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Chemistry

Nanoemulsions of plant-based bioactive compounds with antimicrobial applications: a review

Nanoemulsões de compostos bioativos de base de plantas com aplicações antimicrobianas: uma revisão

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ABSTRACT

The search for alternative antimicrobial agents is attracting increasing scientific interest. Natural products of plant origin are sources of several substances with proven biological activities, including antimicrobial activity. The encapsulation of these products in the form of a nanoemulsion seeks to overcome problems inherent to these products, such as instability and degradation. Based on these considerations, we carried out a bibliographical survey of nanoemulsions produced from plant-derived substances, such as essential oils and extracts, with antimicrobial potential, focusing on antibacterial, antifungal and antiviral activities. Articles and documents published in scientifically relevant journals, as well as keywords classified from Health Sciences Descriptors, were used. All documents relevant to this search reported that nanoemulsions loaded with essential oils and plant extracts from different botanical species had in vitro antimicrobial activity against different microorganisms of medical importance, in addition to enhancing the antimicrobial effects of these bioproducts. Therefore, nanostructured antimicrobials with essential oils and plant extracts can be considered treatment options for microbial diseases: due to their physicochemical properties, they act as better delivery vehicles for natural products with good bioavailability, by reducing toxicity and prolonging the useful life of these natural antimicrobials, thus enhancing treatment for infectious human diseases.

Keywords: Antimicrobian activity; Nanoparticles; Alternative products

RESUMO

A busca por agentes antimicrobianos alternativos vem atraindo crescente interesse científico. Os produtos naturais de origem vegetal são fontes de diversas substâncias com atividades biológicas comprovadas, incluindo atividade antimicrobiana. O encapsulamento desses produtos na forma de nanoemulsão busca superar problemas inerentes a esses produtos, como instabilidade e degradação. Com base nessas considerações, realizamos um levantamento bibliográfico de nanoemulsões produzidas a partir de substâncias derivadas de plantas, como óleos essenciais e extratos, com potencial antimicrobiano, com foco nas atividades antibacteriana, antifúngica e antiviral. Foram utilizados artigos e documentos publicados em periódicos de relevância científica, bem como palavras-chave classificadas nos Descritores em Ciências da Saúde. Todos os documentos relevantes para esta pesquisa relataram que as nanoemulsões carregadas com óleos essenciais e extratos vegetais de diferentes espécies botânicas apresentaram atividade antimicrobiana in vitro contra diferentes microrganismos de importância médica, além de potencializar os efeitos antimicrobianos desses bioprodutos. Portanto, antimicrobianos nanoestruturados com óleos essenciais e extratos de plantas podem ser considerados opções de tratamento para doenças microbianas: devido às suas propriedades físico-químicas, atuam como melhores veículos de entrega de produtos naturais com boa biodisponibilidade, reduzindo a toxicidade e prolongando a vida útil desses antimicrobianos naturais , melhorando assim o tratamento de doenças humanas infecciosas.

Palavras-chave: Atividade antimicrobiana; Nanopartículas; Produtos alternativos

1 INTRODUCTION

Infectious diseases occupy fourth place in the ranking of diseases that caused the most hospitalizations and deaths in the world between 2000 and 2019 (Paho 2020). This fact is directly related to the presence of infectious microorganisms (bacteria, fungi, protozoa and viruses) that cause damage to the host (Madigan *et al*. 2016; Tortora *et al*. 2016). These diseases are generally treated with antimicrobials, substances of natural origin (antibiotics) or synthetic (chemotherapeutics), which act on the microorganisms, inhibiting their growth or causing their death (Sáez-Llorens *et al*. 2000).

Despite the need to use antibiotic therapy to treat infections, there are risks to the health of patients related to the high toxicity of these drugs, some of which are nephrotoxic (Kaloyanides, 1994), hepatotoxic or ototoxic (Oun *et al*. 2018). They also have a narrow therapeutic window and high teratogenic potential (Kaleelullah;

Garugula, 2021). In addition to these drugs' toxicity, another rising problem is microbial resistance, in which these microorganisms develop mechanisms that inactivate the active principle responsible for the antimicrobial action, which may be related to the action of enzymes, changes in the binding sites, physical barriers or action of efflux pumps (Reygaert, 2018; Kember *et al*. 2022).

Due to these drawbacks of antimicrobial therapy, the need has arising to develop new bioactive substances by molecular alteration of existing drugs or the discovery of new substances with antimicrobial potential (Spellberg *et al.* 2015). Among these new substances, the standouts are crude plant-derived substances (isolated by extractive methods) or substances that actively participate in green synthesis processes (Galie *et al*. 2018).

