The use of ozonized oil as a therapeutic conduct for skin lesions

O uso do óleo ozonizado como conduta terapêutica nas lesões de pele

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ABSTRACT
This review work aims to evaluate the use of ozonized oleic compounds as a safe therapeutic alternative for the treatment of skin lesions, considering their antimicrobial potential and their other interactions when in contact with living tissues. The databases Medline, Scielo, and Science Direct, as well as PubMed and Google Scholar, were consulted, using as a search strategy the Boolean descriptors and operators “Ozonized oil” and “Wound Healing”, obtained via the Virtual Health Library – DECS (Descriptors in Health Sciences). The literature consulted suggests that ozonized oleic compounds can be used to treat epithelial lesions, with the exception that both oxidative stress and the preconditioning potential promoted by ozone in contact with tissues require more in-depth studies, especially to more precisely evaluate the role of the gas in tissue repair processes.

Keywords: ozone, ozonized oil, wound healing.

1 INTRODUCTION
The early findings that ozone was a hazardous substance was reinforced by a number of laboratory and epidemiological research, excessive concentrations of the gas in a closed space can result in a number of respiratory symptoms, including coughing, chest pain, congestion, angina pectoris, and, in rare circumstances, a heart attack. This viewpoint designated ozone as a health hazard to people. Since it is a potent oxidizing agent that can redirect energy meant for cellular use, affecting mitochondrial function, reducing ATP production, and creating deadly reactive oxygen compounds, laboratory investigations have confirmed such effects at the cellular and molecular level. (Thorp, 2021).

Ozone (O₃) has been the subject of current research on therapeutic proposals. The gas has been shown to be effective in inactivating a number of pathogens and has been positively
associated with the regulation of endogenous growth factors, local blood flow, and antioxidant potential. Even in the lack of more conclusive studies, there is broad interest in the processes of O₃ interaction in cellular responses, and more especially in the process of tissue healing. Due to the potential for toxicity in this setting, there are undoubtedly still concerns about the use of the gas in respiratory conditions. A few dermatitis bouts and skin irritation cases still don't lend themselves to a blanket prescription for ozone therapy. (Wen at al, 2022).

Notwithstanding these doubts, the development of ozonized oleic compounds has shown to be a safe and efficient means of preventing local infections and promoting tissue healing, rendering it a viable choice for the management of a range of skin and mucosal disorders. Ozone therapy has shown to be a safe substitute, particularly when applied topically. In this regard, ozoneized oil administration has shown particular promise. Significant modifications to current therapeutic procedures, however, call for strong performance in comparison to the market for medicines already on the market and scientific backing. Given the wide variety of products currently available for the treatment of wounds, it is critical that the choice of these agents be made on the basis of evidence, taking into account factors like the patient's overall health, location, type of wound, and accessibility to the intended treatment (Brito Jr., 2022).

Basically, ozonized oil is made when O₃ molecules join with unsaturated fatty acids. The types of compounds that are made depend on how complex their molecular structure is. These can be unsaturated compounds like oleic acid, subacids in vegetable oils, or even hair eicosapentaenoic acids (EPA) and docosahexaenoic acids (DHA) in fish oil (Moureu 2015). The gas in these substrates changes into its active form by directly ozonizing plant compounds and creating the 1,2,4-trioxolane part. The trioxolane ring in the ozonized plant matrices can slowly release O₃ on the skin lesions, which speeds up reactions inside the cells. locus responsible for accelerating the healing process of a significant range of wounds and also presenting vast antimicrobial and antifungal potential. On the other hand, the oil itself acts as a moisturizer and protector, especially for patients with compromised barrier function on the part of the epithelium (Wang 2018).

This review’s objective is to discuss the treatment strategies and procedures that have been used with ozonized oleic substances. It draws from relevant sources, including human clinical trials and laboratory investigations. We plan to demonstrate, based on the literature reviewed, that O₃ is a viable and safe alternative for use in therapeutic approaches for the
treatment of wounds, ulcers, and skin conditions, as well as acting to combat infections, or, to put it another way, a potential aid in the tissue repair process. Complete elucidation and the establishment of use protocols still lack data to be put into practice.

