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## Mechanisms of action involved in ozone-therapy in skin diseases

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## ABSTRACT

Ozone-therapy initially applied in medicine by an empirical approach, has now reached a new stage where most of the biological mechanisms of ozone action have been clarified, that refers to antimicrobial effects, immunoregulation, antioxidant defenses and epigenetic modification. Current ozone medical preparation in dermatology mainly classified as ozone hydrotherapy, ozonated oil externally used and ozone autohemotherapy (OAHT). Admittedly, ozone is widely used in various fields against gram-negative and gram-positive bacteria, viruses, and fungi. More recently, great progress has been obtained in wound healing which is a multiphase process that consists of three overlapping but distinct stages: inflammation, tissue proliferation and remodeling. While the exact mechanisms of ozone-therapy still remain unclear. Therefore, more evidence is required before ozone can be presented as a promising method for the management and prevention of various skin diseases. In this review, we review the application status of ozone in dermatology and summarize possible mechanisms of ozone-therapy on skin diseases, aims to shed a light on providing a series of theoretical basis for its applications.

### 1. Introduction

Ozone was originally applied in medicine in an empirical and rather imprecise manner for the last about 200 years since the first report for sterilization in 1826, fortunately, during the last decade, great progress has been made owing to new medical ozone generators allowing the determination of precise ozone concentrations in real time and the clarification of mechanisms of ozone action on diseases treatment [1,2]. Ozone is an unstable molecule consisting of three oxygen atoms which can quickly break down into oxygen and single oxygen atom acting as a strong oxidant to kill microorganisms. Therefore, in proper concentrations, it serves as an ideal drug [3-5]. Notably, due to its easy quenching, ozone can be used safely in medicine even though it is released into the blood where it possesses potent antioxidant capacity composed of a number of lipophilic, hydrophilic compounds and a variety of antioxidant enzymes [6]. While reports showed monthly exposure to even low troposheric ozone concentrations was toxic for the pulmonary system [7], which implies we should supervise and manage its application more effectively in medicine. This controversial molecule has been widely used as a treatment agent of more than 50 pathological processes [8-10] as well as skin diseases [11]. Currently, there are correspondingly simple application forms and biological mechanisms (Table 1) to be known in medicine. (See Table 2.)

Ozone medical preparations were mainly classified as ozone hydrotherapy, ozonated oil externally used and ozone autohemotherapy (OAHT) in dermatology. Recently, it has been used to treat four types of skin diseases: (1) infectious skin diseases containing virus, bacteria and fungi such as herpes zoster, abscess and athlete's foot [12–15]; (2) allergic diseases such as atopic dermatitis, eczema, urticarial (ozone autohemotherapy) and prurigo [16,17]; (3) erythema scaly diseases such as psoriasis and palmoplantar pustulosis [18,19]; (4) wound healing and ulcer recovery [3]. The mechanisms of ozone's action are omnifarious involved in direct antimicrobial effect, immunoregulation, antioxidant defenses, epigenetic modification, even more other potent properties such as biosynthetic, analgesic and vasodilative effects [11]. There are several statements for its antimicrobial effect, firstly, ozone directly disrupts nucleic acid or liposome shell of microorganisms. After the membrane is damaged, permeability increases and ozone molecules can easily enter into the cells [11]. Moreover, it generates molecularlevel reactions in the medium where it releases oxygen-free radicals and then indirectly destroys the living micro-environment [20,21]. The immunoregulation of ozone in the treatment of diseases is generally accepted that ozone on the one hand, increases the quantity of leukocytes, enhances the phagocytic capacity of granulocytes, facilitates the formation of monocytes and activates T cells. Simultaneously, it boosts the release of cytokines such as interferon and interleukin triggering antibody dependent cellular cytotoxicity (ADCC) [22,23]. On the other hand, ozone augments the production of hydrogen peroxide  $(H_2O_2)$ derived from immune cells of body [24] to kill pathogens. While the strength of the oxidative stress determines the effectiveness and toxicity of ozone. Severe oxidative stress activates nuclear transcriptional factor kappa B (NF-KB), leading to inflammatory responses and tissue injury

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#### Table 1

Ozone therapy in the management and prevention of skin diseases.

