogaddam, M., Safavi Ardabili, N., Maleki, N., & Soflaee, M. (2014). Correlation between the severity and type of acne lesions with serum zinc levels in patients with acne vulgaris. *BioMed research international*, *2014*, 474108. https://doi.org/10.1155/2014/474108

[6]Ikaraoha, C. I., Mbadiwe, N. C., Anyanwu, C. J., Odekhian, J., Nwadike, C. N., & Amah, H. C. (2017). The Role of Blood Lead, Cadmium, Zinc and Copper in Development and Severity of Acne Vulgaris in a Nigerian Population. *Biological trace element research*, *176*(2), 251–257. https://doi.org/10.1007/s12011-016-0839-4

[7]Yee, B. E., Richards, P., Sui, J. Y., & Marsch, A. F. (2020). Serum zinc levels and efficacy of zinc treatment in acne vulgaris: A systematic review and meta-analysis. *Dermatologic therapy*, *33*(6), e14252. https://doi.org/10.1111/dth.14252

[8]Dreno, B., Moyse, D., Alirezai, M., Amblard, P., Auffret, N., Beylot, C., Bodokh, I., Chivot, M., Daniel, F., Humbert, P., Meynadier, J., Poli, F., & Acne Research and Study Group (2001). Multicenter randomized comparative double-blind controlled clinical trial of the safety and efficacy of zinc gluconate versus minocycline hydrochloride in the treatment of inflammatory acne vulgaris. *Dermatology (Basel, Switzerland)*, *203*(2), 135–140. https://doi.org/10.1159/000051728

[9]Shields, A., Ly, S., Wafae, B., Chang, Y. F., Manjaly, P., Archila, M., Heinrich, C., Drake, L., Mostaghimi, A., & Barbieri, J. S. (2023). Safety and Effectiveness of Oral Nutraceuticals for Treating Acne: A Systematic Review. *JAMA dermatology*, *159*(12), 1373–1382. https://doi.org/10.1001/jamadermatol.2023.3949

[10]Brandt S. (2013). The clinical effects of zinc as a topical or oral agent on the clinical response and pathophysiologic mechanisms of acne: a systematic review of the literature. *Journal of drugs in dermatology : JDD*, *12*(5), 542–545.

[11]Cervantes, J., Eber, A. E., Perper, M., Nascimento, V. M., Nouri, K., & Keri, J. E. (2018). The role of zinc in the treatment of acne: A review of the literature. *Dermatologic therapy*, *31*(1), 10.1111/dth.12576. https://doi.org/10.1111/dth.12576

[12]Mavranezouli, I., Daly, C. H., Welton, N. J., Deshpande, S., Berg, L., Bromham, N., Arnold, S., Phillippo, D. M., Wilcock, J., Xu, J., Ravenscroft, J. C., Wood, D., Rafiq, M., Fou, L., Dworzynski, K., & Healy, E. (2022). A systematic review and network meta-analysis of topical pharmacological, oral pharmacological, physical and combined treatments for acne vulgaris. *The British journal of dermatology*, *187*(5), 639–649. https://doi.org/10.1111/bjd.21739

[13]Reynolds, R. V., Yeung, H., Cheng, C. E., Cook-Bolden, F., Desai, S. R., Druby, K. M., Freeman, E. E., Keri, J. E., Stein Gold, L. F., Tan, J. K. L., Tollefson, M. M., Weiss, J. S., Wu,

P. A., Zaenglein, A. L., Han, J. M., & Barbieri, J. S. (2024). Guidelines of care for the management of acne vulgaris. *Journal of the American Academy of Dermatology*, *90*(5), 1006.e1–1006.e30. https://doi.org/10.1016/j.jaad.2023.12.017

[14]Del Rosso, J., Sugarman, J., Green, L., Lain, T., Levy-Hacham, O., Mizrahi, R., & Gold, L. S. (2023). Efficacy and safety of microencapsulated benzoyl peroxide and microencapsulated tretinoin for the treatment of acne vulgaris: Results from two phase 3 double-blind, randomized, vehicle-controlled studies. *Journal of the American Academy of Dermatology*, *89*(4), 719–727. https://doi.org/10.1016/j.jaad.2023.05.093