2 MATERIAL AND METHOD

Evidence-based research models recommend that clinical problems arising from the care process, both teaching and research, be organized through the PICO strategy. (Acronym for: Patient, Intervention, Comparison and "Outcomes" or outcome.) The adoption of such a premise results in a significant gain in the perception of the fundamental elements of the construction of the question as the objective of the study, also favoring the bibliographic search for evidence. Within this context, those with skin injuries and/or conditions were considered as possible patients. The proposed intervention was the use of ozonized oleic compounds in the treatment of these wounds. If the results were capable of measurement, the findings regarding the use of ozone would be associated with such oleic compounds.

2.1 DATABASES AND SEARCH STRATEGIES

During the bibliographic survey, the databases of Medical Literature Analysis and Retrieval System Online (Medline), Scientific Electronic Library Online (Scielo), Science Direct, and PubMed were consulted, using Boolean descriptors and operators as a search strategy: “Ozonized oil” AND “Wound Healing”. The descriptors were consulted through the Virtual Health Library, DECS (Descriptors in Health Sciences). A search strategy combining operators and free terms was used in order to obtain the largest number of usable references (Polleze & Meireles 2020).

For this study, we intended to publish articles in English, Spanish, and Portuguese that have complete texts and feature original works that have been altered since 2010. Only publications pertaining to the fields of health and biological sciences were chosen from all the databases reviewed. The exclusion criteria encompassed works published before 2010, publications from unrelated fields of study, and articles that were inaccessible or unavailable for download during the review's production.
2.2 STUDY SELECTION AND DATA EXTRACTION

Following the application of the exclusion criteria, the references obtained from the initial search were transferred to the Rayyan QCRI Systematic Reviews program developed by the Qatar Computing Research Institute. This process resulted in the creation of a primary database, from which duplicate sources were identified and removed. Using a computerized tool, two reviewers independently conducted a thorough and systematic analysis of titles and abstracts. In cases of disagreement or when a reference was involved, a third party was responsible for providing their viewpoint.

The search and selection method for scientific papers was outlined in a flowchart, as per the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 Statement (PRISMA). This flowchart, referred to as Figure 1, encompasses the essential elements of the process. All relevant information was recorded in a standardized spreadsheet, which included data such as the authors, year of publication, study objective, study type, population and sample characteristics, independent variables (exposure factors), dependent variables, adjustment for confounding factors, study results, and comments.

The methodological compatibility of the chosen publications was confirmed by utilizing review instruments in accordance with standardized methods established by The Joanna Briggs Institute, tailored to each type of study (Moola et al., 2020). The works deemed feasible under such examination were those that formed the foundation for the creation of this evaluation.
3 RESULTS

A flowchart was generated to effectively categorize the selection criteria, encompassing the primary stages of this procedure, based on an initial pool of 212 references. The Rayyan QCRI Systematic Reviews software detected 425 duplicate entries, which were subsequently eliminated by the reviewers. Additionally, 73 articles published before 2010 were excluded, and 8 articles discussing the utilization of ozonized oleic compounds in the chemical industry were disregarded. And constituents, therefore extending beyond the domain of health. Out of the laboratory studies conducted on animal models, four were rejected due to their use of non-murine specimens.
3.1 SELECTION BY INTERVENTION AREA

18 dental publications were removed because they focused on evaluating particularly specific structures. Anatomical features such as periodontal structures, root canals, adjacent mucosa, free gingiva, and palate, although smaller in size compared to the overall structure of the human body, exhibit unique characteristics in terms of moisture, drug accessibility, local bacterial population, and the process of healing.

