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REVIEW PAPER

Antimicrobial activity of ozonated oils and their applications in medicine – a narrative review

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ABSTRACT

Introduction and aim. Ozonated oils have emerged as promising agents due to their potent antimicrobial properties and broad therapeutic potential across various medical fields. This review aims to evaluate the antibacterial activity of ozonated oils, focusing on their applications in dermatology, dentistry, ophthalmology, gynecology, and proctology, while addressing their safety profiles and limitations.

Material and methods. This review compiles and evaluates peer-reviewed publications on the antibacterial properties and therapeutic uses of ozonated oils. The authors conducted a comprehensive literature review by searching through the largest scientific databases using Google Scholar, Google Patents, Scopus, Web of Science, and PubMed within the last 15 years.

Analysis of the literature. Ozonated oils exhibited strong antibacterial effects against a wide range of microorganisms, including those resistant to antibiotics. Their efficacy has been confirmed in treating conditions such as onychomycosis, oral and vaginal candidiasis, and MRSA skin infections, among others. Clinical studies highlight their ability to reduce symptoms and improve outcomes in ophthalmic applications as well. Despite their effectiveness there are limitations which include a lack of long-term safety data, insufficient number of studies conducted on human subjects.

Conclusion. Ozonated oils have a lot of potential as antimicrobials that can be used in a variety of medicinal fields. However, further clinical trials are needed to establish their long-term safety and efficacy.

Keywords. bacterial biofilms, ozonated vegetable oils, ozonide, oxidation, pathogen inactivation

Introduction

Ozone is widely known for its antibacterial properties, which are attributed to its strong oxidative ability.[1,2] As a powerful oxidant, it can damage microbial cell walls, membranes and interfere with their essential cellular functions by proteins damage and loss of organelle functions.[3–5] In its gaseous form, ozone is commonly used to disinfect surfaces in food industry and medicine.[1,6,7] Aqueous ozone, created by dissolving ozone gas in water or by water electrolysis, effectively eliminates bacteria, fungi, and viruses on various surfaces and in liquid environments.[8–10] This allows its utilization in food processing and for wound irrigation.[11–13] The use of ozone in these forms has paved the way for the development of ozonated oils, which offer a more stable and localized application for medical purposes. These oils are a distinct family of ozone-based antibacterial agents, they are relatively new and have attracted a lot of interest lately due to their versatility and broad-spectrum effectiveness in a range of medicinal applications. Additional interest to the antimicrobial activity of such natural products is caused by the increased distribution of multidrug resistant microorganisms.[14] Olive oil has been used for centuries in cosmetic and medical applications.[15] Its

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beneficial properties are now further enhanced through ozonation. Produced by infusing vegetable oils with ozone gas, these oils possess strong oxidative properties, making them effective against microorganisms.[16] Their antibacterial action and possible therapeutic advantages are caused by their bioactive components, which include ozonides and peroxides.[14] The use of ozonated oils has expanded across several medical disciplines due to their ability to promote healing, reduce inflammation, and combat infections.

Despite their promising potential, the application of ozonated oils is not without limitations. Issues such as the stability of ozonated compounds, potential toxic byproducts, and the lack of standardized formulations remain challenges that require further investigation. Understanding these limitations is crucial for the safe and effective use of ozonated oils in clinical practice.

Aim

The aim of this narrative review is to synthesize and evaluate the current publications on the antimicrobial activity of ozonated oils. The review highlights their applications against bacteria (e.g., *Enterococcus faecalis, Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*), fungi (e.g., *Candida* spp., dermatophytes), and viruses (e.g., *Herpesviridae*). Additionally, their safety in medical applications as well as limitations and gaps in the literature are discussed to guide future research.

Material and methods

Google Scholar, Google Patents, Scopus, Web of Science and PubMed were used as web resources to search for relevant literature. The search was conducted using the keywords "ozonated oil", "ozonized oil" and "ozonide" in combination with "antimicrobial activity." Articles were selected based on their relevance to the antimicrobial properties of ozonated oils and medical applications. Both in vitro and in vivo studies were considered. Preference was given to peer-reviewed journal articles published within the last 15 years, although older studies were included when necessary. This review builds upon the author's previous work[17], expanding the scope to include recent advancements and additional perspectives on the antimicrobial activity of ozonated oils and their applications in medicine. Since this paper is a narrative review, PRISMA guidelines were not applied, as no systematic search strategy or meta-analysis was conducted.