The effects of active ingredients of plant origin can vary according to the extraction method used, with emphasis on essential oils, aqueous extracts and ethanolic extracts. These methods are responsible obtaining various chemical compounds from the secondary metabolism of plants (Wallace, 2004). Secondary metabolites have various therapeutic activities, such as antimicrobial and antioxidant (Yang *et al*. 2018; Isah, 2019).

The encapsulation of these plant compounds in the form of an emulsion has strategic advantages by improving kinetic stability, preserving organoleptic characteristics, and enhancing penetration power, thus enhancing the desired effect (Chinnaiyan *et al*. 2022; Sahu *et al.* 2018). In addition, they promote greater bioavailability, increase solubility in water of poorly soluble substances and allow their controlled release (Karim *et al*. 2022).

Therefore, we carried out a bibliographic survey of nanoemulsions produced from active ingredients of plant origin, such as essential oils and extracts, with antimicrobial potential, focusing on antibacterial, antifungal and antiviral activities. The results can contribute to new studies to identify efficient nanoemulsions that can be applied to treat infectious diseases. The information reported here fills in the gaps in knowledge and makes these substances more readily available for future applications in the field of health, thus overcoming the limitations of conventional antimicrobials.

The bibliographic survey was carried out between June and November 2022, in the databases Google Scholar (<https://scholar.google.com.br>), PUBMED (<https://pubmed.ncbi.nlm. nih.gov/>), SciElo (<https://www.scielo.org/>), Science Direct (<https://www.sciencedirect.com/>), Scopus® (<https://www. scopus.com/>), LILACS (<https://lilacs.bvsalud.org/>) and BDTD (<https://bdtd.ibict.br/>). To search for articles, keywords were used that were classified from the Health Sciences Descriptors (<https://decs.bvsalud.org/>): "Nanoemulsion", "Polymeric Nanoparticles", "Lipid Nanoparticles", "Biological Products", "Anti-Infective Agents", "Anti-Bacterial Agents", "Antifungal Agents" and "Antiviral Agents", for sample refinement. Articles that addressed the topic in question, in Portuguese or English, published in journals present in the platforms mentioned above between 2012 to 2022 were selected for reading in full.

2 DEVELOPMENT

2.1 Natural products of plant origin

Extracts, isolates and oils extracted from natural sources are widely used for biomedical purposes, since many of them have antimicrobial properties (Boire *et al*. 2013; Samber *et al*. 2015; Mostafa *et al.* 2018; D'agostino *et al*. 2019). Although natural products have generally presented good results for application in health care, their use faces some limiting factors, such as sensitivity to physical changes, since they are vulnerable to heat, humidity and oxygen. Among the resulting problems are hydrolysis and oxidation reactions, causing structural changes (Bhargava *et al.* 2015; Ghani *et al*. 2018; Bedoya-Serna *et al*. 2018).

Therefore, they need greater care in their storage, packaging and transport, to assure there are no changes in their properties. In order to protect bioactive compounds, nanotechnology can be applied, with benefits such as bioavailability, protection against degradation, increased apparent solubility, and better physical and chemical biocompatibility of the active principle, thus enhancing the pharmacological action and protecting against toxicity (Rao; Khanum, 2016; Bazana *et al*. 2019).

Nanoencapsulated bioactive compounds offer various advantages, such as increased physicochemical stability, better antimicrobial activity, and minimization of side effects (Herculano *et al*. 2015; Donsi; Ferrari, 2016).

Encapsulation is a technique widely used in the pharmaceutical, chemical, food and biomedical sectors, in order to promote protection and make products of natural origin more manageable in formulations. Among the encapsulation techniques, the formation of nanoemulsions stands out for the production of drugs, by providing significant protection of these bioactive compounds (Bhargava *et al*. 2015; Ghani *et al*. 2018).