Five ophthalmology papers discussing the use of ozonized oil in the structures of the eyeball and surrounding areas were removed based on the same concept. Four additional studies were excluded by the reviewers due to their utilization of O₃ as a therapeutic intervention for patients with chronic inflammation or malignant neoplasms in the gastrointestinal tract. This decision was made considering the wide array of variables in this region and the inherent unique characteristics of the organs. Furthermore, research that mimicked these situations in animal models were also excluded, disregarding the involvement of organs and tissues. Experiments involving animal models other than mice were eliminated from the study because it is challenging to compare or find connections between different repair profiles and physiological responses in these animals.

3.2 METHODOLOGICAL DESIGN OF REFERENCES

The papers collected by the reviewers focused on human subjects and utilized randomized clinical trials as the research method. These trials involved comparing the individuals being evaluated with control groups. Two studies (Lu et al., 2018; Menendez et al., 2011) reported positive outcomes of using ozonized oil to treat fungal infections in the lower limbs (Table 1). Solovăstru et al. (2015) conducted a study on venous ulcerations, while Zeng et al. (2020) focused on skin infections. Both studies reported significant clinical improvements in the affected areas, on-site antiseptic effects, and successful execution of the healing process. In a study conducted by Chen et al. (2020), ozonized chemicals were employed to prevent and cure the skin reaction known as palmoplantar erythema, which is caused by chemotherapy medicines. The study yielded positive outcomes, demonstrating the safe application of O₃ topically for both symptom prevention and alleviation.

Anzolin et al. (2021) conducted a study that investigated the use of ozonized oil as a topical treatment for individuals with severe osteoarthritis, a condition that affects the joints.
Given that pain is the primary constraining feature of this illness, the authors deduced that ozonized oil could effectively alleviate pain in those afflicted by the sickness.

Among the articles that were chosen, four systematic reviews were discovered that investigated the utilization of O₃ as a form of treatment. Two of these studies (Fitzpatrick et al., 2018; Wen et al., 2021) examined the potential use of ozonized solutions as a therapeutic intervention for chronic wounds and skin ulcers. Both investigations yielded congruent findings regarding a significant enhancement in wound closure when utilizing ozone therapy, hence endorsing the implementation of an ozoneized oleic solution for managing chronic wounds. Nevertheless, both agree that there is currently insufficient data to establish ozone therapy as a universally accepted practice.

A third review evaluated the use, as an alternative therapy, of an ozonized oleic compound for the treatment of onychomycosis, comparing it with therapeutic proposals that used already established medicines and herbal compounds. The authors mention the faster total remission of fungal infections in patients treated with the oil, but despite the findings, the authors themselves classify their results as preliminary evidence, reiterating the need for large-scale trials (Nickles et al., 2022).