[15]Zaenglein A. L. (2018). Acne Vulgaris. *The New England journal of medicine*, *379*(14), 1343–1352. https://doi.org/10.1056/NEJMcp1702493

[16]Eichenfield, D. Z., Sprague, J., & Eichenfield, L. F. (2021). Management of Acne Vulgaris: A Review. *JAMA*, *326*(20), 2055–2067. https://doi.org/10.1001/jama.2021.17633

[17]Costa, C. S., Bagatin, E., Martimbianco, A. L. C., da Silva, E. M., Lúcio, M. M., Magin, P., & Riera, R. (2018). Oral isotretinoin for acne. *The Cochrane database of systematic reviews*, *11*(11), CD009435. https://doi.org/10.1002/14651858.CD009435.pub2

[18]Măgerușan, Ș. E., Hancu, G., & Rusu, A. (2023). A Comprehensive Bibliographic Review Concerning the Efficacy of Organic Acids for Chemical Peels Treating Acne Vulgaris. *Molecules (Basel, Switzerland)*, *28*(20), 7219. https://doi.org/10.3390/molecules28207219

[19]Chilicka, K., Rogowska, A. M., Szyguła, R., Dzieńdziora-Urbińska, I., & Taradaj, J. (2020). A comparison of the effectiveness of azelaic and pyruvic acid peels in the treatment of female adult acne: a randomized controlled trial. *Scientific reports*, *10*(1), 12612. https://doi.org/10.1038/s41598-020-69530-w

[20]Barbaric, J., Abbott, R., Posadzki, P., Car, M., Gunn, L. H., Layton, A. M., Majeed, A., & Car, J. (2016). Light therapies for acne. *The Cochrane database of systematic reviews*, *9*(9), CD007917. https://doi.org/10.1002/14651858.CD007917.pub2

[21]Dhaliwal, S., Nguyen, M., Vaughn, A. R., Notay, M., Chambers, C. J., & Sivamani, R. K. (2020). Effects of Zinc Supplementation on Inflammatory Skin Diseases: A Systematic Review of the Clinical Evidence. *American journal of clinical dermatology*, *21*(1), 21–39. https://doi.org/10.1007/s40257-019-00484-0

[22]Lin, P. H., Sermersheim, M., Li, H., Lee, P. H. U., Steinberg, S. M., & Ma, J. (2017). Zinc in Wound Healing Modulation. *Nutrients*, *10*(1), 16. https://doi.org/10.3390/nu10010016

[23]Zou, P., Du, Y., Yang, C., & Cao, Y. (2023). Trace element zinc and skin disorders. *Frontiers in medicine*, *9*, 1093868. https://doi.org/10.3389/fmed.2022.1093868

[24]Al-Khafaji, Z., Brito, S., & Bin, B. H. (2022). Zinc and Zinc Transporters in Dermatology. *International journal of molecular sciences*, *23*(24), 16165. https://doi.org/10.3390/ijms232416165

[25]Monteiro, R. C., & Fernandes, M. (2024). Are antibiotics still relevant in acne? A review of the therapeutic conundrum. *International journal of dermatology*, *63*(3), 306–310. https://doi.org/10.1111/ijd.16854

[26]Michaëlsson, G., Vahlquist, A., & Juhlin, L. (1977). Serum zinc and retinol-binding protein in acne. *The British journal of dermatology*, *96*(3), 283–286. https://doi.org/10.1111/j.1365-2133.1977.tb06138.x

[27]Podgórska, A., Kicman, A., Naliwajko, S., Wacewicz-Muczyńska, M., & Niczyporuk, M. (2024). Zinc, Copper, and Iron in Selected Skin Diseases. *International journal of molecular sciences*, *25*(7), 3823. https://doi.org/10.3390/ijms25073823

[28]Bin, B. H., Hojyo, S., Seo, J., Hara, T., Takagishi, T., Mishima, K., & Fukada, T. (2018). The Role of the Slc39a Family of Zinc Transporters in Zinc Homeostasis in Skin. *Nutrients*, *10*(2), 219. https://doi.org/10.3390/nu10020219