2.2 Nanoemulsions

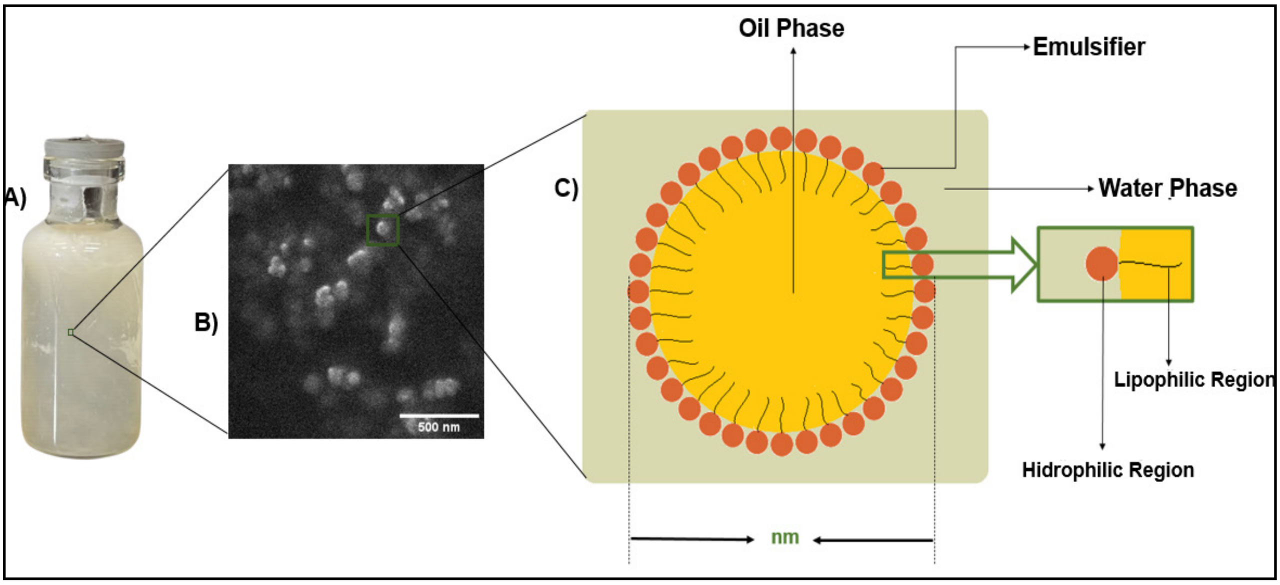
Nanoemulsions are dispersions of two immiscible liquids stabilized by a surfactant, where the size of the dispersed droplets is on a nanometric scale (20 to 500 nm). A nanoemulsion's transparency is directly related to the diameter of the dispersed droplets (translucent < » 200 nm > milky) (Quintão *et al*. 2013; Nascimento *et al*. 2020). Figure 1 represents the behavior of three nanoemulsions with different diameters of dispersed oily particles.

Figure 1 – Nanoemulsions and their behavior against the different diameters of their particles

Source: Authors' private collection (February 2023)

Nanoemulsions are classified as water-in-oil (W/O) or oil-in-water (O/W), depending on the hydrophilicity or lipophilicity of the dispersing medium (Wang *et al*. 2007). The surfactant acts as a stability barrier of nanoemulsions, characterized as an amphiphilic compound that is positioned between the two phases of the emulsion (W/O or O/W), creating an interfacial film that stabilizes the system (Kumar; Mandal, 2018). Figure 2 represents the layout of an O/W nanoemulsion system with the structure of each component, where it is possible to observe the aqueous phase, oil phase and emulsifying agent.

Figure 2 – Representative schematic of oil-in-water nanoemulsion. A) Macroscopic view of nanoemulsion (O/W); B) Nanoemulsion scanning eletron microscopy; C) Schematic representation of a micelle, containing the oil phase inside, surrounded by the surfactant



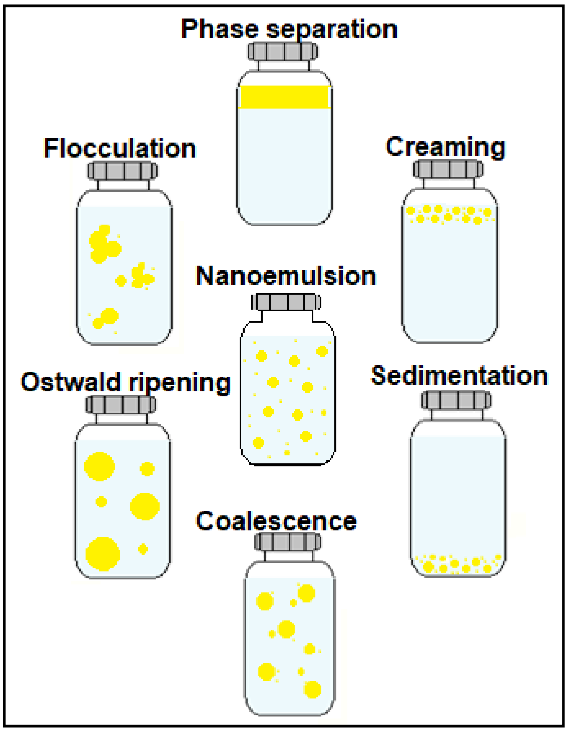
Source: Authors' private collection (February 2023).