The fourth systematic review (Leon et al. 2022) assessed the potential hazards associated with the application of ozonized liquid substances directly on human skin. The evaluation considered factors such as cellular cytotoxicity and monitoring of adverse reactions reported during commercial usage. Upon evaluating several descriptions of therapeutic methods designed for humans, the authors found no substantial dangers that would render the utilization of both water and ozonized oil impractical. All the sources consulted (Fitzpatrick et al. 2018; Wen et al. 2021; Nickles et al. 2022; Leon et al. 2022) did not mention any adverse effects directly associated with the use of O₃ and related health conditions. Instances of treatment abandonment and other complications were not attributed to ozone therapy, but rather to pre-existing conditions and the patients' clinical infeasibility, as reported in their respective studies.
Table 1: Randomized studies with the use of ozonized oil in infectious processes or chronic diseases in humans.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of patients</th>
<th>Sample criteria</th>
<th>Assessment parameters</th>
<th>Dosage</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmoplantar Erythema (PE)</td>
<td>99</td>
<td>Patients diagnosed with advanced PE who were scheduled to receive chemotherapy (Sorafenib)</td>
<td>Appearance or not of reactions in the hands and feet, and their intensity if present</td>
<td>Topical application 3x a day for 12 weeks</td>
<td>Significant reduction in the incidence and aggressiveness in cases of PE</td>
<td>(Chen et al 2020)</td>
</tr>
<tr>
<td>Chronic venous ulcers on the legs</td>
<td>29</td>
<td>Patients over 18 years of age with chronic venous leg ulcers for less than 2 years</td>
<td>Wound size, proportion of wound area, and ulcer healing speed</td>
<td>Topical application 1x a day for 30 days</td>
<td>Significant reduction in the size of ulcerated lesions and clinical improvement in the healing process.</td>
<td>(Solovăstru et al 2015)</td>
</tr>
<tr>
<td>Fungal infection: Tinea pedis</td>
<td>60</td>
<td>Patients over 18 years of age with a positive diagnosis for tinea pedis mycosis</td>
<td>Laboratory tests, clinical evolution, and mycoculture</td>
<td>Topical application 1x a day for 28 days</td>
<td>Remission of symptoms and reduction of residual fungal colonies</td>
<td>(Lu et al 2018)</td>
</tr>
<tr>
<td>Atopic Dermatitis (AD)</td>
<td>12</td>
<td>AD assessment score for skin lesions larger than 4x4 cm2 on both sides of the elbow or axillary fossa</td>
<td>Bacterial culture and mass spectrometric analysis</td>
<td>Topical application 2x a day for 3 days</td>
<td>Remission of symptoms, including relief of itching, reduction of inflammation, and reduction in the local Staphylococcus population</td>
<td>(Zeng et al 2020)</td>
</tr>
<tr>
<td>Onychomycosis</td>
<td>400</td>
<td>Adult patients diagnosed positive for onychomycosis have healthy underlying epithelium</td>
<td>Color, growth, nail thickness, and local mycoculture</td>
<td>Topical application twice a day for 3 months</td>
<td>Remission of infections with better repair when compared to fungicides (ketoconazole)</td>
<td>(Menendez et al 2011)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>80</td>
<td>Patients aged 50 or over with a positive diagnosis of severe osteoarthritis (grade IV)</td>
<td>Visual analogue scale, laboratory tests, and patient perception</td>
<td>Topical application twice a day for 60 months</td>
<td>Reduction of pain sensation in patients with grade IV osteoarthritis</td>
<td>(Anzolin et al 2021)</td>
</tr>
</tbody>
</table>

Source: Data obtained during the research.
Within the literature reviews (Table 2), studies were discovered that examined the utilization of O₃-based compounds for treating chronic wounds, specifically those associated with diabetic foot conditions (Liu et al., 2015; Mota et al., 2020). However, these studies couldn’t produce consistent outcomes in relation to the chosen approach and potential side effects. In the field of dermatology, studies conducted by (Brito Jr. et al. 2022 and Zang & Lu 2018), indicates that ozonized solutions can be safely applied topically, specifically considering the fact that these solutions have antibacterial properties that help avoid the occurrence of opportunistic infections. In a more focused study (Clavo et al. 2019), researchers discussed the use of ozone therapy to prevent and treat chemotherapy-induced toxicity. This therapy works by deliberately inducing a controlled state of oxidative stress, which triggers a cascade of natural antioxidant reactions, these reactions have been linked to protective and therapeutic effects.

Research using animal study models sought to establish parameters for the use of ozonized compounds by comparing them with other therapeutic proposals (Table 3). In order to clarify the effectiveness of O₃ in skin wounds (Valacchi et al., 2011; Soares et al., 2019; Sanguanini et al., 2020), they verified the performance of the aforementioned compounds in induced wounds with regard to tissue repair; all were consistent with reporting significant improvements in healing in individuals treated with ozonized compounds. Other researchers carried out studies promoting the use of ozonized oil to combat fungal infections (Thomson et al., 2011), where they observed that ozonized herbal compounds had antifungal potential for all strains that cause dermatophytosis.