[29]Ogawa, Y., Kinoshita, M., Shimada, S., & Kawamura, T. (2018). Zinc and Skin Disorders. *Nutrients*, *10*(2), 199. https://doi.org/10.3390/nu10020199

[30]Mavranezouli, I., Welton, N. J., Daly, C. H., Wilcock, J., Bromham, N., Berg, L., Xu, J., Wood, D., Ravenscroft, J. C., Dworzynski, K., & Healy, E. (2022). Cost-effectiveness of topical pharmacological, oral pharmacological, physical and combined treatments for acne vulgaris. *Clinical and experimental dermatology*, *47*(12), 2176–2187. https://doi.org/10.1111/ced.15356

[31]Walocko, F. M., Eber, A. E., Keri, J. E., Al-Harbi, M. A., & Nouri, K. (2017). The role of nicotinamide in acne treatment. *Dermatologic therapy*, *30*(5), 10.1111/dth.12481. https://doi.org/10.1111/dth.12481

[32]Gao, X., Yu, Z., Yang, J., Gao, Y., Li, S., & Zhang, W. (2020). An integrated RNA-Seq and network study reveals the effect of nicotinamide on adrenal androgen synthesis. *Clinical and experimental pharmacology & physiology*, *47*(5), 821–830. https://doi.org/10.1111/1440-1681.13258

[33]Bukvić Mokos, Z., Tomić Krsnik, L., Harak, K., Marojević Tomić, D., Tešanović Perković, D., & Vukojević, M. (2025). Vitamin D in the Prevention and Treatment of Inflammatory Skin Diseases. *International journal of molecular sciences*, *26*(11), 5005. https://doi.org/10.3390/ijms26115005

[34]Eguren, C., Navarro-Blasco, A., Corral-Forteza, M., Reolid-Pérez, A., Setó-Torrent, N., García-Navarro, A., Prieto-Merino, D., Núñez-Delegido, E., Sánchez-Pellicer, P., & Navarro-López, V. (2024). A Randomized Clinical Trial to Evaluate the Efficacy of an Oral Probiotic in Acne Vulgaris. *Acta dermato-venereologica*, *104*, adv33206. https://doi.org/10.2340/actadv.v104.33206

[35]Sardana, K., Gupta, T., Garg, V. K., & Ghunawat, S. (2015). Antibiotic resistance to Propionobacterium acnes: worldwide scenario, diagnosis and management. *Expert review of anti-infective therapy*, *13*(7), 883–896. https://doi.org/10.1586/14787210.2015.1040765

[36]Liu, H., Yu, H., Xia, J., Liu, L., Liu, G. J., Sang, H., & Peinemann, F. (2020). Topical azelaic acid, salicylic acid, nicotinamide, sulphur, zinc and fruit acid (alpha-hydroxy acid) for

acne. *The Cochrane database of systematic reviews*, *5*(5), CD011368. https://doi.org/10.1002/14651858.CD011368.pub2

[37]Holland, K. T., Bojar, R. A., Cunliffe, W. J., Cutcliffe, A. G., Eady, E. A., Farooq, L., Farrell, A. M., Gribbon, E. M., & Taylor, D. (1992). The effect of zinc and erythromycin on the growth of erythromycin-resistant and erythromycin-sensitive isolates of Propionibacterium acnes: an in-vitro study. *The British journal of dermatology*, *126*(5), 505–509. https://doi.org/10.1111/j.1365-2133.1992.tb11826.x

[38]Dreno, B., Foulc, P., Reynaud, A., Moyse, D., Habert, H., & Richet, H. (2005). Effect of zinc gluconate on propionibacterium acnes resistance to erythromycin in patients with inflammatory acne: in vitro and in vivo study. *European journal of dermatology : EJD*, *15*(3), 152–155.