The addition of texture modifiers such as polymeric matrices of natural origin to the aqueous phase has often been used to improve the stability of nanoemulsions, since they have surfactant properties, thus possessing emulsifying and thickening capacity. They also coat the individual droplets, reducing their movement and avoiding the destabilization of emulsions and nanoemulsions due to the decrease of the gravitational movement of the oil droplets. This delays or prevents the droplets' coalescence due to the increased viscosity of the aqueous phase (Guerra-Rosas *et al*. 2016; Maphosa; Jideani, 2018).

Emulsifiers or surfactants are fundamental to prevent the aggregation of nanoparticles, even after prolonged storage, by promoting the physicochemical stability of the nanoemulsion (Surassmo *et al*. 2010). Surfactants are amphiphilic substances and have a polar (hydrophilic) and a nonpolar (lipophilic) region, an ideal characteristic for the formation of O/W or W/O nanoparticles (Botelho *et al.* 2018).

Nanoemulsions have good stability of suspended nanoparticles, and the appearance of these systems is strongly related to the size of the formed particles (Weiss *et al*. 2009). The physical destabilization of emulsions is related to the spontaneous tendency to occupy the minimum interfacial space between their immiscible phases (Anton *et al*. 2008). Figure 3 shows the possible types of physicochemical instabilities related to nanoemulsion systems.

Figure 3 – Representative schematic of nanoemulsion instability



Source: Authors' private collection (February 2023)

Among the destabilization processes, creaming stands out. It is more likely to occur in O/W nanoemulsions, while sedimentation is more prevalent in W/O nanoemulsions (Zhang; Mcclements, 2018). Creaming is the formation of a creamy layer on the surface of the emulsion, which occurs due to the difference in density of the nanoemulsion components and the presence of forces external to the system, such as gravitational and centrifugal forces (Reddy *et al.* 1981; Rabinovich *et al*. 2004). In both sedimentation and creaming, the difference in the density of the materials and their low solubility in an aqueous medium occur (Tadros, 2006).

Coalescence, flocculation and Ostwald ripening occur due to partial solubilization of the oil phase in the aqueous phase, thus forming larger oil droplets dispersed in the system, which can lead to total phase separation. Flocculation can also be understood as the aggregation between the oil droplets, which consequently can lead to the formation of larger droplets, characterized as coalescence. Ostwald ripening, on the other hand, consists of an increase in the droplet size and a decrease in the total number of dispersed droplets in the system (Tadros, 1996; Franzol, Rezende, 2015).

2.3 Antimicrobial potential of nanoemulsions produced with plant-based bioactive e compounds

The nanoemulsions synthesized with different essential oils and plant extracts have been tested *in vitro* against different microorganisms of medical importance, such as bacteria, viruses and fungi, as shown in Table 1. It summarizes the main reported findings regarding the active plant components, dispersing medium, surfactant, particle size of the nanoemulsions and the species of microorganisms.

Table 1 – Nanoemulsions produced from different plant extracts with antibacterial, antifungal and antiviral properties, in addition to presenting the dispersant medium, surfactant, particle size and the potentiated effect of nanoemulsions

(Continue)

Plant Antimicrobial	Dispersant/ Surfactant	Size/ Potentiation	Antimicrobian Activity	Ref.
Allium sativum Oil	Water/ Tween 80	36,6 nm / -	*Staphylococcus aureus, Escherichia coli.*	Hassan; Mujtaba (2019)
Artemisia annua Oil	Water/ Tweem 80	130-160 nm / -	*E. coli, S. aureus, Bacillus subtilis, Pseudomonas aeruginosa, Streptococcus pyogenes, Schizosaccharomyces pombe, Candida albicans, C. tropicalis, C. dubliniensis, C. krusei.*	Das *et al.* (2020)
Azadirachta indica Oil	Water/ Tween 20	70 nm/ +	*Vibrio vulnificus*	Jerobin *et al*. (2015)
Cinnamomum spp. Oil	Water/ Tweem 80	2040-40,4 nm/ -	*E. coli, S. aureus*	Valizadeh *et al*. (2018)
Citrus limonum Oil	Water/ Tweem 80	181,5 nm/ +	*S. aureus, Klebsiella pneumoniae, Salmonella typhimurium, Enterococcus faecalis, Photobacterium damselae, Vibrio vulnificus, Proteus mirabilis, Serratia liquefaciens, Pseudomonas luteola*	Yazgan *et al.* (2019)
Citrus paradisi Oil	Water/ Tweem 80	173,9-0,105 nm/ +	*E. coli, S. aureus*	Wang *et al*. (2022)
Copaifera langsdorffii Oil	Water/ Tweem 80	641,3-29,98 nm/ -	*Paracoccidioides lutzii, P. brasiliensis, P. americana, P. restrepiensis*	Silva *et al.* (2020)
Croton cajucara Oil	Water/ Pluronic	45,56 nm/ -	*Absidia cylindrospora, Cunninghamella elegan, Mucor circinelloide, M. muceno, M. ramosíssimo, Rhizopus microsporu, R. oryzae, Syncephalastrum racemosum, C. albicans*	Azevedo *et al.* (2021)
Cymbopogon martini Oil	Water/ Tween 80	118-12 nm/ +	*E. faecalis*	Marinkovic *et al.* (2022)