Lu et al. (2023) conducted a study to explore alternative therapeutic methods for chronic skin conditions and infections. They examined the impact of applying ozonized oil topically on wound healing in mice with induced diabetes. The researchers found that the use of topical ozonized oil enhanced the healing process of lesions and improved blood vessel formation at the edges of the wounds in the ozonation-treated animals. In order to further investigate the application of O₃ in epithelial lesions. Lima et al. (2022) utilized infrared thermography to assess the impacts of 660 nm laser photobiomodulation, ozone therapy, and ozonized oil following skin surgery, the study concluded that ozonized oil has the ability to disrupt microcirculation during the tissue healing process.
Table 2: Literature review studies referring to the use of ozonated compounds in the treatment of illnesses published from 2010 to 2023

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of valid articles</th>
<th>Purpose</th>
<th>Inclusion criteria</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic foot</td>
<td>2 articles with 101 individuals</td>
<td>To evaluate the effects of ozone therapy on the healing of foot ulcers in people with diabetes mellitus. To evaluate the influence of ozone therapy on the healing of diabetic foot wounds.</td>
<td>Randomized clinical trials reporting the use of ozone therapy in the topical treatment of chronic wounds, published in English. Complete articles containing systematic reviews, meta-analyses, in vivo studies, and clinical trials in Portuguese and English.</td>
<td>The authors were unable to establish apparent improvements in the reduction of ulcer size, the number of foot ulcers, or the occurrence of adverse events.</td>
<td>(Liu et al 2015)</td>
</tr>
<tr>
<td>Skin diseases</td>
<td>30 classified articles</td>
<td>Summarize the application status of ozone therapy in dermatology and provide more evidence for ozone applications.</td>
<td>Full articles containing systematic reviews, meta-analyses, in vivo studies, and clinical trials in Chinese and English.</td>
<td>Ozone can be used safely in dermatology and is efficient against bacteria, fungi, and viruses, activating the cellular and humoral immune systems, in addition to acting as an antioxidant.</td>
<td>(Zeng &amp; Lu 2018)</td>
</tr>
<tr>
<td>Post-chemotherapy toxicity</td>
<td>13 articles</td>
<td>Describes the use of ozone in the treatment and prevention of chemotherapy-induced toxicity.</td>
<td>Original peer-reviewed articles, focusing on the evaluation of oxidative stress parameters and related conditions.</td>
<td>Although the literature considers the use of ozonated compounds to be favorable, the authors suggest that the potential role of ozone therapy in the treatment of chemotherapy-induced toxicity deserves further research.</td>
<td>(Clavo et al 2019)</td>
</tr>
<tr>
<td>Wound care</td>
<td>13 articles</td>
<td>Analyze the use of ozonized oils in tissue repair and antimicrobial potential.</td>
<td>Full-text articles, systematic reviews, meta-analyses, in vivo studies, and clinical trials without language restrictions.</td>
<td>The authors suggest the effectiveness of ozonated oleic compounds for the treatment of local infections, which could be a promising therapeutic alternative for tissue repair.</td>
<td>(Brito Jr. et al 2022)</td>
</tr>
</tbody>
</table>

Source: Data obtained during the research.
### Table 3: Studies that used ozonized oil in murine animal models, considering disease, purpose, and main findings

