*Review Article*

**OZONE'S ANTIMICROBIAL POTENTIAL: AN INTEGRATIVE LITERATURE REVIEW AND CLINICAL PERSPECTIVES**

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**ABSTRACT**

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| **Objective:** This integrative literature review aimed to investigate the potential antimicrobial activity (AA) of O3. **Methodology:** To this end, a search was conducted for articles in the PubMed, Scielo and Cocharne databases, published from July 2014 to July 2024. Four keywords were established and checked on the DeCs - Health Sciences Descriptors website, namely “ozone”, “antimicrobial activity”, “anti-bacterial” and “antifungal”. The search and critical reading of studies related to ozone AA in 3 databases led to the inclusion of 11 articles. **Results:** The analysis of these articles in this integrative review led to the conclusion that ozone is a molecule that does indeed have antimicrobial potential, and that its application and use takes place in different physical forms, such as the application of ozone in gas, in aqueous form, in oily vehicles or even in nanoparticles. **Discussion:** It was noted that there is a need for more clinical studies and animal models to assess the applicability of O3 in infectious conditions in vivo, such as dental-alveolar abscesses, skin infections and respiratory and digestive tract infections, since the vast majority of the articles found belonged to laboratory-based *in vitro* trials. **Conclusion:** Therefore, this article describes an analysis of data that point to ozone's potent AA and reinforces the need for clinical trials to evaluate its effect on pathogens in vivo and thus promote good prospects for clinical application. |

*Keywords:*  ***“ozone”, “antimicrobial activity”, “anti-bacterial” and “antifungal”.***

**1. INTRODUCTION**

The evolution of drug resistance mechanisms by bacteria and fungi is one of the best documented processes in the scientific community, as its consequences affect both developed and developing countries. This scenario leads to a major problem due to the pharmaceutical industry's constant need to develop new drugs that can be used effectively to treat fungal and bacterial infections in humans. Some research already points to serious prospects regarding the effectiveness of antibiotics, given that the frequency of antimicrobial resistance (AR) genes increases [1]. In addition, the incidence of fungal infections has increased in recent decades [2].

Currently, Antimicrobial Resistance (AMR) is considered one of the biggest problems for global public health. It is estimated that approximately four million people acquire healthcare-associated infections every year in the European Union. European Union (EU), and that around 37,000 people die as a result of resistant infections acquired in hospital environments. The majority of these deaths (67.6%) are caused by bacteria that are multi-resistant to antibiotics [3].

Thus, given the need to obtain more drugs with antimicrobial properties, new molecules are being studied the bioprospecting of new products with the prospect of clinical application in the treatment of infections [4]. In this scenario, ozone stands out for its ability to suppress the growth of pathogens, since it is already known that ozonated vegetable oils have antibacterial activity, with studies proving their effectiveness against Gram-positive bacteria [5, 6]. (2024) pointed out the efficacy of applying ozonized sunflower oil against *Candida albicans* [7].

The literature describes that ozone is generally used with a vehicle. This substance carries the ozone molecules and helps maintain its useful life, giving it its properties. Among the vehicles used, vegetable oils such as sunflower [7] and olive [8] stand out. The process of adding O3 to these compounds, ozonation, occurs in the unsaturation of the hydrocarbon chains present in the oil, leading mainly to the formation of cyclic ozonated species [9]. The ozonolysis mechanism is called the Criegee oxidation reaction, in which ozone reacts chemically on an unsaturated bond to form an unstable initial primary ozonide. It is then rapidly decomposed into carbonyl fragments that can combine to generate cyclic trioxolane compounds in anhydrous environments [10]. From this reaction, ozonides, hydroperoxides, aldehydes, peroxides, diperoxides and polyperoxides are produced, promoting antibacterial, fungicidal and antiviral properties of ozonated oils, which can therefore be applied in the cosmetic and pharmaceutical areas [11]. After the ozonation process, vegetable oils undergo a drastic change in chemical composition, leading to alterations in their physical appearance, with a slight change in taste and smell and an increase in viscosity [12]