[39]Inoue, Y., Hasegawa, S., Ban, S., Yamada, T., Date, Y., Mizutani, H., Nakata, S., Tanaka, M., & Hirashima, N. (2014). ZIP2 protein, a zinc transporter, is associated with keratinocyte differentiation. *The Journal of biological chemistry*, *289*(31), 21451–21462. https://doi.org/10.1074/jbc.M114.560821

[40]Ogawa, Y., Kawamura, T., & Shimada, S. (2016). Zinc and skin biology. *Archives of biochemistry and biophysics*, *611*, 113–119. https://doi.org/10.1016/j.abb.2016.06.003

[41]Bin, B. H., Bhin, J., Kim, N. H., Lee, S. H., Jung, H. S., Seo, J., Kim, D. K., Hwang, D., Fukada, T., Lee, A. Y., Lee, T. R., & Cho, E. G. (2017). An Acrodermatitis Enteropathica-Associated Zn Transporter, ZIP4, Regulates Human Epidermal Homeostasis. *The Journal of investigative dermatology*, *137*(4), 874–883. https://doi.org/10.1016/j.jid.2016.11.028

[42]Bin, B. H., Lee, S. H., Bhin, J., Irié, T., Kim, S., Seo, J., Mishima, K., Lee, T. R., Hwang, D., Fukada, T., & Cho, E. G. (2019). The epithelial zinc transporter ZIP10 epigenetically regulates human epidermal homeostasis by modulating histone acetyltransferase activity. *The British journal of dermatology*, *180*(4), 869–880. https://doi.org/10.1111/bjd.17339

[43]Mitchell, B. L., Saklatvala, J. R., Dand, N., Hagenbeek, F. A., Li, X., Min, J. L., Thomas, L., Bartels, M., Jan Hottenga, J., Lupton, M. K., Boomsma, D. I., Dong, X., Hveem, K., Løset, M., Martin, N. G., Barker, J. N., Han, J., Smith, C. H., Rentería, M. E., & Simpson, M. A. (2022). Genome-wide association meta-analysis identifies 29 new acne susceptibility loci. *Nature communications*, *13*(1), 702. https://doi.org/10.1038/s41467-022-28252-5

[44]Teder-Laving, M., Kals, M., Reigo, A., Ehin, R., Objärtel, T., Vaht, M., Nikopensius, T., Metspalu, A., & Kingo, K. (2024). Genome-wide meta-analysis identifies novel loci conferring risk of acne vulgaris. *European journal of human genetics : EJHG*, *32*(9), 1136–1143. https://doi.org/10.1038/s41431-023-01326-8

[45]Heng, A. H. S., Say, Y. H., Sio, Y. Y., Ng, Y. T., & Chew, F. T. (2021). Gene variants associated with acne vulgaris presentation and severity: a systematic review and meta-analysis. *BMC medical genomics*, *14*(1), 103. https://doi.org/10.1186/s12920-021-00953-8

[46]Lansdown, A. B., Mirastschijski, U., Stubbs, N., Scanlon, E., & Agren, M. S. (2007). Zinc in wound healing: theoretical, experimental, and clinical aspects. *Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society*, *15*(1), 2–16. https://doi.org/10.1111/j.1524-475X.2006.00179.x

[47]Palmieri, B., Vadalà, M., & Laurino, C. (2019). Nutrition in wound healing: investigation of the molecular mechanisms, a narrative review. *Journal of wound care*, *28*(10), 683–693. https://doi.org/10.12968/jowc.2019.28.10.683

[48]Ågren, M. S., Chafranska, L., Eriksen, J. O., Forman, J. L., Bjerrum, M. J., Schjerling, P., Larsen, H. F., Cottarelli, E., Jorgensen, L. N., & Gjerdrum, L. M. R. (2021). Spatial expression of metallothionein, matrix metalloproteinase-1 and Ki-67 in human epidermal wounds treated with zinc and determined by quantitative immunohistochemistry: A randomised double-blind trial. *European journal of cell biology*, *100*(3), 151147. https://doi.org/10.1016/j.ejcb.2020.151147

[49]Ravanti, L., & Kähäri, V. M. (2000). Matrix metalloproteinases in wound repair (review). *International journal of molecular medicine*, *6*(4), 391–407.