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type/number of individuals</th>
<th>Purpose</th>
<th>Experimental design</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatofitose</td>
<td>60 CF1 mice</td>
<td>Verify the safety and antifungal activity of ozonized sunflower oil</td>
<td>Comparison of three treatment approaches for experimentally induced dermatophytosis</td>
<td>The ozone-based herbal compound showed antifungal potential for all strains that cause dermatophytosis. Topical ozonized oil accelerated wound healing, increased phosphorylation of IGF1R, EGFR, and VEGFR, and improved vascularization at the wound edge in mice with diabetes.</td>
<td>(Thomson et al 2011)</td>
</tr>
<tr>
<td>Feridas diabéticas</td>
<td>24 male C57BL mice</td>
<td>Investigate the effect of topical ozonized oil on wound healing in</td>
<td>Evaluation of wound healing in an animal model with induced diabetes compared with a control group</td>
<td>Ozone is capable of interfering with microcirculation, and the use of thermograms can be useful to monitor the microcirculation pattern during tissue repair.</td>
<td>(Lu, et al 2023)</td>
</tr>
<tr>
<td>Doenças de pele</td>
<td>40 Wistar rats</td>
<td>To evaluate the effects of 660 nm laser photobiomodulation, ozone therapy, and ozonized oil on the thermal coefficient of tissues</td>
<td>Evaluation of four treatment proposals involving laser and ozone via infrared thermography after skin surgery</td>
<td>Injectable ozone accelerates and improves the healing of cutaneous wounds in the animal model in both the acute and chronic phases of wound healing.</td>
<td>(Lima, et al 2022)</td>
</tr>
<tr>
<td></td>
<td>24 male Wistar rats</td>
<td>Establish the patterns of FGF2 expression and myofibroblastic</td>
<td>Assessment of the wound healing process is induced through morphometric analyses and digital quantification of smooth muscle actin and FGF2 immunoreactivity.</td>
<td>Injectable ozone accelerates and improves the healing of cutaneous wounds in the animal model in both the acute and chronic phases of wound healing.</td>
<td>(Soares, et al 2019)</td>
</tr>
<tr>
<td>Feridas induzidas</td>
<td>36 female nude SK1 mice</td>
<td>To evaluate the wound closure rate, histological parameters, and</td>
<td>Verify the effect of topical application of three concentrations of ozonized oil, comparing them with a control group.</td>
<td>When ozonized sesame oil was used to help skin wounds heal, cells that help with wound repair responded faster and better. There was also more angiogenesis and a rise in vascular endothelial growth factors.</td>
<td>(Valacchi, et al 2011)</td>
</tr>
<tr>
<td></td>
<td>48 female Wistar rats</td>
<td>vascular endothelial growth factors using different concentrations of ozonized oil</td>
<td>The study compared four therapeutic approaches, evaluating morphometric profile, cellular response, and revascularization.</td>
<td>Ozonized water favors wound retraction, while ozonized oil promotes greater neovascularization during tissue repair and greater deposition of type I collagen.</td>
<td>(Sanguani ni et al 2020)</td>
</tr>
</tbody>
</table>

Source: Data obtained during the research.
4 DISCUSSION

Certain physiological, anatomical, and functional factors should be considered in order to comprehend the pharmacological effects of ozone on the skin. O$_3$ typically has a limited ability to penetrate the structure of the epithelium. Its rapid reaction with fatty acids is the primary reason of this feature. polyunsaturated compounds and tissue water, which result in the production of lipooligopeptides (LOP) and reactive oxygen species (ROS). These molecules are then partly absorbed through lymphatic and venous microcirculation and easily removed by antioxidant molecules in the skin (Di Mauro 2019). O$_3$ may be a remarkably effective preconditioning agent (PC) based on such mechanisms. The primary in situ effect of ozone is the induction of oxidative stress, which starts in the epithelial tissues but quickly sets off a response from blood cells, especially those red blood cells that are metabolically active, able to release energy and antioxidant compounds, and which, when combined with the cells' release of pro-inflammatory cytokines, constitute a significant response to an inactive etiological factor because O$_3$ solubilizes instantly in bodily fluids. Through an alternative automation pathway, certain molecules arising from lipid oxidation ultimately serve as intermediaries for the initiation of genetic activity, promoting the transcription of biomolecules with the ability to counteract the deleterious effects of ozone on tissues and thereby diminishing their potential cytotoxicity to insignificant levels (Sagai and Bocci 2011; Günaydın et al. 2018; Thorp 2021).

Ozone is particularly notable as a tissue repair process enhancer when combined with oleic chemicals. According to reports, ozonized oil is effective at relieving pain and hastening the healing process, making it a promising integrative treatment option for tissue injuries, particularly in patients with conditions like diabetes mellitus, atherosclerosis, and dermatitis (Anzolin et al. 2020). From this angle, there is compelling evidence that topical use of ozonated oil can promote tissue healing while blocking the division, development, and proliferation of cells. The authors claim that the mechanism of ozone's topical action on chronic wounds is clarified by O$_3$'s possible role in increasing the phosphorylation of the insulin-like growth factor 1 receptor (IGF1R), the epidermal growth factor receptor (EGFR), and the receptors for vascular endothelial growth factor (VEGFR), this strengthens Ozone's potential therapeutic application. (Lu et al., 2023).