Ozone (O3) is a highly reactive molecule made up of three oxygen atoms that act as oxidizers [13]. When bacteria are exposed to ozone in vitro, the phospholipids and lipoproteins of the bacterial cell envelope are oxidized. This mechanism disrupts the integrity of the cytosolic membrane, causing ozone to infiltrate the microorganisms and oxidize glycoproteins and glycolipids, blocking enzymatic function. In addition, evidence has shown that ozone interacts with the cell walls of fungi as well as bacteria [14,15]. Another interesting aspect related to the use of ozonides in the field of medical sciences is the absence of cytotoxicity, since in cell culture tests they showed no cytotoxic effect on fibroblasts or keratinocytes and induced fibroblast migration, which could help in the wound healing process [16].

In this context, this work aimed to analyze the antimicrobial activity of ozone in its different applications, formulations and vehicles, as well as to elucidate whether there are reports of antimicrobial resistance associated with this agent.

**2. METHODOLOGY**

After establishing the research's focal question, this integrative literature review was conducted by searching for articles in the PubMed, Scielo and Cocharne databases, published from July 2014 to July 2024 in the PubMed, Scielo, and Cocharne databases. Four keywords, “ozone,” “antimicrobial activity,” “anti-bacterial,” and “antifungal,” were established and checked on the DeCs - Health Sciences Descriptors website.

**2.1- Criteria for considering studies for this analysis**

The selection of articles for analysis in this review was based primarily on the inclusion of articles that evaluated the AA of ozone using a well-described method, including any formulation, vehicle substance or physical state of the molecule (gaseous or aqueous). Only articles published in the last 10 years were selected, with no language restrictions.

**2.1.1- Types of studies and inclusion criteria**

To include studies that answered and met the focal question, the inclusion of studies that belonged to the following methodological delimitations was delimited.

 (i)- *In vitro* studies

(ii)- Animal studies

(iii)- Clinical trials

(iv)- Cohort studies

**2.1.2 – Exclusion criteria**

Studies that did not involve quantitative and qualitative analysis of the AA of ozonated compounds, studies without full text or that did not clearly describe the method or the microbial species studied, and literature reviews were also excluded. No exclusion criteria were applied to the type of microorganism with which the tests were carried out.

**2.2- Data collection, extraction and management**

After critically reading the titles and abstracts, articles that met the inclusion criteria were downloaded to read the full text. At the end of this stage, 27 articles were obtained, as described in Table 1 and Figure 1. In addition to the exclusion criteria already mentioned, duplicate studies were excluded, so this literature review was carried out using 11 articles. Figure 1 shows how many articles were selected.

**3. RESULTS**

The process of data management, study selection, inclusion and exclusion of studies is described and illustrated in Figure 1. The search and critical reading of studies related to ozone AA in 3 databases led to the inclusion of 11 articles, the main results of which are described in table 1. Of this amount, most studies dealt with *in vitro* laboratory tests, and there was a lack of clinical trials and cohort studies.

~~Figure 1 - Illustration of the methodology for managing, selecting and including studies in the work.~~



Figure 1 - Illustration of the methodology for managing, selecting and including studies in the work.

