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Review Article

Ozone in Dermatology – Between Science and Therapy

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Abstract

Ozone therapy is increasingly utilized in dermatology owing to its multimodal antimicrobial, anti-inflammatory, antioxidant, and regenerative properties; however, its clinical implementation remains heterogeneous and the quality of supporting evidence varies across indications. This review critically evaluates the mechanisms of action, clinical applications, safety profile, and future perspectives of ozone therapy in dermatological practice. A structured literature search of PubMed, Scopus, and Web of Science covering the period from January 2000 to December 2024 identified 60 eligible human studies, which were assessed according to study design and methodological quality. Biologically, ozone exerts its effects through controlled oxidative stimulation, leading to activation of the Nrf2/EpRE pathway, improvement of microcirculation, and promotion of immunomodulation, tissue oxygenation, and wound healing. Moderate-quality evidence supports the use of ozone as an adjunctive treatment for chronic ulcers and burns (evidence level B), while limited to moderate evidence suggests potential benefits in acne, atopic and seborrheic dermatitis, cutaneous infections, and psoriasis (evidence levels C–D). Aesthetic and regenerative applications remain largely experimental (evidence level D). When administered by trained professionals using appropriate protocols, ozone therapy demonstrates a generally favorable safety profile, with adverse events being infrequent and typically mild. Overall, ozone therapy shows meaningful therapeutic potential as an adjunctive modality in dermatology, particularly for chronic and treatment-resistant dermatoses; nevertheless, broader adoption will require standardized dosing and delivery protocols, high-quality randomized clinical trials, and robust long-term safety data, supported by continued technological advances and molecular research to enable more targeted, evidence-based integration into clinical practice.

Keywords

Ozone Therapy, Dermatology, Oxidative Stress, Antimicrobial Effect, Anti-inflammatory Activity, Skin Diseases

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1. Introduction

Ozone therapy is a non-pharmacological method based on the application of medical ozone—a gaseous mixture containing a precisely defined ratio of oxygen (O_2) and ozone (O_3) [1, 2]. Ozone, a triatomic allotrope of oxygen, possesses potent oxidative and antimicrobial properties that determine its biomedical potential [3]. Its antimicrobial, anti-inflammatory, analgesic, and regenerative effects are well documented [4-6]. Although initially used primarily in infectious and surgical disciplines [7], in recent years ozone therapy has gained increasing application in dermatology due to its biomodulatory effects on the skin and its appendages, as well as in regenerative medicine [8-12].

The mechanism of action of ozone involves controlled oxidative stimulation that activates the antioxidant defense system via the Nrf2/EpRE pathway, leading to subsequent regulation of the inflammatory response [13, 14]. This hormetic effect distinguishes ozone therapy from other oxidative methods and positions it as a potential modulator of the cellular redox balance [15]. Controlled oxidative stress triggers upregulation of antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase), improves tissue oxygenation and microcirculation, and enhances both local and systemic immune responses [16-18]. These effects account for the broad therapeutic potential of ozone therapy in inflammatory, infectious, and degenerative skin diseases [19, 20].

In dermatological practice, ozone can be administered topically (as gas, ozonated water, ozonated oils, ozone baths, or gas saunas), parenterally (infusions, autohemotherapy), or via injection (subcutaneous, intradermal, or perifocal) [21, 22]. Clinical and experimental studies indicate that ozone therapy may improve outcomes in acne, atopic and seborrheic dermatitis, psoriasis, chronic ulcers, and skin infections [23-27]. In addition to its antimicrobial properties, ozone enhances microcirculation and tissue oxygenation, and accelerates epithelialization, which may contribute to improved healing outcomes [28, 29].

Despite growing evidence supporting its therapeutic value, its clinical application remains subject to scientific debate due to variability in ozone concentrations, administration protocols, and treatment duration across studies [30-33]. High-quality randomized trials are still lacking for many indications.

The aim of the present review is to summarize current evidence on the mechanisms of action, clinical applications, efficacy, and safety of ozone therapy in dermatology, while critically evaluating the quality of available evidence and identifying gaps requiring further investigation.