When it comes to the connection between O$_3$ interference and vascular neoformation processes (Valacchi et al., 2011; Sanguanini et al., 2020), they found that ozone treatment
significantly increased the amount of vascular endothelial growth factors in subjects. A faster reaction and a more active profile of the cells engaged in the wound repair process were identified by the developers of an enhanced cellular response profile employing O₃.

Through an analysis of current research on ozone therapy, it is evident that O₃ has already been linked to the treatment of wounds and skin ulcers (Liu et al., 2015; Brito Jr. et al., 2020; Mota et al., 2020). Ozonized oleic compounds are efficacious in treating chronic dermal lesions due to their antibacterial and antifungal properties. These variables promote tissue healing and prevent opportunistic infections. According to Zeng and Lu (2018), ozonized oil is a cost-effective and practical therapy that may be applied topically in dermatological treatments for different infectious conditions. Additionally, it serves as an antioxidant in various pathological processes. Nevertheless, the physical-chemical features of O₃-based molecules, including their biosynthetic potential, vasodilator potential, and pain modulator potential, remain little understood.

This pattern is consistently observed in studies utilizing animal models, with notable findings (Lu et al., 2023; Lima et al., 2022; Valacchi et al., 2011; Sanguanini et al., 2020) across various research models and investigative approaches. In addition to enhancing the healing response of skin wounds, the application of ozonized oil has been shown to promote the formation of new blood vessels in the wound area and/or epithelial lesions. This intervention appears to significantly facilitate the healing and tissue repair process by influencing and potentially mediating the in situ angiogenesis process.

Several literature reviews (Fitzpatrick et al., 2018; Di Mauro, 2019; Wen et al., 2021) have concluded that the use of ozonized solutions for dermatological purposes is regarded safe, particularly when certain factors are taken into account: 1) The biocompatibility of ozonized substances refers to their ability to not be poisonous to the skin upon touch, and their use can actually have a beneficial effect on the afflicted tissues by inducing oxidative stress. 2) Noticeable enhancement in the healing of persistent wounds and ulcers; 3) The prospective utilization of O₃-based substances as topical antifungals and antibiotics.

Staphylococcus aureus (S. aureus) and Staphylococcus epidermidis (S. epidermidis) are commonly found on human skin and are often associated with infections. This is mostly because they have the ability to colonize wounds and injuries to the outer layer of cells. Zang & Lu (2018) argue that ozonized oleic compounds have the potential to be effective antibiotics against these
illnesses due to their moderate bactericidal activity, sustained bacterial inactivation, low cost, and broad range of effectiveness. It is important to note that several mechanisms by which it works are still not fully understood, such as its ability to activate both the cellular and humoral immune systems, as well as its antioxidant properties against various disease processes.

Zeng et al. (2020) found that Staphylococcus aureus (S. aureus) is responsible for 90% of the microbiota in atopic dermatitis (AD) lesions, which hinders the progress of the disease. They reported that O₃ has a bactericidal effect that can restore the microbiological diversity in the affected areas. This leads to improved healing of dermatitis lesions, noticeable reduction in symptoms, relief from itching, and decreased local inflammation.

To determine the effectiveness of ozonized oils in treating infected wounds and ulcers on mucous membranes and skin, Zanardi et al. (2013) conducted experiments using cultures of microorganisms commonly found in these areas. The reference strains included Enterococcus faecalis, Pseudomonas aeruginosa, Escherichia coli, Candida albicans, and Staphylococcus aureus. The ozonized chemicals exhibited efficacy in inhibiting the development and propagation of bacteria and fungus throughout the research. The authors highlight the necessity of cleansing the affected area before applying an oily substance topically. This involves removing necrotic tissue, pus, fibrin deposits, and excessive liquid exudates.