(+)Enhanced antimicrobial effect of plant products in the form of nanoemulsions; (-)Effects not potentiated or indifferent in the form of nanoemulsion.

Source: Authors' (February 2023)

Table 1 – Nanoemulsions produced from different plant extracts with antibacterial, antifungal and antiviral properties, in addition to presenting the dispersant medium, surfactant, particle size and the potentiated effect of nanoemulsions

(Continue)

Plant Antimicrobial	Dispersant/ Surfactant	Size/ Potentiation	Antimicrobian Activity	Ref.
Eucalipto globulus Oil	Sorbitan monooleate/ Tween 80	100 nm/ -	*P. aeruginosa, C. albicans, C. tropicalis, C. glabrata*	Quatrin *et al.* (2017)
Jasminum humile L. Oil Jasminum grandiflorum L. Oil	Water/ Tween 80	12-8 nm/ -	*HAV* (Vírus Hepatite A), HSV (Herpes Vírus)	Mansour *et al.* (2022)
Lippia sidoides Cham Oil	Compritol 888/ Sodium Odecyl Sulfate	445,5-213,1/ +	*Candida auris*	Baldim *et al.* (2022)
Mauritia flexuosa Lf. Total Oil	Water/ Tween 80	270-196 nm/ -	*E. coli*	Leão *et al.* (2019)
Melaleuca alternifólia Oil	Water/ Tween 80	500-100 nm/ -	*E. coli*	Wei *et al.* (2022)
Mentha pulegium Oil	Water/ Tween 80	125 nm/ -	*E. coli, S. typhi, S. aureus, Listeria monocytogenes*	Damani *et al.* (2022)
Mentha spicata L. Oil	Water/ Tween 80	51,46 nm/ +	*S. typhimurium, S. aureus, E. coli, Bacillus cereus, L. monocytogenes*	Zamaniahari *et al.* (2022)
Poiretia latifólia Oil	Water/ Tween 80	-	*C. albicans, Candida krusei, C. tropicalis, C. glabrata, M. canis, Microsporum gypseum, T. rubrum, T. mentagrophyte*	Paim *et al.* (2018)
Satureja hortensis Oil	Water/ Tween 80	219 nm/ -	*K. pneumoniae, P. aeruginosa, Serratia marcencens, E. coli, S. typhi, S. aureus, L. monocytogenes, Staphylococcus haemolyticus*	Maccelli *et al.* (2020)
Syzygium aromaticum Oil	Water/ Tween 80	-	*A. niger, Colletotrichum gloeosporioides, Penicillium chrysogenum.*	Lima *et al.* (2021)
Stenachaenium megapotamicum Oil	Water/ Tween 80	210 nm/ +	*Epidermophyton floccosum, Scytalidium dimidiatum, T. rubrum*	Danielli *et al.* (2013)

(+)Enhanced antimicrobial effect of plant products in the form of nanoemulsions; (-)Effects not potentiated or indifferent in the form of nanoemulsion.