2. Literature Search Methodology

A structured literature search was performed in PubMed, Scopus, and Web of Science, covering the period from January 2000 to December 2024. The following keywords and combinations were used:

"ozone therapy", "dermatology", "skin disease", "ozonated oil", "autohemotherapy", "cutaneous infections", "wound healing".

Inclusion criteria:

1) Human clinical studies (randomized or controlled), observational studies, and systematic reviews
2) Articles reporting dermatological outcomes of ozone therapy
3) English-language publications

Exclusion criteria:

1) Animal studies (unless mechanistic relevance required)
2) Case reports without measurable outcomes
3) Non-dermatologic applications

A total of 60 articles were included in the qualitative synthesis. Evidence levels were assessed according to study design and methodological quality.

3. Ozone in Dermatology

3.1. Mechanisms of Action of Ozone in Dermatology

Ozone is one of the most reactive allotropes of oxygen and exerts its biological effects primarily through controlled, dose-dependent oxidative stimulation. At therapeutic concentrations (10–70 μg/mL), ozone does not directly damage cells but activates adaptive mechanisms involved in antioxidant defense and tissue repair [1, 34]. This effect is mediated by a mild oxidative challenge that stimulates key cellular signaling pathways, increases antioxidant enzyme activity, and improves tissue oxygenation [7]. Upon exposure to biological fluids, ozone rapidly interacts with lipids and antioxidants, generating reactive oxygen species (ROS) and lipid oxidation products (LOPs) that function as secondary messengers [35]. These mediators activate the Nrf2/EpRE pathway, upregulating cytoprotective enzymes such as superoxide dismutase and catalase, ultimately supporting redox homeostasis [2].

In the skin, this controlled oxidative signaling also contributes to anti-inflammatory activity and immunomodulation [36]. Formation of ROS and lipid peroxidation products—particularly 4-hydroxynonenal (4-HNE)—influences pathways associated with oxidative stress and cytokine regulation, thereby modulating cutaneous inflammatory responses [9, 37]. While these effects form the mechanistic basis for ozone's therapeutic potential in dermatology, their clinical relevance remains dependent on precise dosing and administration protocols.

Ozone demonstrates broad-spectrum bactericidal, virucidal, and fungicidal properties by oxidizing microbial membranes and disrupting enzymatic systems, resulting in rapid pathogen inactivation—including strains resistant to conventional ther-

apies [38]. These antimicrobial effects support its clinical usefulness in infected dermatoses, chronic ulcers, pyodermas, and onychomycosis [20]. By improving local oxygenation and reducing microbial burden, ozone is particularly advantageous in chronic wounds where hypoxia and superinfection impede healing [39, 40].

Beyond its direct antimicrobial activity, ozone exhibits important immunomodulatory and anti-inflammatory effects. It reduces the production of pro-inflammatory cytokines (IL-1β, TNF-α, IFN-γ) while promoting anti-inflammatory mediators such as IL-10 and TGF-β [41]. These actions contribute to symptom relief in chronic inflammatory conditions including atopic dermatitis and psoriasis [42]. Additionally, ozone enhances phagocytic activity of neutrophils and macrophages, contributing to improved cutaneous innate defense [6]. Evidence also suggests modulation of cytokine signaling and activation of regulatory T cells, indicating potential value in autoimmune dermatoses [43, 44].

Ozone also improves cutaneous microcirculation and tissue oxygen delivery. Through the generation of reactive oxygen species and lipid peroxides, it stimulates the formation of vasodilatory mediators such as prostacyclin and nitric oxide, facilitating enhanced microvascular flow [45]. This optimization of oxygen availability supports keratinocyte and fibroblast metabolism and contributes to accelerated epithelial repair [1, 11, 12].

In addition, controlled ozone exposure activates endogenous antioxidant systems. By stimulating the Nrf2-dependent transcription of enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, ozone helps maintain redox balance and counteract oxidative stress in damaged or inflamed skin [2, 46, 47]. This hormetic response, triggered by low-dose oxidative stimulation, underlies ozone's cytoprotective potential in dermatologic settings [11, 12, 45].