**Table 1-** Synthesis matrix used in this integrative review

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| --- | --- | --- | --- | --- | --- |
| Reference  | Study design | O3 formulation/use vehicle | Microorganism(s) studied | Method for evaluating O3 AA | Results |
| [Britton](https://pubmed.ncbi.nlm.nih.gov/?term=Britton+HC&cauthor_id=34368688) *et al.,* (2019) [17] | Laboratory study and *in vitro* test | The antimicrobial effects of aqueous ozone were studied in combination with short-chain fatty acids (SCFA) of acetate, propionate or butyrate, as well as citrate or oxalate buffer formulations | *Salmonella enterica* and  *Klebsiella* *pneumoniae* | Agar diffusion method | All buffer systems tested had a significantly greater reduction in CFUs after treatment with the combination of buffer and ozone, compared to treatment with buffer or ozone alone, which has not previously been reported for hard surfaces |
| Shu *et al*., (2021) [18] | Laboratory study and *in vitro* test | Ozone gas | *Escherichia coli* and *Listeria monocytogenes*  | Bacterial growth assay (log CFU/g) was determined by comparing O3-treated samples with the control according to standard procedures. The reduction in the viable cell count was calculated as the log change in the bacterial population expressed as log UFC/g recovered from tomato fruit treated with O3 compared to that recovered from the untreated control | For *E. coli*, low (1 μg O3 /g fruit) and moderate (2 μg O3 /g fruit) doses caused an insignificant reduction in survival, while high doses (3 μg/g fruit) caused a significant reduction in survival in a time-dependent manner. For *L. monocytogenes*, a moderate dose caused a significant reduction even with short-term exposure. Distinct responses to O3 xenobiosis between *E. coli* and *L. monocytogenes* are probably related to differences in the structure and components of the cytoplasmic membrane |
| Sabanci *et al.,* (2022) [19] | Laboratory study and *in vitro* test | Liposomal solution loaded with ozonized hyaluronic acid with nanobubbles (NAHAL) | *Staphylococcus aureus* (ATCC 6538), *Streptococcus pneumoniae* (ATCC 49619) and *E. coli*(ATCC 25922) | Broth microdilution assay | Bacterial growth was inhibited by the NAHAL solution in a time/dose dependent manner |
| [Piletić](https://pubmed.ncbi.nlm.nih.gov/?term=Pileti%C4%87+K&cauthor_id=35627712) *et al*., (2022) [20] | Laboratory study and *in vitro* test | Ozone gas | Standard strains of *K. pneumoniae* ATCC 700603 and *K. pneumoniae*NCTC 13442. Clinical isolates of *K. pneumoniae* producers of OXA-48 |  Bactericidal activity was analyzed using methods for quantifying mature biofilm. | Total biomass reduction was observed for all *K. pneumoniae* strains tested after treatment with 25 ppm ozone for 1 h of exposure. The reduction was statistically significant compared to the control group for all *K. pneumoniae* strains tested (p < 0.05) |
| [Rangel](https://pubmed.ncbi.nlm.nih.gov/?term=Rangel+K&cauthor_id=35807244)*et al*., (2022) [21] | Laboratory study and *in vitro* test | Ozone gas | Standard strains *S. aureus* (ATCC 6538), *Salmonella enterica* (ATCC 10708), *E. coli* (ATCC 25922) and  *Pseudomonas aeruginosa*  (ATCC 15442). Four clinical strains isolated from IRAS: *S. aureus* resistente à meticilina (MRSA), *K. pneumoniae*producer of carbapenemase (KPC+), *Acinetobacter baumannii* PDR gene carrier *bla* OXA-3 and an environmental strain of *P. aeruginosa* (XDR) of hospital effluent | Bacterial inactivation (growth and cultivability) was investigated using colony counts and resazurin as metabolic indicators. Scanning electron microscopy (SEM) was performed | Exposure of the culture to a high level of O3 inhibited the growth of all bacterial strains tested with a statistically significant reduction in colony count compared to the control group. The cell viability of *S. aureus* (MRSA) (99.6%) and *P. aeruginosa* (XDR) (29.2%) was considerably reduced, and SEM showed damage to the bacteria after treatment with O3 |