Analysis of the literature

Applications of ozonated oils in dermatology

At this time, the market offers a variety of ozonated oils designed for topical use. Additionally, a variety of cosmetic formulations are currently on the market that emphasize the inclusion of ozonated oil as one of their constituents. These formulations include cream, shampoo, shower gel, aftershave balm, body lotion, emulgel, toothpaste, makeup remover, intimate wash, and lip balm.[14] The therapeutic potential of ozonated oils extends beyond skincare to medical applications in dermatology. Their antimicrobial and wound-healing properties make them valuable in treating various dermatological conditions. Huang et al. demonstrated the topical application of ozone in treatment of viral skin infection. Although their study did not directly evaluate the antiviral activity of ozonated oil, it demonstrated the clinical efficacy of ozonated oil and water application in patients with herpes zoster. Specifically, the results revealed a significant difference between the group treated with oral valacyclovir plus topical 2% mupirocin and the group receiving oral valacyclovir combined with topical ozone application. The ozone-treated group exhibited significantly faster clinical improvement without any side effects.[18] Silva et al. evaluated the antimicrobial and antibiofilm activity of ozonated vegetable oils against methicillin-resistant *S. aureus* (MRSA) strains isolated from diabetic foot ulcers. They demonstrated that ozonated oils had moderate to high potential to remove adhered bacterial cells and showed a high ability to eliminate 24 hour old biofilms. According to the results of their study, most MRSA strains were inactivated by ozonated oil at a concentration of 4.24 mg/g.[19] Song et al. demonstrated the antistaphylococcal activity of camellia oil with a peroxide index (PI) of 2000–2200 in vitro, as well as the resolution of MRSA skin infections following the topical application of ozonated water and ozonated camellia oil.[20] In addition to their well-documented antimicrobial properties, ozonated oils have also demonstrated significant antifungal activity, making them valuable in the treatment of dermatological conditions caused by fungal infections. The study conducted by Ouf et al. investigated the efficacy of ozonated oil against five dermatophyte species commonly responsible for superficial infections of the skin, nails, and hair. Their findings revealed that ozonated oil was more effective than gaseous ozone. Among the tested strains, *Microsporum gypseum* and *Microsporum canis* were the most susceptible, while *Trichophyton interdigitale* and *T. mentagrophytes* showed relative resistance.[21] In a phase III clinical trial involving 400 outpatients with onychomycosis, Menéndez et al. reported that the topical application of ozonated sunflower oil was more effective in treating onychomycosis than ketoconazole. After one year of follow-up, the experimental and control groups showed relapse rates of 2.8% and 44.4%, respectively.[22]

Applications of ozonated oils in dentistry

Beyond their applications in dermatology, ozonated oils have also shown promise in dentistry and oral care, where their antimicrobial and healing properties can address a variety of conditions. These oils are increasingly being explored as adjuncts to traditional dental treatments, offering potential benefits for managing infections and promoting oral health. In 2016, O'Malley proposed, and later patented in 2017, the incorporation of micro-encapsulated ozonated oils into a two-part oral care system. This system can be integrated into various dental and oral hygiene products, such as dental floss, toothbrush bristles, chewing sticks, comforters, denture bases, plastic retainers, and orthodontic devices.[23]

The efficacy of ozonated olive oil against *Streptococcus mutans*, the primary causative agent of dental caries, was examined by Nardi et al. Two commercial mouthwashes containing ozonated olive oil were tested in vitro. Both formulations successfully inactivated the principal pathogen of dental caries, effectively overcoming the salivary dilution effect in the oral cavity.[24] Pietrocola et al. compared the effectiveness of a commercial ozonated oil with two chlorhexidine digluconate-based agents. The study revealed a relatively moderate antiseptic effect for ozonated oil, which was more pronounced against Gram-negative bacteria than Gram-positive ones, and demonstrated its ability to inhibit dental plaque formation. However, the antibacterial activity of ozonated oil was found to be lower than that of the tested chlorhexidine-based agents.[25] Crastechini et al. investigated 493 *Candida* spp. isolates to evaluate the in vitro antifungal activity of ozonated olive oil and its in vivo effects on oral *Candida* spp. levels in patients with prosthetic stomatitis. The antifungal activity was tested against *Candida albicans* and five non-albicans species (*C. dubliniensis, C. guilliermondii, C. krusei, C. parapsilosis,* and *C. tropicalis*). In vitro, ozonated oil demonstrated antifungal activity against all tested *Candida* species and exhibited anti-biofilm activity against *C. albicans*. In vivo, 30 patients were treated with ozonated oil, while another 20 received sodium bicarbonate for 14 days. Both treatments significantly reduced oral candidiasis levels compared to baseline. After seven days of treatment, all patients in both groups showed complete remission of prosthetic stomatitis. According to the study's findings, ozonated oil could be a useful substitute for biofilm control in individuals suffering from prosthetic stomatitis.[26] Elshinawy et al. compared the antimicrobial and anti-biofilm activities of ozonated olive oil, chitosan, and silver nanoparticles, both individually and in combination, against the endodontic pathogens *E. faecalis*, *S. mutans*, and *C. albicans*. Ozonated oil demonstrated an 86% and 79% reduction in biofilms, respectively. The combination of ozonated oil and chitosan nanoparticles was the most effective, achieving a significant killing effect with a 6-log reduction in viable cells.[27]