Source: Authors' (February 2023)

Table 1 – Nanoemulsions produced from different plant extracts with antibacterial, antifungal and antiviral properties, in addition to presenting the dispersant medium, surfactant, particle size and the potentiated effect of nanoemulsions

(Continue)

Plant Antimicrobial	Dispersant/ Surfactant	Size/ Potentiation	Antimicrobian Activity	Ref.
Thymus vulgaris Oil	Water/ Tween 80	127 nm/ +	*C. albicans, C. glabrata, Candida parapsilosis, A. fumigatus, T. tonsurans, T. rubrum, T. mentagrophytes, M. canis* *Staphylococcus* sp., *Enterococcus* sp., *Escherichia sp., Pseudomonas* sp.	Moazeni *et al.* (2021) Sienkiewicz *et al*. (2012)
Myrtus commnis L. Oil	Water/ Tween 80	179 nm/ +	*E. coli, S. aureus*	Roozitalab *et al*. (2022)
Matricaria chamomilla L. Oil	Water/ Tween 80	20 nm/ +	*E. coli, P. aeruginosa, B. subtilis, S. aureus, S. pyogenes, S. pombe, C. albicans, C. tropicalis*	Das *et al*. (2019)
Capsicum annum L.Ethanol Extract	Water/ Tweem 80	-	*E. coli, S. aureus, C. albicans, Aspergillus niger.*	El-Naggar *et al.* (2020)
Cuphea ígnea Ethanol Extract	Water/ Tween 80	119 nm/ +	*SARS CoV-2 (COVID-19)*	Mahmoud *et al.* (2021)
Curcuma spp. Extract	Water/ Cremophor RH40	40 nm/ +	*DENG-1, DENG-2, DENG-3, DENG-4* (DENGUE VÍRUS)	Nabila *et al***.** (2020)
Pimpinella anisum Oil	Water/ Tween 80	117-275 nm/ +	*E. coli, L. monocytogenes*	Topuz *et al*. (2016)
Pimpinella anisum Ethanol Extract	Water/ Tween 80	400 nm/ +	*S. aureus, B. cereus, L. monocytogenes, E. coli, S. typhimurium, P. aeruginosa, Yersinia enterocolitica*	Ghazy *et al*. (2021)
Ginkgo biloba Ethanol Extract	Water/ Tween 80	97 nm/ +	H3N2 (Vírus influenza), HBV (Hepatitis B vírus)	Wang *et al***.** (2015)

(+)Enhanced antimicrobial effect of plant products in the form of nanoemulsions; (-)Effects not potentiated or indifferent in the form of nanoemulsion.

Source: Authors' (February 2023)

Table 1 – Nanoemulsions produced from different plant extracts with antibacterial, antifungal and antiviral properties, in addition to presenting the dispersant medium, surfactant, particle size and the potentiated effect of nanoemulsions

(Conclusion)

Plant Antimicrobial	Dispersant/ Surfactant	Size/ Potentiation	Antimicrobian Activity	Ref.
Coriadrum sativum Oil	Chitosan/ Tween 80	80-57 nm/ +	*A. Niger, Aspergillus fumigatus, A. sydowii, A. repens, A. versicolor, A. luchuensis, Alternaria alternata, Penicillium italicum, P. crysogenum, P. spnulosum, Mycelia sterilia, Clasoaporium herbarum, Fusarium poae, F. oxysporum.*	Das *et al*. (2019)
Eucalipto citriodora Oil	Chitosan/ Tween 80	1271-388 nm/ +	*S. aureus, S. typhimurium*	Abreu *et al*. (2020)
Ocimum gratissimum Linn. Oil	Cashew gum/ Tween 80	500-10 nm/ +	*E. coli, S. aureus, Salmonella enterica, Mycobacterium smegmatis, Mycobacterium bovis,*	Okonkwo *et al*. (2020)
Psidium guajava L.Oil	Chitosan/ Tween 80	96-40 nm/ +	*K. pneumoniae*	Zhang *et al*. (2020)
Phyllanthus niruri Methanolic Extract	Sodium Alginate/ Tween 80	192 nm/ +	*E. coli, K. pneumonia, S. aureus. S. typhimurium, Streptococcus mutans, B. subtilis, Trichophyton rubrum, Trichophyton mentagrophytes.*	Pathania *et al*. (2022)

(+)Enhanced antimicrobial effect of plant products in the form of nanoemulsions; (-)Effects not potentiated or indifferent in the form of nanoemulsion.

Source: Authors' (February 2023)

Among the studies analyzed in this review, 91.34% involved nanoemulsions produced with water as the aqueous phase, while the remaining 8.66% involved natural polymer matrices, with chitosan being most prevalent in the formulations. Among the hydrophilic surfactants, Tween 80 is the predominant one, due to its excellent solubility of essential oils and water miscibility. Among the most frequent natural products, essential oils stood out (91.34%), although ethanolic and hydroalcoholic extracts (8.66%) were also observed as active principles in some formulations.