Medical preparations types	Effects	Skin diseases included	Ref.
Ozonated hydrotherapy Ozonated oil	Antimicrobial, relieving itching, Antimicrobial, moisturizer, reducing exudate	Infectious, allergic, erythema scaly diseases, wound healing and ulcer recovery	[3] [9,11] [13,36]
Ozonated autohemo- therapy	Antioxidant defenses, immunoregulatory effect, epigenetic modification	Chronic systemic conditions, autoimmune diseases, postherpetic neuralgia, beauty care items	[37] [19,44,45,48]

by the production of COX2, PGE2, and cytokines. Conversely, moderate oxidative stress activates nuclear factor-erythroid 2-related factor 2 (Nrf2) and represses NF-KB and inflammatory responses. Additionally, moderate oxidative stress induced the production of hypoxia inducible factor-1a (HIF-1a) which has been elucidated in vascular and degenerative diseases as well as skin lesions [25]. In recent years, the mystery of epigenetic modification induced by ozone therapy is gradually unveiling.

Unfortunately, there is not enough solid theoretical foundation and clinical evidence to support the ozone-therapy in dermatology at present, and most of the current applications just depend on clinical experience, which presents a great challenge in this field. Thus, a more exact mechanism of action how ozone works and a more reliable evidence-based medical data are in great need. In this review, we summarize the application status of ozone-therapy in dermatology, discuss the possible mechanisms of action and strive for providing more evidence for ozone applications.

## 2. The application status of ozone-therapy in dermatology

Ozone was first performed for treating German soldiers suffering gaseous gangrene during World War I owing to its strong bactericidal effect on *Clostridium* anaerobic [26], while this approach is very empirical and unprecise. Until 2001, Werkmeister [27] mastered the use of ozone in several skin ulcers affected by atherosclerosis and diabetes, however, he just used a polythene-bag (the so-called bagging system) or using an ozone-resistant plastic cup to store ozone but difficult to control its concentration. Later on, Werkmeister [27] could release a continuous gas flow with a moderate pressure that improved the vasodilation of the ulcer's site and enhanced blood circulation. Via such strategy he treated plenty of extensive and otherwise incurable lesions within 50-200 days. Remarkable, ozone functions well only in a water vapour-saturated bag because it must dissolve into superficial water or exudate to react precisely. And during the treatment process normal skin did not suffer from any damage. Now owing to the drawback of cumber and air contamination in use these procedures have been abandoned. Thus, various medical preparations have been manufactured to more accurately and conveniently serve for patients.

## 2.1. Ozonated hydrotherapy

With the good knowledge of medical equipment, we have developed an ozone generator which allowed us to control and measure the precise ozone concentrations in real time during treatment procedure and maintain optimum therapeutic dose instead of respiratory injury [28]. This instrument was designed for patients to take a bath or soak the skin lesions in clinic through producing ozone water. Generally, the

he exact studies of ozone t	therapy applied in r	nedicine included.					
Diseases	Patients number	Patients' criteria	Assessment indicators	Medical preparations types	Frequency of treatments	Outcomes	Ref.
Diabetic foot	101	Type 2 diabetes and diabetic feet	Glycemic index, the area and perimeter of the lesions and biochemical markers of oxidative stress and endothelial damage	Ozonated Hydrotherapy	Twice weekly	The healing of the lesions improved	[102]
Wound healing	18	Free gingival graft surgery	Wound sizes and shape factor	Ozonated oil	Daily for 1 week.	A significant improvement in wound size and epithelial healing	[103]
Peripheral arterial occlusive disease	152	Ankle-brachial index below 0.40	Walking distance	OAHT	Once or thrice weekly for 12 weeks	A significant improvement in blood flow	[104]

Table 2

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