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Emerging roles of ozone in skin diseases

WANG Xiaoqi[1, 2]

(1. Department of Dermatology, Third Xiangya Hospital, Central South University, Changsha 410013, China;
2. Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago IL 60611-3008, USA)

ABSTRACT Ozone was discovered in the mid-nineteenth century and is proven to have many therapeutic effects, including its common application as a disinfectant to kill microorganisms in various conditions. Ozone therapies have been utilized for various purposes ever since it was discovered. Extensive studies over a century have verified its therapeutic effects, consistency, and safety with minimal and preventable side effects in medical care. Emerging evidence revealed that ozone also plays important roles in the management and prevention of various skin disorders including infectious skin diseases, skin related allergic diseases, erythema scaly diseases, wound healing and ulcer recovery. Herein, the author now summarizes the recent clinical applications of ozone therapy in dermatology and provide commentary on what we have learned in our practice. Our focuses are the efficacy and safety of ozone therapies as well as the application prospects of ozone on various skin disorders. In addition, the author discusses the potential mechanisms involved in ozone therapy and the efforts we should make for.

KEY WORDS ozone; skin disorders; clinical application; therapy; dermatology

医用臭氧在皮肤疾病中的创新性应用

王晓琦[1, 2]

(1. 中南大学湘雅三医院皮肤科，长沙 410013； 2. 西北大学费因伯格医学院皮肤科，伊利诺伊州 芝加哥 60611-3008，美国)

[摘要] 自19世纪中期人们发现了臭氧，臭氧的多种治疗作用已被广泛接受并常用于杀菌消毒。一个多世纪的研究表明臭氧在实施多种治疗作用的同时，其毒副作用完全可控。近期的研究更证明了臭氧在感染性皮肤病、皮炎湿疹类皮肤病及皮肤慢性溃疡等疾病中的治疗作用。本课题组将臭氧广泛应用于治疗多种皮肤疾病，并致力于研究医用臭氧的疗效和安全性。此外本文也讨论了臭氧治疗的可能作用机制和未来的研究方向。

[关键词] 臭氧；皮肤病；临床应用；治疗；皮肤病学

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First author: WANG Xiaoqi, Email: xiaoqiwang26@gmail.com
Corresponding author: WANG Xiaoqi, Email: xiaoqiwang26@gmail.com

Ozone is a triatomic gaseous molecule, which acts as a powerful oxidant to be used in medicine for more than 150 years[1]. Ozone has broad medical applications due to its effective antimicrobial function[2] and antioxidant defence[3]. It also involves in regulating immune response[4] and accelerates wound healing[1, 5]. Ozone has recently been used in dermatology to treat various skin disorders including chronic inflammatory conditions[6], diabetic foot ulcers[7], herpes simplex and herpes zostervirus infections[8], allergic and itch dermatoses[9-10]. Three forms of ozone are commonly used for topical application: ozonated water, ozonated oil and ozone gas (predominantly used in autohemotherapy). The ozonated autohemotherapy (O_3-AHT) is considered as an effective adjuvant therapeutic approach for treating systemic conditions[11]. The earlier concern for ozone usage was exposure to ozone that increases incidence of respiratory morbidity and central neural system injuries such as asthma[12] and Alzheimer's disease[13] in humans. However, increased evidence suggested that only chronic exposure to high level of environmental ozone would lead to diseases such as asthma by affecting the immunopathogenesis of airway and increase the allergic sensitisation by both allergic mechanisms and impaired immune responses. Indeed, the toxicity of ozone is minimal or preventable when the appropriate dosage is used. Ozone application increases the antioxidant capacity of blood and it has great clinical benefits when used in medical therapy. A study[14] found that treatment of O_3-AHT in asthma patients effectively reduces the levels of IgE and HLA-DR, thus, improves lung function, and reduces related symptoms. This study suggests that the effectiveness of ozone therapy in reducing IgE and inflammatory mediators is associated with the induction of antioxidant elements by its immunomodulatory and oxidative stress regulation properties. The strength of the oxidative stress determines the effectiveness and toxicity of ozone. Accumulating evidence demonstrated that moderate oxidative stress induced by low doses of ozone activates nuclear factor-erythroid 2-related factor 2 (Nrf2), represses nuclear transcriptional factor kappa B (NF-κB), and reduces inflammatory responses. In contrast, severe oxidative stress triggered by high concentrations of ozone activates NF-κB, leading to elevated inflammatory responses and tissue injury by producing COX2, PGE2, and cytokines[15]. Admittedly, it is the key to control appropriate ozone concentration during medical ozone therapy to minimize the toxicity and maximize the beneficial effects by activation of immune system and antioxidant defenses[16].