Applications of ozonated oils in ophthalmology

A variety of microorganisms, including bacteria, viruses, and fungi, can cause ocular infections. Among bacterial pathogens, *Staphylococcus* spp., including *S. aureus*, and *P. aeruginosa* are the most common culprits behind acute and chronic eye infections.[28] Representatives of *Adenoviridae* and *Alphaherpesvirinae* families may cause such eye infections as conjunctivitis and keratitis.[29] Fungal eye infections can affect any part of the ocular surface and, in severe cases, spread to internal ocular structures, leading to endophthalmitis.[28]

Numerous studies have highlighted the use of ozonated oils in ophthalmology. Spadea et al. reported the successful application of a commercial product containing ozonated oil in liposomes and hypromellose for treating blepharitis, conjunctivitis, keratitis, and corneal ulcers in both humans and animals. Additionally, they demonstrated the antibacterial effects of ozonated oil against streptococci and enterococci.[30] Studies conducted by Pérez-Santonja et al. demonstrated the in vitro bactericidal activity of liposomal ozonated oil against *S. aureus*, *P. aeruginosa*, and *Porphyromonas gingivalis*. They also reported its effectiveness in treating recurrent conjunctivitis and corneal ulcers caused by MRSA and *P. aeruginosa* in animals.[28] Research completed by Cagini et al. confirmed that using ozonated oil-containing eye drops in combination with topical tobramycin 0.3% and dexamethasone 0.1% eye drops, administered four times daily, effectively reduced the signs of conjunctivitis and shortened the duration of the viral infection.[29] Celenza et al. reported that clinical *Candida* spp. isolates were susceptible to a commercial eye lubricant containing ozonated oil. They suggested that its antifungal activity was due to mitochondrial dysfunction and the accumulation of reactive oxygen species.[31] Since bacterial biofilms pose a significant challenge in both general medicine and ophthalmology, some researchers have investigated the anti-adhesion and anti-biofilm activities of ozonated oil-based eye drops. For example, Gentili et al. evaluated the effectiveness of a commercial eye drop preparation containing ozonated sunflower oil liposomes against *S. aureus*, MRSA, *Staphylococcus epidermidis*, *P. aeruginosa*, and *E. coli*. Their study demonstrated that the preparation exhibited substantial microbicidal and anti-biofilm activity, with the ozonated sunflower oil liposomes effectively preventing bacterial adhesion to human corneal cells.[32]

Applications of ozonated oils in gynecology and proctology

The application of ozonated oils in gynecology and proctology remains an emerging area of research, with limited studies directly addressing both their antibacterial properties and rectal use. Ozonated olive oil has been reported to be effective against *C. albicans* in the treatment of vaginal mucosa and has demonstrated antifungal activity in vitro.[33] Tara et al. reported that ozonated olive oil appears to be as effective as clotrimazole in the treatment of vulvovaginal candidiasis, both in reducing clinical symptoms and achieving laboratory-confirmed results.[34]

The potential of ozonated olive oil for rectal administration is demonstrated by the available data. For instance, Gültekin et al. demonstrated in their study the successful rectal application of ozonated olive oil in a rat model of acute radiation proctitis, showing promising therapeutic effects.[35] Additionally, several studies have confirmed the antibacterial activity of ozonated oils against pathogens that may be associated with vaginal and rectal infections. In particular, Yekanipour et al. demonstrated that commercially obtained ozonated oil exhibited bacteriostatic and bactericidal effects on *Neisseria gonorrhoeae* at concentrations of 3.12 PI and 6.25 PI, respectively.[36] While the laboratory-obtained data suggest a possible role for ozonated oils in managing rectal conditions, there is not enough clinical studies to validate their efficacy and safety in human proctological applications.