Essential oils are aromatic compounds of natural origin with recognized biological activities. They are used as flavoring additives in foods and stabilizers in cosmetics. Their use as medicinal agents is variously due to their insecticidal, antioxidant, anti-inflammatory, anti-allergic and anticancer activities. Many essential oils also have antibacterial, antiviral and antifungal activities, stimulating their application also as natural antimicrobials in foods and beverages (Donsì; Ferrari, 2016).

Over the years, a plethora of research has shown the potent *in vitro* antimicrobial activity of various essential oils and their constituents against a wide range of microorganisms. However, as discussed earlier, the use of essential oils in biomedical systems is challenging due to their low stability and sensitivity to physical changes, since they are highly vulnerable to heat, moisture and oxygen. These problems can be overcome by encapsulating essential oils in suitable delivery systems, helping to improve their stability and biological activity (Bhargava *et al.* 2015; Ghani *et al*. 2018; Bedoya-Serna *et al*. 2018).

Research has shown that nanoemulsion formulations containing essential oil of *Mentha pulegium* (pennyroyal) (Damani *et al.* 2022), *Capsicum annum* L. (pepper) (El-Naggar *et al.* 2020), *Myrtus communis* L. (myrtle) (Roozitalab *et al.* 2022), *Allium sativum* (garlic) (Hassan; Mujtaba, 2019), *Cinnamomum* spp. (cinnamon) (Valizadeh *et al*. 2018) and *Citrus paradisi* (grapefruit) (Wang *et al.* 2021) have shown antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli*. It is important to note that the authors reported that the nanoemulsions based on the essential oils of *M. pulegium, C. annum, M. communis, A. sativum* and *Cinnamonum* spp. showed no enhancement effect in comparison with the free form of essential oils in antibacterial tests. In contrast, the nanoemulsion based on the essential oil of *C. paradisi* had a significantly lower minimum inhibitory concentration (MIC) than the free essential oil. In this respect, many reports have shown that the conversion of spice extracts or essential oils into nanoemulsions greatly improves their antibacterial activity, presumably because the small lipid droplets interact better with microbial cells.

In this respect, it is relevant to highlight the research data of Zamaniahari *et al.* (2022), when investigating the antimicrobial effect of *Mentha spicata* (mint) against pathogens of medical importance. The researchers found that the MIC of the free essential oil was greater than that of the nanoemulsion against *S. typhimurium*, with concentrations of 6 mg/mL of the essential oil in free form and 2 mg/mL in nanoemulsion form. They also reported similar results for *S. aureus* (5mg/mL vs. 2mg/mL), *E. coli* (6mg/mL vs. 2mg/mL), *B. cereus* (4mg/mL vs. 2mg/mL) and *Listeria monocytogenes* (5mg/mL vs. 1mg/mL), respectively. The authors further stated that the bacterial cells were greatly disintegrated and that levels of cell membrane damage were caused by the nanoencapsulated oil against all bacterial species in this study.

Wei *et al*. (2022) analyzed the antimicrobial effects of nanoemulsions carried with the essential oil of *Melaleuca alternifolia* (melaleuca) and conjugated with antibiotics against six clinical strains of multiresistant *E. coli.* They observed, curiously, that the antibacterial activity of unblended nanoemulsion showed similar results for all multidrug resistant strains of *E. coli* and the reference strain (*E. coli* ATCC 25922) with MIC values of 1 mg/mL. The results of the synergism assays of the nanoemulsion combined with the standard drug had synergy with several antibiotics against multidrug-resistant *E. coli* strains. The researchers also stated that the nanoemulsion combined with doxycycline exhibited bactericidal activity, and that usually bactericidal agents can be clinically recommended instead of bacteriostatic agents, since they can reduce the development of resistance and the spread of infection.

Nanoemulsions prepared with the essential oil of *Artemisia annua* (chamomile), using Tween 80 as surfactant agent, had particles with an average diameter of 160 nm. These were tested to characterize their antimicrobial activity in gram-positive and gram-negative bacteria, as well as in *Candida* species. The nanoemulsions exhibited notable antibacterial and antifungal activities against various microbial strains, with MICs ranging from 1.42 ± 0.64 μg/mL to 3.15 ± 0.16 μg/mL against bacterial strains and from 3.62 ± 0.65 μg/mL to 4.29 ± 0.82 μg/mL against yeasts (Das *et al.,* 2020). They also observed antimicrobial effects of nanoemulsions based on essential oil of *Citrus limonum* (lemon), Tween 80 and water, which generated nanoemulsions with a mean particle diameter of 181.5 nm. These had minimum inhibitory concentrations ranging from 3,125 to 25 mg/mL against the bacteria *S. aureus*, *Klebsiella pneumoniae*, *Salmonella typhimurium*, *Enterococcus faecalis*, *Photobacterium damselae*, V*ibrio vulnificus*, *Proteus mirabilis*, *Serratia liquefacien* and *Pseudomonas luteola* (Yazgan *et al*. 2019).