Through its combined effects on cellular proliferation, collagen synthesis, and angiogenesis—partially mediated by growth factors including VEGF, TGF-β, and PDGF—ozone therapy also contributes to regeneration and wound healing [48]. These mechanisms explain its beneficial role in chronic ulcers, postoperative wounds, and scar tissue remodeling.

Table 1 demonstrates the mechanisms of action of ozone therapy, emphasizing their relevance to dermatological benefits.

Table 1. *Mechanistic Pathways of Ozone Therapy and Associated Dermatologic Effects.*

Mechanism of Action	Key Biological Processes	Primary Dermatologic Benefits
Antimicrobial activity	Oxidation of microbial membranes; enzyme inactivation; reduction of aerobic/anaerobic burden	Treatment of infected dermatoses, chronic wounds, pyodermas, onychomycosis
Anti-inflammatory and immunomodulation	↓ IL-1β, TNF-α, IFN-γ; ↑ IL-10, TGF-β; ↑ phagocytic activity; regulatory T-cell activation	Reduction of erythema, pruritus, and chronic inflammatory processes (e.g., AD, psoriasis)
Improved microcirculation and oxygenation	↑ Prostacyclin and NO synthesis; ↑ microvascular flow; ↑ tissue oxygen delivery	Enhanced epithelial repair and metabolic recovery in hypoxic tissues
Antioxidant and cytoprotective effects	Nrf2 pathway activation; ↑ antioxidant enzymes (SOD, catalase, GPx); redox homeostasis restoration	Protection against oxidative stress and inflammatory damage
Regeneration and wound healing	↑ Fibroblast activity; ↑ collagen synthesis; ↑ VEGF, TGF-β, PDGF; ↑ angiogenesis	Accelerated healing of chronic ulcers, burns, postoperative wounds; scar remodeling

3.2. Clinical Applications of Ozone Therapy in Dermatology

Clinical data suggest that ozone therapy may provide therapeutic benefit across several dermatological conditions, although evidence strength varies substantially between indications. In acne vulgaris, ozone exhibits strong bactericidal activity against Cutibacterium acnes while reducing inflammation and sebum production [8, 34, 35]. Topical application of ozonated oils has been shown to decrease comedonal and papulopustular lesions, particularly when used as an adjunct to retinoids or antibiotics, with potential reduction in post-inflammatory hyperpigmentation [25]. However, most studies are small and lack rigorous controls; therefore, the current evidence level is moderate (C) for adjunctive use.

In chronic inflammatory dermatoses such as atopic dermatitis (AD) and seborrheic dermatitis (SD), ozone demonstrates immunomodulatory and antipruritic properties that contribute to improvement in erythema, xerosis, and pruritus, while reducing reliance on topical corticosteroids [16, 36]. Ozonated baths and topical preparations may also reduce Malassezia spp. in SD and normalize sebum secretion [9, 29]. Despite promising symptomatic improvement, the available data are heterogeneous with limited randomized trials; thus, the evidence

level is low to moderate (C–D).

Psoriasis has also been explored as a therapeutic target due to ozone's anti-inflammatory and antiproliferative effects, including reduced expression of TNF-α, IL-6, and IL-17 [18, 24]. Clinical observations report improvements in PASI scores and prolonged remission when ozone is used as an adjunct to phototherapy or systemic treatment [26]. Nevertheless, controlled trials are scarce, and ozone monotherapy lacks robust support, indicating a limited evidence level (C).

Among all dermatologic indications, ozone therapy is most strongly supported in the management of chronic ulcers—including venous, diabetic, and pressure ulcers—as well as burns [30]. Enhanced angiogenesis, microbial control, and collagen synthesis contribute to accelerated granulation and epithelialization, reduced pain, and decreased need for antibiotic therapy [27, 28, 37]. Given the consistency of clinical outcomes across multiple studies, although many remain non-randomized, the evidence level is moderate (B), particularly when ozone is used as an adjunct to standard wound care.