Up to date, there are extensive theoretical and clinical evidence to support the application of ozone-therapy for treating skin related diseases effectively. Our research team has investigated the biological mechanisms of ozone action in various skin disorders according to the orthodox biochemical and physiological laws and we are developing more effective ozone therapies to treat skin disorders. This review aims to discuss current status of medical ozone therapies based on the mechanisms of ozone action and provide a commentary on our experience of ozone application in both bed and bench sides. The existing challenges and issues in current ozone therapies, as well as the future directions we should pursue are also discussed.

1 A brief history of ozone

Ozone was first identified by a German chemist Christian Friedrich in 1839. Ozone was initially used in the sterilization of drinking water before it applied for medical use. During the past over 150 years, ozone has been broadly used to treat infections and wounds, as well as more than 100 various diseases in medicine[17-18]. In 1896, Nikola Tesla patented the first ozone generator in the United States, and the invention of ozone generator accelerated more broad ozone application including in medical usage. As a bactericidal material, ozone was used during World War I to treat gaseous gangrene infections[19]. Usually, ozone therapy was conducted by introducing the mixture of ozone with various gases or liquids into the body via various methods including the vagina, rectum, intramuscular, subcutaneous, or intravenously. However, ozone is known to have hemodynamic and anti-inflammatory properties, and can also be introduced into the body through autohemotherapy. When HIV was discovered in 1980s, there was no any available therapy to treat HIV infected patients. Ozone was considered as autohemotherapeutic agent to treat patients infected with HIV[20]. Without any available treatment, it allowed physicians to evaluate the benefits of ozone treatment to HIV infected patients in 1980s. The initial attempt of using ozone to treat patients with HIV infection was claimed to be effective to disinfect extracorporeal blood in HIV patients. However, later study proved that ozone therapy

neither improves nor worsens the dynamics of HIV-1 replication in vivo[21].

Although ozone has been applied to treat over 100 various diseases with various outcomes, the supportive evidence for most medical application of ozone is limited. The United States Food and Drug Administration (FDA) initially stated the concern about the toxicity of ozone gas inhalation inducing inflammation and pulmonary edema in lungs in 1976, and reiterated this concern in 2006. FDA had also emphasized the effective therapeutic ozone concentration must be far greater than it can be safely tolerated by humans and other animals. Nevertheless, the mechanisms of ozone on various conditions are still obscure, although the significance and effectiveness of ozone therapies has being gradually recognized, including its immunoregulation effects and antioxidant defenses, and no any noticeable toxicity was claimed.

In this mini-review, we will focus on the emerging role of ozone in skin biology and skin related disorders. Ozone is widely used to treat infectious skin diseases against gram-negative and gram-positive bacteria, viruses, and fungi as well as chronic inflammatory[6], allergic skin conditions[9], and some autoimmune diseases (AID)[22-23]. Due to its role as an antioxidant defenses, ozone is even widely used for cosmetic related service[24] and standard healthcare[25].

Ozone is an unstable pale bluish gas with a molecular weight of 48 u. Due to its capability to oxidize substances and destroy microorganisms, ozone has been widely used to sterilize air, clean water and remove odors. Ozone exists naturally on the earth surface at concentrations of less than 2–8 parts per million (one of the standard way to express total ozone levels in the atmosphere) and forms a layer to prevent harmful ultraviolet (UV) radiation to the earth and to stop heat loss from the earth[26]. Ozone is produced by UV radiation through splitting oxygen molecules into two reactive atoms of oxygen, followed by a reaction in which each of these atoms combines to oxygen and forms ozone in the stratosphere[27]. Ozone has a sharp pungent odor and is soluble in water. Once in water, ozone quickly dissolves and reacts with inorganic and organic molecules in water to create free radicals of oxygen.

