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Nanoemulsions: A Promising Strategy in the Fight against Bacterial Infections †

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Abstract: In recent years, bacterial infections have become a major global concern, causing significant morbidity and mortality. Unfortunately, the development and commercialization of new antibacterial drugs have been slow, while pathogens continue to rapidly adapt and evolve. To address this challenge, nanotechnology offers a promising strategy by protecting, targeting, and releasing active compounds to fight against these emerging strains. The aim of this study was to explore the antibacterial potential of nanoemulsions (NEs), as reported in the scientific literature. A literature review was carried out utilizing the keywords "nanoemulsion", "antibiotic activity", "antibacterial activity", and "antimicrobial activity". All of the scientific articles that were related to the area of health and published in the last 5 years were included. All of the studies indicated that oil-based NEs with inherent antibacterial activity, even without the presence of drugs, had superior action against strains compared to non-emulsified oil, as well as other systems incorporating drugs or actives. Although the results are promising, further investigations and testing of formulations against resistant bacterial strains are necessary. This review aims to provide valuable insights for researchers and contribute to future advancements in this field.

Keywords: nanoemulsion; drug delivery system; antibacterial; microbial infections

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1. Introduction

Bacterial infections have been causes of morbidity and mortality and have experienced alarming growth in recent years. This scenario is the result of the rapid adaptation and evolution of pathogens through various strategies, such as by means of antibiotic destruction or reflux and the modification of the target structure [1]. On the other hand, the development and commercialization of new antimicrobials to combat these emerging bacterial strains is extremely slow [2].

In this context, nanotechnology emerges as a promising area of research in the search for innovative antimicrobial solutions. This strategy, characterized as nanoscale drug delivery systems, has aroused considerable interest due to its capabilities to improve the availability and targeted efficacy of drugs, being an attractive proposal to mitigate several problems [3,4]. Under this perspective, several innovative nanosystems can be listed, such as liposomes, solid lipid nanoparticles, polymeric nanoparticles, and metallic nanoparticles.

These nanoformulations offer the opportunity to improve therapeutic performance by modifying their composition, particle size, and surface characteristics, aiming to increase their efficacy, reduce side effects, and overcome drug resistance [5]. At this juncture, nanoemulsions (NE) can also be listed, which have been recognized as an advantageous

approach for drug delivery, due to their ability to improve solubility, stability, and bioavailability, as well as their potential for targeting organs and cells [3–6].

2. Methodology

The scientific literature was reviewed, following the steps set out in accordance with the methodological protocol described by Almeida et al. [7]. For this purpose, the acronym PICo was adopted to write the inquiry, as shown in Table 1.

Table 1. Definition of search terms based on the PICo acronym.

Acronym	Definition	Corresponding Term
P	Population	Scientific Bibliography
I	Interest	Antibacterial Activity
co	Context	Nanoemulsion

Source: Research data.

Thus, this study question was presented: "what does the scientific literature (P) present about the antibacterial activity (I) of nanoemulsified systems (Co)?". Then, the bibliographic search began in May 2023 in PubMed, Web of Science, and Scopus. The search terms "nanoemulsion", "antibiotic activity", "antibacterial activity", and "antimicrobial activity" were used, and studies published in the last five years were prioritized. We selected studies that explicitly stated in their abstract or title that the text referred to the activity of NE systems against bacterial strains. The inclusion criteria were studies published in the form of scientific articles. Duplicate articles, studies published in events, editorials, and literature reviews that did not deal with applications for health sciences, reporting gels, membranes, or freeze-dried formulations were excluded from the sample.

Data collection took place after the individual study. From this point onwards, a construction of the state-of-the-art strategy began to answer the guiding question. There was no need to appeal to ethics committees. All of the consulted authors were made available, guaranteeing the due ethical principles implicit.

3. Results and Discussion

Nanotechnology is used in the field of health for the development of diagnostics and delivery of drugs to improve therapeutic efficacy. This type of technology is very attractive because it can obtain nanosystems, which can reach and be specific to active sites, in addition to causing fewer adverse effects. From the perspective of antibiotic therapy, this strategy arouses interest among researchers, given the chaotic scenario related to the global need for innovative antimicrobial therapies [1,3,4,6]. From this brief review of the scientific literature, it was observed that 100% (n = 20) of the studies analyzed developed NE with biological activity against various pathogenic bacterial strains.

These formulations can be prepared by methods that provide low energy or high energy for the formation of nanometer-scale droplets. Both have their advantages and specific applications. Among the studies analyzed, 60% (n = 12) used high-energy methods to obtain the systems. The high-energy method most cited in the articles was ultrasound, which generates high-frequency mechanical waves, resulting in cycles of compression and expansion in the liquid, which causes cavitation, which in turn creates strong shear forces and turbulence, breaking the larger oil droplets into smaller sizes, forming an NE [8,9]. Despite the ease of obtaining nanometric droplets through this procedure, the large amount of energy that the system requires makes this method expensive.