Ozone's broad antimicrobial activity is also clinically valuable in cutaneous infections involving bacterial, viral, and fungal pathogens [6]. It effectively reduces bacterial load and supports epithelialization in infected lesions [23], demonstrates antifungal activity against Candida albicans and dermatophytes [38], and provides symptomatic relief in herpesvirus infections, including pain reduction and faster lesion resolution in Herpes zoster [39]. These benefits are clinically meaningful, but validation through controlled studies remains limited, suggesting moderate evidence (C).

In aesthetic and regenerative dermatology, ozone is applied as a biorevitalizing agent to enhance microcirculation, stimulate collagen and elastin synthesis, and improve skin turgor and hydration [20, 26, 48]. It is often combined with other procedures such as mesotherapy, platelet-rich plasma, and laser therapy, potentially reducing inflammatory reactions and improving recovery [45, 47]. However, outcomes are largely based on observational or industry-driven research, yielding low evidence (D) and supporting use only within multimodal settings.

Emerging but preliminary applications include scleroderma, vitiligo, and lichen planus, in which ozone may improve microcirculation and modulate inflammatory pathways [31]. Although early results indicate good tolerability and compatibility with standard treatments, data remain insufficient for definitive conclusions.

Table 2 presents the clinical uses of ozone therapy in dermatology and the quality of evidence that supports these therapeutic implications.

Table 2. *Dermatologic Indications for Ozone Therapy: Evidence Summary.*

Dermatologic Condition	Primary Therapeutic Effects	Clinical Role	Evidence Level*
Chronic ulcers and burns (venous, diabetic, pressure ulcers, thermal injury)	↑ Granulation & epithelialization, ↓ microbial load, ↓ pain, ↑ oxygenation & microcirculation	Adjunct to standard wound care	B
Acne vulgaris	Antimicrobial vs. *C. acnes*, ↓ inflammation & sebum production	Adjunct to topical/systemic therapy	C
Atopic dermatitis & seborrheic dermatitis	Immunomodulation, barrier restoration, antipruritic effects, ↓ *Malassezia* spp.	Steroid-sparing adjunct	C–D
Cutaneous infections (bacterial, fungal, viral)	Broad-spectrum antimicrobial, faster lesion resolution in HSV/VZV	Adjunctive antimicrobial therapy	C
Psoriasis	↓ Pro-inflammatory cytokines, improved plaque regression	Combination therapy only	C
Aesthetic & regenerative indications (skin rejuvenation, elasticity improvement)	↑ Collagen & elastin synthesis, ↑ microcirculation	Investigational / adjuvant use	D
Emerging uses (scleroderma, vitiligo, lichen planus)	↓ Inflammation, ↑ microcirculation	Experimental; insufficient data	D

3.3. Safety, Contraindications, and Potential Adverse Effects of Ozone Therapy

When properly administered, ozone therapy generally demonstrates a favorable safety profile. The use of medical-grade ozone produced by certified devices, combined with adherence to standardized dosing parameters and aseptic technique, contributes to high treatment tolerability [1, 2, 7]. Evidence from systematic reviews indicates a low incidence of adverse events, particularly with topical applications and autohemotherapy performed under appropriate conditions [4, 21].

Although ozone therapy is generally well tolerated, potential toxicity is primarily linked to excessive oxidative stress and lipid peroxidation, which can damage cellular membranes and structural proteins [6, 9]. High ozone concentrations or accidental inhalational exposure pose the greatest risk, potentially leading to airway inflammation, bronchoconstriction, and pulmonary edema—particularly in individuals with pre-existing respiratory disease [49]. When systemic exposure exceeds the body's antioxidant capacity, an overproduction of reactive oxygen species may result in oxidative injury [18].