Our research team has developed an ozone generator, which allows us to control and monitor the precise ozone concentrations in real time during treatment procedure. This instrument was designed to produce ozonated water for patients to either take a bath or soak the skin lesions in clinic. Ozonated water bath is also proved to be more practical for children, elder people and patients who couldn't tolerate the adverse effects of current available drugs[28]. Our research team also developed a new ozone mixture, ozonated oil, which consists of ozone and unsaturated fatty acids. Ozonated oil is used topically as an antimicrobial and antimycotic drug. Ozonated oil has 2-year shelf life and is easily accessible in daily life by patients. In addition, the oil itself can also act as a moisturizer and protect patients with impaired barrier function in skin.

2 Available ozone treatment in medical use

Ozone is available for medical usages through various formulation.

Ozone gas: Initially used in the treatment of gaseous gangrene in German soldiers during World War I. Afterwards, it was used to treat open wounds and viral infections. When ozone gas is used topically, the skin is covered with ozone gas-oxygen mixture (70 and 80 μg/mL) filled plastic bag.

Ozonated water: Obtained through an ozone generator that mixes ozone with water. The liquid ozonated water is highly effective for topical treatment and effective for many skin-related disorders.

Ozonated oil: Obtained by mixing ozone with cold pressed oils such as olive oil, sesame oil and many other unsaturated fatty acids[29]. Ozonated oil requires being refrigerated storage with a shelf life of 2 years. Topical application of ozonated oil can be conducted outside of the clinic and reduce patient clinic visits. When in combination with ozonated water treatment in clinic, the use of ozonated oil significantly improves the outcome to ozone treatment in management of bacterial, viral, and fungal skin infections.

O_3-AHT and extracorporeal blood oxygenation and ozonation (EBOO): Extracorporeal exposure blood to ozone, followed by intravenous re-infusion, is a general procedure for ozone-based AHT. For over a half century, O_3-AHT to ozonized blood has been increasingly used in medicine and has been found to be beneficial for various diseases. However, the effectiveness of AHT is still far behind the clinic expectation. More recently, a

new and more effective ozone therapy, EBOO, has been established. EBOO can ozonate whole body blood while O_3-AHT can only ozonate a quarter liter blood within an hour of extracorporeal circulation. Unlike the respiratory system, exposure of human blood to ozone has no any evidence indicating toxic effect. Exposure of human blood to a mixture of ozone with oxygen is known to trigger various signaling cascades to stimulate the production of antioxidants by which to activate immune response in infectious diseases and cancers[30-31]. It has also showed that ozone treatment increased the release of growth factors by which to reduce the extent of ischemic lesions in vascular diseases. This technique has been shown to be effective in treating patients with severe peripheral arterial disease, coronary disease, cholesterol embolism, severe dyslipidemia, Madelung disease, and sudden deafness of vascular origin[25].

Rectal insufflation: Ozone can also be applied rectally for gastrointestinal diseases like colitis, Chrohn's disease, irritable bowel syndrome and even cancer, with impressive benefits to the patients.

3 Application status of ozone-therapy in dermatology

3.1 Ozone hydrotherapy

With the good knowledge of medical equipment, our research team has produced an ozone generator which is able to determine the precise ozone concentrations in real time and maintain optimum therapeutic ozone dose to prevent respiratory injury during the procedure. This instrument was designed to produce therapeutic dose of ozone containing water for patients to take either a bath or soak the skin lesions in clinic. Generally, the treatment is about 15 minutes each time, and one course contains totally of 3–5 times for treating acute dermatitis and infections. The treatment course can also be adjusted according to the age, entity and the degree of pathogenetic conditions of each patient. There is no age limitation for ozone-therapy. This provides more options for refractory skin diseases, especially in children, elderly patients and patients who are intolerant to the adverse effects of currently available drugs. Ozone hydrotherapy is wildly used for treatment of infectious skin diseases including bacterial, virus and fungi, as well as itch dermatoses such as eczema, atopic dermatitis, prurigonodularis etc. Ozone hydrotherapy can ameliorate effusion of tissue fluid, reduce inflammatory response, promote wound healing, ease the pain and pruritus[32]. However, the drawback of ozone hydrotherapy is the short shelf life with instability feature that makes this treatment option available in equipped clinic only. To make the ozone therapies more convenient and easy to use, ozonated oil agent is developed. The ozonated oil made in Hunan Health Care Technology Co. Ltd. (Changsha, China) has longer shelf life, easy to use with effective outcome in the preliminary observations, and meets a great need for patients.