Only 8 of the 20 studies analyzed mentioned a low-energy supply to obtain antibacterial nanoformulations. NEs obtained using low-energy consumption present economic advantages for large-scale production. The low-energy methods mentioned in the articles were spontaneous emulsification (n = 5; 25%) and phase inversion (n = 3; 15%), using constant magnetic stirring. Spontaneous emulsification is a natural process in which there is a variation in the amount of surfactants, which can be combined with changes in temper-

ature. These variations alter the surface energy of the interface between the phases, leading to the spontaneous formation of an NE [10,11]. The phase inversion method involves gradually adding water or another solvent to the oil–water or water–oil mixture. As the amount of water increases, the emulsion inverts, transforming an oil-in-water emulsion into a water-in-oil emulsion (or vice versa), forming an NE [12–16].

The oily phase of the systems was predominantly composed of essential oils (EO) in 70% of the articles consulted (n = 14). In these studies, the incorporation of bioactives or additional drugs into the system was not identified [17–22]. Only 30% (n = 6) of the authors added some type of bioactive molecule to the nanosystem. This fact is inferred because the authors used other types of compounds to compose the NE matrix, such as vegetable oils and oleic acid. Only one study incorporated antibiotics into the NE (clindamycin, linezolid, and doxycycline). The other studies added natural bioactive molecules: scalene, green tea catechins, 1,8-cineol, curcumin extract, and green coffee extract (Figure 1) [23–30].

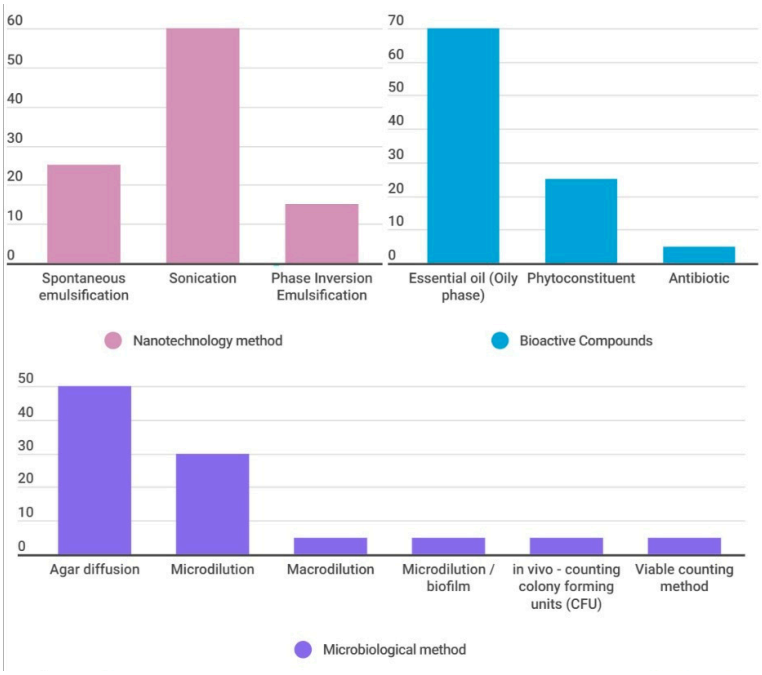

Figure 1. Bioactive compounds, microbiological methods, and nanotechnology summarized. Source: Research data.

As for microbiological tests, 50% (n = 10) of the studies used diffusion in the medium as a method to evaluate the sensitivity of the strains. This type of test is economical, quick, and consists of verifying the inhibition halo. Diffusion can occur using filter paper discs or perforation of the agar, in which the compound to be investigated is deposited after the bacteria have been seeded. The serial dilution method was used in 9 investigated studies, with plate microdilution being the most prevalent. Regarding strains, Gram-positive strains of the genus *Staphylococcus* have been extensively evaluated for their sensitivity to nanocarriers [30–37].

An attempt was made to establish some relationship between droplet size and the antibacterial activity identified. This size/activity relationship had already been discussed in other studies, as described by Álvarez-Chimal et al. [38], concerning greater bacterial inhibition in Gram-positive strains with smaller nanoparticles (up to 10 nm). A similar result was observed in the study by Naqvi et al. [39].