| [Khachatryan](https://pubmed.ncbi.nlm.nih.gov/?term=Khachatryan+G&cauthor_id=36430484)*et al*., (2022) [22] | Laboratory study and *in vitro* test | Hydrogel based on hyaluronic acid containing ozonized olive oil micro/nanocapsules | *Candida albicans* | Broth microdilution assay | The Hyal/O3 leaves examined exhibited a very weak inhibitory effect against the commensal bacterial microbiota of the skin and pathogenic yeasts |
| [Takizawa](https://pubmed.ncbi.nlm.nih.gov/?term=Takizawa+F&cauthor_id=37043490) *et al.*, (2023) [23] | Laboratory study and *in vitro* test | Ozone ultra fine bubble water (OUFBW) | *S. pneumoniae* susceptible and resistant to antibióticos, *P. aeruginosa, Streptococcus mutans, Streptococcus sobrinus, Fusobacterium nucleatum, Prevotella intermedia and Porphyromonas gingivalis* | The bactericidal activity of OUFBW against planktonic cells was analyzed using standard plating methods.  | Results indicated that OUFBW exerts a bactericidal effect instantly and non-specifically against all the bacteria studied |
| Salaie et al., (2024) [24] | Laboratory study and *in vitro* test | Ozonized olive oil gel  | *S. mutans* and *Granulicatella adiacens* isolated from peri-implantitis | Agar diffusion method | The results showed that ozonized olive oil applied to microbial biofilms grown on titanium implants significantly inhibited the growth of *G. adiacens*, but showed no significant effect against *S. mutans*. The same result was obtained when testing the antibacterial activity of ozone using the agar diffusion method. |
| Donato *et al.* (2024) [25] | Laboratory study and *in vitro* test | Different formulations of ozone, either as a gas or dissolved in liquid matrices, specifically distilled water or oil  | *E. coli, S. aureus, Streptococcus equi subsp. zooepidemicus, P. aeruginosa, K. pneumoniae and C. albicans* | Disc diffusion method, Minimum inhibitory concentrations (MICs) and minimum bactericidal/fungicidal concentrations (MBCs/MFCs) were determined by the broth dilution method according to CLSI. | The results showed a reduction in the microbial count of more than 99.9% for each pathogen. Ozonated oil showed bactericidal/fungicidal activity against all strains tested (MIC range 12.5-25% v/v, MBC/MFC range 12.5-50% v/v), while ozonated distilled water did not show an observable antimicrobial effect, discouraging its use as an antimicrobial agent  |
| [Puxeddu](https://pubmed.ncbi.nlm.nih.gov/?term=Puxeddu+S&cauthor_id=38338423)*et al.,* (2024) [26] | Laboratory study and *in vitro* test | Commercial olive oil (OOO) and sunflower seed oil (OSO) ozonized | *C. albicans,**Enterococcus faecalis,**S. aureus, K. pneumoniae,**P. aeruginosa and**E. coli* | Agar diffusion and broth dilution methods | Results revealed that both OOO and OSO showed a potent microbicidal effect, especially against C. albicans (IC50 = OOO: 0.3 mg/mL and OSO: 0.2 mg/mL) and E. faecalis (IC50 = OOO: 0.4 mg/mL and OSO: 2.8 mg/mL), while also exerting a certain effect against *S. aureus and E. coli*. |
| Borón *et al.*, (2024) [27] | Laboratory study and *in vitro* test | Ozonized olive oil nano/microencapsulated in a hyaluronan matrix | *E. faecalis,**S. aureus, P. aeruginosa,**E. coli, Acinetobacter, Bacillus pumilus,**Microbacteum maritypicum,**Macrococcus luteus or**Sporosarcina luteola, Aeromonas media, Citrobacter freundi, Kocuria rhizophila, Psychrobacter sanguinis* | Disk diffusion method | Nano/microencapsulated ozonated olive oil in a hyaluronan matrix was effective against a variety of bacteria, not only opportunistic and mild pathogens, but also those with a high potential for pathogenicity and resistance to antimicrobial agents, such as *Enterococcus* and *Acinetobacter* |