Reported adverse reactions are uncommon but documented in the literature. Local effects include transient erythema, mild edema, injection-site pain, burning, or pruritus following topical or injected ozone applications, typically resolving within 24–72 hours [29]. Systemic symptoms such as headache, dizziness, nausea, or fatigue may occur when dosing during autohemotherapy is not properly controlled [16]. Inhalation-related injury represents the most serious risk and can result in bronchospasm, coughing, dyspnea, or, in severe cases, pulmonary edema; therefore, strict prevention of gas leakage into the respiratory tract is mandatory [28, 49]. Rare hematologic or cardiovascular complications have been reported, mainly in patients with underlying heart disease or when major autohemotherapy is administered improperly [31].

Contraindications should be carefully considered prior to treatment. Absolute contraindications include severe hemolytic anemia, thyrotoxicosis, acute myocardial infarction, and decompensated heart failure, conditions in which ozone may provoke hemodynamic instability [50]. Treatment in oncology patients with unstable clinical status requires individualized assessment. Relative contraindications include pregnancy, epilepsy, uncontrolled hypertension, acute systemic infections, and severe pulmonary disorders such as chronic obstructive pulmonary disease or asthma, where even minimal inhalational exposure is undesirable [51].

Table 3 summarizes the toxicity risks, adverse reactions, and contraindications of ozone therapy.

Table 3. *Safety Considerations, Adverse Reactions, and Contraindications of Ozone Therapy.*

Category	Key Symptoms	Clinical Notes
Mechanisms of potential toxicity	Excessive oxidative stress; lipid peroxidation; membrane and protein damage	Risk increases with high ozone concentration and inadequate technique
Inhalation-related risks	Airway inflammation, bronchospasm, pulmonary edema	Highest severity; requires strict prevention of ozone leakage
Local adverse reactions	Transient erythema, mild edema, injection-site discomfort, burning, pruritus	Typically self-limited within 24–72 h
Systemic adverse reactions	Headache, dizziness, nausea, fatigue	Most often linked to incorrect dosing during autohemotherapy
Rare complications	Hematologic or cardiovascular instability	Mainly in patients with underlying cardiovascular disease or incorrect administration
Absolute contraindications	Severe hemolytic anemia, thyrotoxicosis, acute MI, decompensated heart failure	Risk of hemodynamic deterioration; treatment prohibited
Relative contraindications	Pregnancy, epilepsy, uncontrolled hypertension, acute infections, COPD/asthma	Caution required due to increased sensitivity and inhalational risk

4. Perspectives and Future Directions

Ozone therapy is gaining a steadily stronger position among complementary medical approaches, with clear potential for broader integration into dermatological practice. Accumulating clinical and experimental evidence over the past two decades highlights promising directions for therapeutic and preventive use [52, 53]. However, meaningful advancement of the field needs to address several key challenges.

A central priority is the development of internationally standardized protocols for ozone concentration, dosage, frequency, and routes of administration—whether topical, injectable, autohemotherapy, or ozonated oils [3]. The current lack of methodological consistency significantly limits meta-analytic synthesis and the strength of clinical recommendations [35]. Large randomized controlled trials employing uniform outcomes (e.g., inflammatory marker reduction, epithelialization time, microbiota changes, patient-reported outcomes) are essential for establishing ozone therapy within evidence-based dermatology [21].

Future progress is also linked to its integration as part of multimodal therapeutic strategies rather than as a stand-alone

intervention. When combined with phototherapy, topical retinoids, antibiotics, or biologic agents, ozone may enhance treatment response through synergistic anti-inflammatory and antimicrobial effects [8]. Its role in regenerative medicine is expanding, particularly in combination with platelet-rich plasma or laser-based procedures, where ozone may reduce inflammation and support accelerated repair [54].

Advances in formulation and delivery technologies offer additional opportunities. Ozonated nanoemulsions, liposomal systems, and novel biopolymer dressings are being designed to achieve more stable, controlled release of reactive oxygen species, improving clinical precision and patient usability [46]. Ozonated oils such as olive and sunflower derivatives continue to demonstrate favorable results in acne, trophic ulcers, and dermatophytoses [55], while hydrogels incorporating ozone may optimize chronic wound management [56].

At the molecular level, transcriptomic and proteomic studies are beginning to clarify ozone-induced modulation of antioxidant pathways and genes linked to skin barrier function [9, 57]. Such insights may ultimately support personalized therapeutic selection based on individual biochemical and genomic profiles [47].