According to Ali et al. [40], the antibacterial action optimized by nanocarriers with smaller particle sizes would be related to the increase in intracellular oxidative stress. This is because the smaller the size of the particles, the greater the interaction between the electron-donating and electron-accepting active sites, generating the activation of several molecular cascades and an increase in reactive oxygen species. The hydrodynamic sizes of

the droplets present in the NEs varied, and all were reported to have antimicrobial action (Figure 2), especially depending on the concentration of the active ingredient. However, the composition of NEs has a great influence on their outstanding antibiotic action, as well as aspects related to solubility [41,42]. This argument about the influence of the physicochemical on improving the delivery of the active ingredient properties of the NE can be validated by its antibiotic potential.

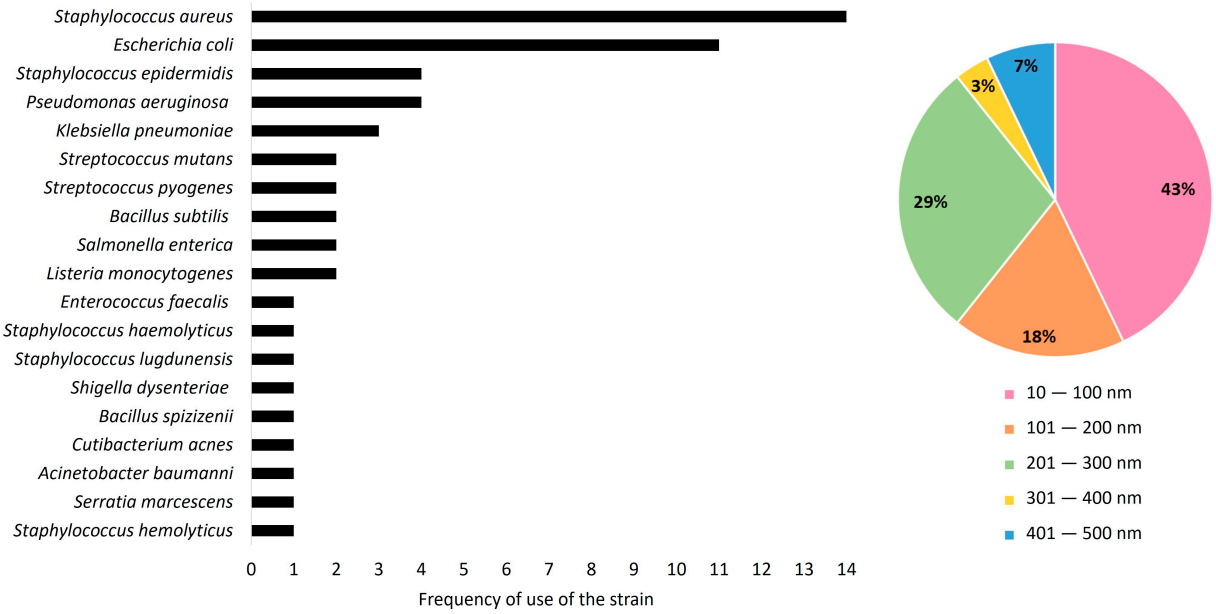

Figure 2. Frequency of the use of bacterial strains and droplet size range of nanoemulsions presented in the studies analyzed. Source: Research data.

This is exemplified in data from the chamomile EO-NE, with a hydrodynamic size close to 300 nm, presenting a minimum inhibitory concentration against several strains: *E. coli*: 2.19 µg/mL and *P. aeruginosa*: 1.02 µg/mL, as well as fungal strains, namely: *S. pombe*: 1.28 µg/mL; *C. albicans*: 2.65 µg/mL; and *C. tropicalis*: 1.69 µg/mL [34]. Here the highlight is the demonstration of antimicrobial activity of the NE at an average concentration that is 14 times lower compared to the free EO in ethanol. Another larger NE was that of *Cymbopogon pendulus* EO, with around 500 nm [32], which resulted in inhibition zones of 3.5 cm for *S. aureus* and complete inhibition for *E. coli* strains, *B. subtilis*, and *P. aeruginosa*.

Furthermore, we highlight the study of Mohamed et al. [26] who developed a nanobiotics NE (an NE loaded with antibiotics) and tested them on strains of resistant bacterial isolates. The study, in addition to showing greater safety (in cytotoxicity tests) than traditional drugs, managed to overcome the barrier of bacterial resistance. The authors justify this response by the ability of nanostructures loaded with antibiotics to deliver high concentrations of antibiotics to their target sites. However, further investigations from this perspective are necessary to obtain greater conclusions about the potential of these nanocarriers to overcome antibiotic resistance.

4. Conclusions

The data from this preliminary review indicate that NEs may be promising routes for the development of antibacterial drugs, including resistant strains. However, further evaluations are needed regarding the use of antibacterial drugs and their incorporation into nanosystems, as well as further elucidation regarding the relationship between droplet size and the antimicrobial effect.

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