3.2 Ozonated oil

Ozonated oil is made with ozone and unsaturated fatty acids to meet topical application criteria. The available unsaturated fatty acids are classified into three types: ω-9 series of unsaturated fatty acids represented by oleic acid in tea oil, ω-6 series of unsaturated fatty acids represented by sub-acid in vegetable oils, and ω-3 series of unsaturated fatty acids represented by eicosapentaenoic acid (EPA) and docosahexaenoic acids (DHA) in fish oil[29]. Notably, the direct ozonation of vegetable oils with unsaturated fatty acids leads to the formation of the 1, 2, 4-trioxolane moiety[33-34], which represents the active form of ozone in these materials. The trioxolane ring within the ozonated vegetable oil vehicle quickly produces compounds that accelerate the healing process in either a humid wound or an ulcer. Moreover, these compounds are responsible for antimicrobial and antimycotic treatments[35-37]. In addition, the oil itself can act as the moisturizer and protectant materials particularly for patients with impaired skin barrier. More importantly, ozonated oil has longer shelf life and is easy to access in daily life to greatly meet the need of patients.

3.3 O_3-AHT

For treatment of systemic conditions, O_3-AHT is one of the ideal choices[38-39]. In clinic, ozone based autohemotherapy (100–150 mL blood venoclysis) is more common than minor autohemotherapy (3–5 mL blood intramuscular). The applications of autohemotherapy are justified in broad pathological conditions, including the potential antimicrobial effect, the activation of the immune system, the stimulation of wound healing, the improvement of erythrocyte metabolism and the regulation of body's antioxidant capacity[15, 40].

Common skin-related diseases that can be treated with autohemotherapy including chronic inflammatory diseases, diabetic foot ulcers[7, 40], herpes zoster, postherpetic neuralgia[8, 41], AID, psoriasis, and atopic dermatitis. It is worth noting that the concentration of ozone used in medical application cannot exceed 80 μg/mL in serum, suggesting that controlling the precise ozone concentration during the treatment progress is critical to ensure the treatment efficacy in non-toxic dose. The induction of distinct cytokines requires different doses of ozone, such as 11.5 μg/mL ozone inducing the expression of IFN-γ, and 25 μg/mL ozone inducing the production of IL-6 and TNF-α[42-43]. In summary, ozone dose range from 20 to 40 μg/mL is the optimum concentration to activate immune system[15, 44]. Additionally, an adequate duration of the ozone treatment is also an essential factor to ensure the efficacy of treatment. Generally, 10–15 treatments are recommended in one course and 1–2 courses are required annually[1, 44]. Fortunately, O_3-AHT is regarded as a strategy for management of anti-aging and health care with great benefits to many patients due to its antioxidant defenses, such as inducing and activating the antioxidant enzyme system of body to produce SOD, a free-radical scavenger, clearing excessive free-radicals formed in chronic joint and vascular inflammation. In contrast with conventional medical therapeutic modalities, ozone therapy is a cost effective treatment leading to significantly reduction of medical bills as well as preventing the aggravation and recurrence of various diseases.

4 Mechanisms of action of ozone

Various mechanisms participate in the regulation of the effectiveness of ozone therapy. Firstly, ozone inactivates bacteria, viruses, fungi, yeast and parasites through different mechanisms. In bacteria, ozone disrupts the integrity of the bacterial cell wall through its products, oxidized phospholipids and lipoproteins[45-46]. In fungi, ozone inhibits fungi growth[47-48]. In viruses, ozone damages the viral capsid and breaks the reproductive cycle by disrupting the contact between the virus and the cell through the process of peroxidation. The cells vulnerable to the invasion of viruses are coated with weak enzymes, susceptible to oxidation and can be eliminated from the body when interacting with ozone[49]. Secondly, ozone therapy can increase oxygen metabolism in the red blood cells by increasing the glycolysis rate. Consequently leading to increased oxygen delivered into tissues by stimulation of 2, 3-diphosphooglycerate[50]. Ozone enhances oxidative carboxylation of pyruvate, increases the production of ATP during the Krebs cycle, significantly reduces NADH and oxidizes cytochrome C. As a result, it increases the production of enzymes like glutathione peroxidase, catalase and superoxide dismutase that serve as free radicals scavengers and protectors for healthy cells[51]. Ozone also induces the production of prostacyclin, which is a potent vasodilator[52]. Thirdly, ozone activates the immune system by inducing the secretion of interferon and tumoral necrosis factor, IL-2 and other cytokines and chemokines involved in the inflammatory response[44, 53-54]. Fourthly, topic ozone treatment accelerates wound healing, even under diabetic condition[55]. The underlying mechanism involves in the interaction of ozone with wound exudates that leads to the decomposition of ozone into peroxides and stimulates tissue repair by improving oxygenation in the area[56]. Reactive oxygen species stimulate platelet aggregation and lead to the release of growth factors, which also play a key role in wound healing[57].