**~~Table 1-~~** ~~Synthesis matrix used in this integrative review~~

**4. DISCUSSION**

 The analysis of 11 articles included in this integrative review led to the conclusion that ozone is a molecule that does indeed have antimicrobial potential. Its application and use takes place in different physical forms, such as the application of ozone in gas [18,20,21], aqueous [17,19,23] or even in nanoparticles [22,27], as well as in oily vehicles [24,25]. However, there is a need for more clinical and animal model studies to assess the applicability of O3 in infectious conditions in vivo, such as dento-alveolar abscesses, skin infections and infections of the respiratory and digestive tracts, since the vast majority of the articles found were laboratory-based *in vitro* tests. Broth microdilution and agar diffusion tests were the most frequently used to assess the antimicrobial activity of O3.

 It was found that the application of gaseous ozone was effective in reducing standard strains of *S. aureus, S. enterica, E. coli* and *P. aeruginosa* and was also able to reduce the cell viability of some clinical strains isolated from healthcare-related infections (HAIs), such as *S. aureus* methicillin-resistant (MRSA), *K. pneumoniae* carbapenase-producing (KPC+), *A. baumannii* PDR carrying the bla OXA gene. aureus (MRSA), carbapenemase-producing *K. pneumoniae* (KPC+), *A. baumannii* PDR carrying the bla OXA-23 gene and an environmental strain of *P. aeruginosa* (XDR) from hospital effluent [21]. This finding is clinically relevant, as it offers good prospects for the application of this compound in cases of infections caused by microorganisms resistant to the antibiotics commonly used to treat HAIs, given the growing global problem of AMR [1]. Other studies have also shown similar results with the application of gaseous O3 in *in vitro* tests, with an effective reduction in standard strains of K. pneumoniae ATCC 700603 and clinical isolates of K. pneumoniae producing OXA-48 [20]. Shu et al. (2022) investigated and proved the efficacy of ozone gas against *E. coli* and *L. monocytogenes*, highlighting that its effect is dose-time-dependent, making it a viable alternative for disinfecting foodstuffs such as tomatoes [18]. Even so, it is important to highlight the antifungal activity of the gas, which showed a 99.9% reduction in viable C. albicans cells [25].

 The transport of O3 particles in oily substances, especially plant-based ones, has also been described. In this perspective, results showed that ozonized olive oil applied to microbial biofilms developed on titanium implants significantly inhibited the growth of G. adiacens, but showed no significant effect against S. mutans isolated from peri-implantitis. The same result was obtained when testing the antibacterial activity of ozone using the agar diffusion method [24]. It is suggested that aerobic gram-positive bacteria have greater resistance to ozone, given their better tolerance to radical species of oxygenated products. (2024) investigated the applicability of ozonized commercial olive oil (OOO) and sunflower seed oil (OSO) against *C. albicans, E. faecalis, S. aureus, K. pneumoniae, P. aeruginosa* and *E. coli* and the results revealed that both OOO and OSO showed a potent microbicidal effect, especially against C. albicans [25]. A similar result was also obtained by Araújo et al., (2024) [7].

 Studies have also reported the application of nanomolecular modifications of these compounds. Ozonated olive oil nano/microencapsulated in a hyaluronan matrix is effective against a variety of bacteria, not only opportunistic and less virulent pathogens, but also those with a high potential for pathogenicity and resistance to antimicrobial agents, such as Enterococcus and Acinetobacter [27]. Also noteworthy in this field is the use of a liposomal solution loaded with ozonized hyaluronic acid with nanobubbles (NAHAL), developed using nanotechnology, which was able to prevent bacterial growth in a time/dose-dependent manner for *S. aureus, Streptococcus pneumoniae* and *E. coli*. [27].

**5. CONCLUSION**

As a result of this review, it can be concluded that ozone has a great capacity to inhibit the growth of various microbial species, such as gram-positive and gram-negative bacteria, as well as fungi. These findings have a major impact in the context of the increased occurrence of antimicrobial resistance, since the results of the articles analyzed point to the efficacy of this molecule against pathogens carrying antibiotic resistance genes. Another relevant characteristic observed about O3 is its versatility of application, varying in physical form and vehicles. This characteristic favors its clinical applicability. Thus, this article gathers and analyzes data that point to ozone's potent antimicrobial action and reinforces the need for clinical trials to evaluate its effect on pathogens in vivo and thus promote good prospects for clinical application.

**Interesses concorrentes**

Authors have declared that no competing interests exist.

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