[50]Nishida, K., Hasegawa, A., Yamasaki, S., Uchida, R., Ohashi, W., Kurashima, Y., Kunisawa, J., Kimura, S., Iwanaga, T., Watarai, H., Hase, K., Ogura, H., Nakayama, M., Kashiwakura, J. I., Okayama, Y., Kubo, M., Ohara, O., Kiyono, H., Koseki, H., Murakami, M., … Hirano, T. (2019). Mast cells play role in wound healing through the ZnT2/GPR39/IL-6 axis. *Scientific reports*, *9*(1), 10842. https://doi.org/10.1038/s41598-019-47132-5

[51]Li, X., Du, W., Xu, W., Ling, G., & Zhang, P. (2023). Dissolving microneedles based on ZnO nanoparticles and an ionic liquid as synergistic antibacterial agents. *Journal of materials chemistry. B*, *11*(19), 4354–4364. https://doi.org/10.1039/d3tb00127j

[52]Zhou, L., Xu, S., & Li, S. (2025). Microneedle-Mediated Transdermal Drug Delivery for the Treatment of Multiple Skin Diseases. *Pharmaceutics*, *17*(10), 1281. https://doi.org/10.3390/pharmaceutics17101281

[53]Yang, D., Chen, M., Sun, Y., Jin, Y., Lu, C., Pan, X., Quan, G., & Wu, C. (2021). Microneedle-mediated transdermal drug delivery for treating diverse skin diseases. *Acta biomaterialia*, *121*, 119–133. https://doi.org/10.1016/j.actbio.2020.12.004

[54]Dada, K. S., Olekhnovich, R. O., & Zaripova, F. F. (2026). Review of Polymers and Nanocomposites Based on Hyaluronic Acid and Zinc Oxide Nanoparticles in Synthesizing Microneedles for Transdermal Drug Delivery. *Polymers*, *18*(2), 217. https://doi.org/10.3390/polym18020217

[55]Shao, X., Ou, Y., Chen, T., Deng, B., Zhang, J., & Chen, J. (2025). Trace Elements and Risk of Immune-Mediated Skin Disease: A Systematic Review and Meta-analysis. *Nutrition reviews*, *83*(8), 1462–1474. https://doi.org/10.1093/nutrit/nuaf015

[56]Gray, N. A., Dhana, A., Stein, D. J., & Khumalo, N. P. (2019). Zinc and atopic dermatitis: a systematic review and meta-analysis. *Journal of the European Academy of Dermatology and Venereology : JEADV*, *33*(6), 1042–1050. https://doi.org/10.1111/jdv.15524

[57]Wei, Y., Zhu, X., Lin, S., Yang, W., Wang, T., Nie, X., Shi, Z., Liu, Z., Zhang, R., & Li, D. (2024). Zinc gluconate improves atopic dermatitis by modulating CXCL10 release of keratinocytes via PPARα activation. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, *177*, 117129. https://doi.org/10.1016/j.biopha.2024.117129

[58] Killilea, D. W., & Schultz, K. (2023). Pre-analytical variables influence zinc measurement in blood samples. *PloS one*, *18*(9), e0286073. https://doi.org/10.1371/journal.pone.0286073

[59]King, J. C., Brown, K. H., Gibson, R. S., Krebs, N. F., Lowe, N. M., Siekmann, J. H., & Raiten, D. J. (2015). Biomarkers of Nutrition for Development (BOND)-Zinc Review. *The Journal of nutrition*, *146*(4), 858S–885S. https://doi.org/10.3945/jn.115.220079

[60] Newton J. N. (1997). How cost-effective is oral isotretinoin?. *Dermatology (Basel, Switzerland)*, *195 Suppl 1*, 10–40. https://doi.org/10.1159/000246014

[61]Xia, E., Han, J., Faletsky, A., Baldwin, H., Beleznay, K., Bettoli, V., Dréno, B., Goh, C. L., Stein Gold, L., Gollnick, H., Herane, M. I., Kang, S., Kircik, L., Mann, J., Nast, A., Oon, H. H., See, J. A., Tollefson, M., Webster, G., Zip, C., … Mostaghimi, A. (2022). Isotretinoin Laboratory Monitoring in Acne Treatment: A Delphi Consensus Study. *JAMA dermatology*, *158*(8), 942–948. https://doi.org/10.1001/jamadermatol.2022.2044