5 Efficacy and safety of ozone therapy in dermatology

High dose of ozone triggers inflammatory reactions and severely impairs the organs, like lungs and eyes, when directly contact. Therefore, the effectiveness of ozone therapy relies on the well-controlled precise non-toxic concentration. To avoid toxicity while ensure achieving therapeutic effect, the optimal dose of ozone defined by the concentration of ozone and its precise gas volume should be strictly controlled[53]. Ozone treatment can reduce bacterial colonization by inactivating microorganisms and releasing decomposition products like peroxides and reactive oxygen species to further kill bacteria[58]. Overall, ozone treatment is highly beneficial to patients with infectious diseases caused by bacteria, viruses or fungus. The efficacy of ozone therapy is greatly augmented when combination with topical application of ozonated oil to manage bacterial infections, especially methicillin-resistant *Staphylococcus aureus*, a multi-antibiotic resistant microorganism[1]. Topical application of ozone can easily penetrate through skin to sterilize the infectious

lesional area and effectively killing microorganisms[53]. Consequently, it leads to rapid healing of the infectious area and accelerated cicatrization due to ozone application enhanced oxygenation in the affected area. Viral infections, especially infectious by herpes 1 and 2, herpes zoster and papilloma viruses, have been also shown greatly improvement after combination of ozone therapy with antiviral treatment[59].

Ozonated water and oils act as excellent healing stimulators. Both forms of ozone-based medicine effectively improve blood circulation in affected tissue; enhance the delivery of oxygen and up-regulate antioxidant enzymes to activate the immune system and promote the releasing of growth factors. With negligible side effects, ozone water/oil dramatically improves the condition of patients by activating neuroprotective systems[60]. Small doses of ozone exposure to the skin topically can dramatically improve skin conditions without toxicity. This is accomplished because ozone immediately reacts with the polyunsaturated fatty acids presented in the stratum corneum to generate reactive oxygen species and lipo-oligopeptides, the only substances that can be partially absorbed by the skin antioxidants, capillaries and lymphatics. Topical ozone for the management of cutaneous conditions can be effective when it is stabilized between the two bonds of monounsaturated fatty acids as an ozonide. This makes the ozone stable for 2 years in oil. Ozonated oil is used in many conditions including wounds, anaerobic, viral and fungal infections as well as ulcers, anal fissures, vulvovaginitis and so on without any noticeable side effects[61]. It is also useful for patients with cancer who suffering from radio dermatitis[62].

Additionally, O_3-AHT with proper dosage of ozone is a safe and effective therapeutic approach for the systemic diseases mentioned above. The safety of ozone has been a consistently concern for ozone medical use. In fact, ozone cannot damage healthy cells or tissues due to the protection from the serum and cellular antioxidants. The potent antioxidant capacity of serum contains hydrophilic (ascorbic acid, uric acid, free Cysteine, GSH and albumin) and lipophilic (vitamin E, thioredoxin, α-lipoic acid and bilirubin) compounds. Consequently, most of ozone is neutralized through the bulk rapidly reaction with n-3 and n-6 polyunsaturated fatty acids (PUFA) engendering its vital messengers: hydrogen peroxide (H_2O_2) and active aldehydes, principally 4-hydroxy-2, 3-trans-nonenal (4-HNE)[63]. H_2O_2 is a reactive oxygen species (ROS) with a half-life of about 20 s in the blood. H_2O_2 activates several relevant biochemical pathways to kill pathogens[27]. Simultaneously, the sudden infusion of ozonated blood into patients boosts the release of cytokines such as interferon and interleukin, triggers antibody dependent cellular cytotoxicity (ADCC) to activate immune system of the body[64-65].