Additional growth is anticipated in aesthetic dermatology and anti-aging applications, where ozone shows potential to stimulate fibroblast function, collagen synthesis, and microcirculation, benefiting scar management and enhancing post-procedural healing following interventions such as laser resurfacing or microneedling [17, 58].

To ensure safe and ethical implementation, the establishment of internationally recognized training standards, certification processes, and regulatory guidelines is required [32, 59, 60]. Clinical registries and long-term follow-up will improve transparency, facilitate safety monitoring, and support broader clinical acceptance of ozone-based therapies [30].

Table 4 outlines the essential development needs and existing constraints that must be addressed for broader and evidence-based integration of ozone therapy in dermatology.

Table 4. *Future Prospectives of Ozone Therapy in Dermatology.*

Strategic Area	Focus of Development	Expected Clinical Impact
Standardization	Unified dosing, concentration, frequency, and administration routes; large RCTs with consistent outcomes	Stronger evidence base and clinical guidelines; improved reproducibility
Multimodal Approach	Combination with phototherapy, retinoids, antibiotics, biologics, PRP, or lasers	Enhanced treatment response via synergistic effects
Innovative Delivery Systems	Nanoemulsions, liposomes, biopolymer dressings, hydrogels	More precise dosing, higher stability, improved usability in chronic ulcers and infections
Molecular and Genomic Insights	Transcriptomic/proteomic studies on oxidative signaling and barrier gene modulation	Foundation for personalized therapy and targeted indications
Regenerative Aesthetic Medicine	Scar remodeling, post-procedural healing, anti-aging applications	Improved skin structure, elasticity, and healing outcomes
Training Regulatory Framework	Professional certification, clinical registries, long-term monitoring	Enhanced safety, ethical practice, and international acceptance

5. Conclusion

The future implementation of ozone therapy in dermatology will rely on rigorous scientific validation, continued technological innovation, and close collaboration among dermatologists, biochemists, and clinical pharmacologists [52, 53]. In an era of rising antimicrobial resistance and increasing demand for minimally invasive therapeutic options, ozone represents a promising adjunctive modality with potential benefits across a variety of dermatologic conditions [3].

Clinically, ozone therapy should be applied as an adjunct rather than a primary intervention, particularly in chronic and treatment-resistant inflammatory skin diseases, and only by trained practitioners adhering to strict safety and dosing standards [35]. A tailored approach that considers patient-specific characteristics, disease severity, and therapeutic goals is essential for achieving optimal and durable outcomes [8].

When used appropriately, ozone therapy may support restoration of the skin barrier, reduce inflammation, control microbial colonization, and improve overall patient quality of life [9]. Its favorable safety profile, low relative cost, and high compatibility with established dermatologic treatments further highlight its potential role within integrative and multimodal care frameworks [31].

Ultimately, widespread clinical acceptance will depend on the generation of high-quality evidence, the development of standardized treatment protocols, and the integration of robust

long-term outcome monitoring, ensuring that ozone therapy evolves into a fully validated and evidence-based component of modern dermatologic practice [21].

Abbreviations

O_2	Oxygen
O_3	Ozone
Nrf2/EpRE pathway	Nuclear Factor Erythroid 2–related Factor 2 / Electrophile Response Element Pathway
Nrf2	Nuclear Factor Erythroid 2–Related Factor 2
ROS	Reactive Oxygen Species
4 HNE	4 Hydroxynonenal
LOPs	Lipid Oxidation Products
NO	Nitric Oxide
VEGF	Vascular Endothelial Growth Factor
TGF β	Transforming Growth Factor Beta
PDGF	Platelet Derived Growth Factor
COPD	Chronic Obstructive Pulmonary Disease
RCT	Randomized Controlled Trial (s)
PRP	Platelet Rich Plasma
SOD	Superoxide Dismutase
GPx	Glutathione Peroxidase

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Conflicts of Interest

The authors declare no conflicts of interest.

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