Safety and limitations of ozonated oils

To responsibly incorporate ozonated oils into medical practice, it is essential to thoroughly assess their safety. This ensures the effective use of these promising agents, maximizing their benefits while preserving patient health. Unfortunately, high-quality literature on the potential risks and side effects of ozonated oils on human tissues is limited. In one such study, researchers tested commercial ozonated olive and sunflower oils against *C. albicans*, *E. faecalis*, *S. aureus*, and *E. coli*, while also evaluating their toxicity on keratinocytes and epithelial cells. The results demonstrated significant microbicidal effects with no observed cytotoxicity.[37] Elshinawy et al. reported that, among the tested substances – ozonated olive oil, chitosan, and silver nanoparticles – ozonated olive oil exhibited the least cytotoxic effect on normal human fibroblasts.[27] Comparatively, De Oliveira et al. tested ozonated neem oil against laboratory and clinical strains of *E. faecalis*, *Enterococcus faecium*, *S. aureus*, *P.aeruginosa*, *E. coli*, and *Klebsiella pneumoniae*, as well as on two human cell lines: HaCaT (Immortalized Human Keratinocytes) and HCEC (Human Corneal Epithelial Cells). They reported greater antimicrobial activity of the ozonated neem oil compared to literature data for other ozonated oils, with no cytotoxicity observed at the concentrations tested.[38] In contrast, Radzimierska-Kaźmierczak et al. reported some cytotoxicity. They evaluated refined and ozonated olive oil for their antimicrobial properties against *E. coli*, *S. aureus*, *C. albicans*, and *Aspergillus brasiliensis* using the agar diffusion method, as well as for cytotoxicity using the MTT assay on two normal cell lines (LLC-PK1 and HaCaT) and two cancerous cell lines (Caco-2 and HeLa). Their findings showed that the ozonated oil exhibited a weak inhibitory effect against the tested microorganisms and a slight cytotoxic effect on HaCaT cells at concentrations of 312 and 1250 μg/mL.[33] Another study evaluated adverse drug reactions (ADRs) associated with a commercial ozonated sunflower oil in a Phase IV open clinical trial for the treatment of tinea pedis. The authors reported that out of the 2,165 patients who completed the trial, only six experienced ADRs, all of which were rated as mild by the study participants.[39] Similarly, Lu et al. evaluated the combination of laboratory-prepared ozonated water and commercial ozonated oil in a clinical trial for the treatment of tinea pedis. Their results demonstrated that this combination was effective in treating tinea pedis, as confirmed by mycological examination, and revealed no side effects.[40] Despite the growing amount of evidence supporting the in vitro effectiveness of ozonated oils, there remains a critical need for more comprehensive clinical trials to establish their safety and efficacy in medical applications. Significant gaps persist in the existing literature, including the lack of long-term safety data and a limited number of studies conducted on human subjects. Addressing these gaps is essential to ensure that ozonated oils can be responsibly and effectively integrated into clinical practice.

Study limitations

This review has several limitations. First, as a narrative review, it does not include a systematic search strategy, which may introduce selection bias. Second, while many *in vitro* and animal studies suggest promising antimicrobial properties of ozonated oils, human clinical trials remain limited, making it difficult to generalize findings. Third, differences in ozone concentration and oil type across studies may contribute to variability in reported effectiveness. Future systematic reviews and meta-analyses should aim to consolidate standardized data on ozonated oil applications.

Conclusion

The antibacterial properties of ozonated oils and their wide range of uses in dermatology, dentistry, ophthalmology, gynecology, and proctology are explored in this review. Ozonated oils have demonstrated significant potential as effective agents against a wide range of microorganisms. They confirmed to be as good options for addressing microbial resistance to antibiotics, dealing with bacterial biofilms and enhancing patient outcomes. The reviewed papers highlight the many uses of ozonated oils, especially their effective use in the treatment of gynecological and proctological illnesses, mouth infections, ophthalmic diseases, and dermatological conditions. Additionally, clinical research indicates that ozonated oils have good safety profiles with very few reported side effects. However, these conclusions should be interpreted cautiously due to the limited availability of high-quality, long-term safety data and the relatively small number of human studies conducted to date, which should be addressed in the future research.

Declarations

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Author contributions

Conceptualization, T.P. and O.P.; Methodology, T.P.; Writing – Original Draft Preparation, T.P.; Writing – Review & Editing, O.P.; Supervision, O.P.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

No datasets were generated or analyzed during the current study.

Ethics approval

Not applicable.

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