6 Prospects of ozone therapy applied in dermatology

Ozone is an instable molecule, thus ozone is usually mixed with oxygen in ozone therapy[66]. The resulting product has powerful oxidative properties and is able to form free oxygen radicals with the destruction of microorganisms and improvement of blood supply as well as stimulation of healing in wounded tissue[19]. As a result, the immune system is activated to fight pathogens. Over the past years, it has gained more attention due to its effectiveness against bacterial, fungal and viral infections. Ozone therapy is effective in the management of many cutaneous conditions, including wound healing mainly by its ability to promote inflammation in the body. This produces inflammatory responses, secretion of immunomodulators and resolution of the condition by reduction in the oxidative damage. Ozone therapy has been widely studied in infected wounds, gangrene, burns and circulatory disorders with high effectiveness[67]. It is a safe, low cost treatment, with little adverse effects, and reduces the need to use antibiotics. Direct ozonization of vegetable oils reacts with unsaturated fatty acids and leads to the formation of 1, 2, 4-trioxolane rings, which are the active form of ozone[68]. Along with peroxides, these are the two main compounds involved in the bactericidal, tissue repair and regeneration properties of ozone[69]. Altogether, these compounds act directly on wounds, ulcers or any damaged tissue and the healing process is faster[5]. As for more potential physicochemical properties of ozone, such as biosynthetic, analgesic and vasodilators secretion, we can explore a wider application value in dermatology, particularly in beauty service and healthcare. Therefore, ozone therapy strategy in dermatology even in medicine suggests a great potential and has a more striking

application prospects waiting for us to explore, to seek and to enrich.

7 What efforts should we make for?

Ozone therapy has been proven to be effective for many diseases. In diabetic complications, ozone activates the antioxidant system to affect the levels of glycaemia and prevent oxidative stress by normalizing peroxide levels[70]. Ozone also plays a role in the inactivation of the HIV with non-toxic effects, via reducing the p24 core protein[71], and improves the host immunity by stimulating the secretion of cytokines[72]. It is also used as a disinfectant for many complex microorganisms, including *Acinetobacter baumannii*, *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus*. Ozone is effective as an antibacterial agent to treat oral infections caused by *Actinomyces naeslundii*, *Lactobacilli casei* and *Streptococcus* mutans with high efficiency[73]. The powerful functions of ozone used in medicine are amazing and stirring. Better yet, there is no age limit on ozone-therapy which supplies a very good option for refractory skin diseases, especially for children, old people and those who cannot tolerate the adverse effect of available drugs. More importantly, in contrast with conventional medical therapeutic modalities, ozone therapy is quite economical leading to an obvious decrease of medical costs and prevents the aggravation and recurrence. 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 precise mechanism of action for how ozone works and a more reliable evidence-based medical data proven the efficacy of ozone treatment are in great need. In future, we should make efforts to better understand the mechanisms of action of ozone in medicine and explore its more treatment potential for a variety of diseases.

8 Conclusion

Ozone therapy has been applied in clinic to destructively and effectively kill bacteria, fungi and viruses, activate cellular and humoral immunity and act as an antioxidant molecule to defend human body from various pathologic conditions. Up to date, ozone has been widely used to treat over 100 pathological processes[74-76] including various skin disorders. The ozone medical preparations are mainly classified into ozonated water and ozonated oil, and ozone has also been used in autohemotherapy with encouraging outcomes. We have invented and patented the technologies to effectively generate ozonated water and ozonated oil for both bench and bedside applications. Thus far, we have accomplished a significant amount of bench work to support the safety and effectiveness of ozone therapy to treat certain skin diseases. Notably, the ozone therapy is inexpensive, predictable and conservative with negligible side effects at low effective concentration. Extensive efforts are desired to further evaluate whether ozone therapy can be a treatment regimen for standard healthcare broadly. Understanding the underlying molecular mechanisms of ozone action, and increased unbiased medical observations from multicenter clinical studies would further demonstrate the reliability and practicability of ozone therapy. Remarkably, the effects of ozone therapy are dose-dependent. Thus, precisely and easy controlled ozone generator and effective carrier agents to ensure ozone stability and longer shelf life are the essential considerations moving forward. We have focused on all our efforts to produce easy manageable instruments and exploit more proper ozone preparations to meet the needs of treatments for different diseases.

Conflict of interest: The author declares that she has no conflicts of interest to disclose.

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