Examining superficial fungal infections that impact various areas of the human body, including the skin, mucosa, hair, and nails (Gonzales 2016), the researcher investigated novel approaches for treating fungal infections. This involved conducting in vitro tests on aqueous and oleic compounds containing O₃, using cultures of Candida albicans, Trichophyton rubrum, Fusarium spp., and Microsporum canis. The researcher observed the antifungal properties of these compounds in samples obtained from the first three specimens. In a prior investigation conducted by Thomson et al. in 2011, it was discovered that oily O₃ solutions were both safe and efficacious when applied topically in animal models. These solutions demonstrated effectiveness against several types of fungi responsible for causing dermatophytosis. Consequently, it is recommended that further research should compare these solutions with alternative treatment methods. Therapeutics being evaluated in trials to determine their effectiveness.

Considering the well-documented antifungal properties and favorable skin compatibility of ozonized oils (Menendez et al., 2011; Lu et al., 2018), the researchers conducted comparative tests using commonly used medications and alternative therapy approaches. Both investigations
reported a notable alleviation of symptoms and decrease in remaining fungal colonies, with no occurrence of side effects or adverse reactions associated with the application of ozone. It is important to mention that researchers examined several types of fungi and came to similar conclusions on the efficacy of oleic chemicals compared to established medications like ketoconazole for treating fungal infections.

Currently, there is a significant manufacturing and commercialization of chemicals based on O3, largely attributed to its easy-obtaining process, these can be produced by bubbling the gas into bottles containing oil. The ozone molecule is incorporated into the vegetable oil by a chemical reaction that occurs with the double carbon bonds found in the lipid chains, this chemical process yields a sequence of novel compounds, including ozonides and lipoperoxides (Anzolin et al., 2021). The optimal amounts of O3 in oleic compounds still need more conclusive data. It is inaccurate to claim that more is always better, as studies have cautioned that the gas concentration influences these substances' effectiveness. Higher concentrations do not necessarily lead to better outcomes (Martinez-Sanches, 2021). Researchers have expressed concerns about the safety of ozonated compounds, particularly in relation to their usage in domestic settings. Adverse events have been attributed to a lack of attention during product administration, which raises concerns about the lack of discretion in their use (Wen et al., 2022). The safety of using the epithelium largely depends on its superficial topical application. However, more intrusive methods should employ more careful and cautious procedures.

In addition to the existing inquiries about the utilization of O3, it is worth noting that there are significant challenges in carrying out multicenter population studies, particularly in the context of clinical trials that involve individuals from diverse regions. This is necessary to ensure adequate sample sizes that can effectively identify various responses to the proposed treatments (Wen et al., 2022). Particularly in studies focusing on persistent skin lesions, several variables can greatly disrupt the acquired results. Patients with well-managed blood glucose levels and consistent use of prescribed medication have more favorable outcomes in cases of diabetic foot lesions. This finding highlights the importance of studying patients' adherence to their preferred drug therapies and potential interactions with other treatment approaches (Liu et al., 2015).
5 CONCLUSION

A framework exists in the literature that aids in ensuring the secure utilization of ozonized oleic chemicals for treating skin lesions. Their wide-ranging antibacterial capabilities, together with their ease of acquisition and favorable cost-effectiveness, support their utilization as adjunctive therapy in both chronic and non-chronic wounds, which are susceptible to deterioration caused by opportunistic infections. Another point that justifies the usage of these compounds is that O₃, as a singular chemical, does not elicit any adaptability or resistance in susceptible strains, despite its efficacy against a broad spectrum of bacteria. Considering the findings of oxidative stress and preconditioning induced by ozone in contact with living tissues, it would be wise to conduct more extensive trials to investigate those mechanisms, this will help determine the specific role of ozone in tissue repair processes.
REFERENCES