Some authors have suggested that the size of the droplets forming the nanoemulsion can affect the desired biological effect, among them the antimicrobial activity, and that this effect depends not only on the individual chemical components used in the formulations, but also on the system's structure (Baker *et al*. 2003).

Marinkovic *et al.* (2022), investigating the activity against *E. faecalis* of nanoemulsions composed of the essential oil of *C. martinii* (palmarosa) in different concentrations, observed that the most and least efficient nanoemulsions were those with concentrations of 6 mg/mL and 2.5 mg/mL, which had respective droplet sizes of 87 nm and MIC of 0.37 mg/mL versus droplets of 12 nm in diameter and MIC of 2.45 mg/mL. Thus, they noted that the size of the particles was linked to the amount of essential oil used in the formulations, and the antimicrobial effectiveness was not always linked to smaller particle size.

Nanoemulsions with antifungal activity have also been analyzed. Silva *et al.* (2020) evaluated the antifungal activity of nanoemulsions of the essential oil of *Copaifera langsdorffii* (copaíba), using Tween 80 and water, resulting in nanoparticles with an average diameter ranging between 641.3 and 29.98 nm, which showed inhibitory activity against the species *Paracoccidioides lutzii*, *P. brasiliensis*, *P. americana* and *P. restrepiensis*. The nanoemulsion presented MIC value of 125 μg/mL for all studied species. The encapsulation of *Coriandrum sativum* (coriander) essential oil in a chitosan nano-matrix, with an encapsulated nanoparticle size of 57–80 nm, was studied against the fungal species *Aspergillus spp.*, *Alternaria alternata*, *Penicillium* spp., *Mycelia sterilia*, *Clasoaporium herbarum* and *Fusarium* spp., and the oil-encapsulated nanoemulsion showed antifungal efficacy by hampering the biosynthesis of ergosterol, the main component of the fungal cell membrane, by providing fluidity and permeability to the membrane (Das *et al.* 2019).

The antifungal activity of nanoemulsions containing the essential oil of *Croton cajucara* (sacaca), using pluronic as surfactant, generating droplets with an average size of 40 nm, was evaluated against the fungal species *Absidia cylindrospora, Cunninghamella elegan, Mucor* spp, *Rhizopus* spp, *Syncephalastrum racemosum* and *C. albicans*, with minimum inhibitory concentrations ranging from 12.21 to 195.31 μg/mL against the studied fungal species (Azevedo *et al.* 2021).

The essential oil of *Lippia sidoides* (alecrim pepper) was loaded into lipid-based systems, such as oleic acid along with compritol and sodium dodecyl sulfate. The authors determined a particle size range of 213.1-445.5 nm. Lipid nanoparticles loaded with the essential oil of *L. sidoides* showed minimum inhibitory concentrations between 281 and 563 μg/mL against multiresistant *C. auris* (Baldim *et al*. 2022).

The potential has been studied of nanoemulsions synthesized from the ethanolic extract of *Cuphea ignea* (flor-de-santo-antonio), in addition to formulations with the essential oil of *Jasminum humile* L. (jasmine) and ethanolic extract of *Ginkgo biloba*, with findings of antiviral activity against important viruses that cause human infections: SARS CoV-2 (Covid-19) (Mahmoud *et al.* 2021), HAV (hepatitis A virus), HSV (herpes virus) (Mansour *et al*. 2022), H3N2 (influenza virus) and HBV (hepatitis B virus) (Wang *et al.* 2015).

The investigation of physicochemical properties and the carrying capacity of nanoparticle emulsions has led to successful antiviral applications administered by different routes in several *in vitro* and *in vivo* studies. A recent *in vitro* study showed that the cationic particles of a nanoemulsion loaded with *Curcumin* spp. (golden ginger) increased the antiviral activity of *Curcumin* spp. against dengue virus serotypes and improved biocompatibility with target cells (Nabila *et al*. 2020). The cationic surfaces of the particles facilitated binding to negatively charged infected and uninfected cells, improving load delivery and therapeutic efficiency.

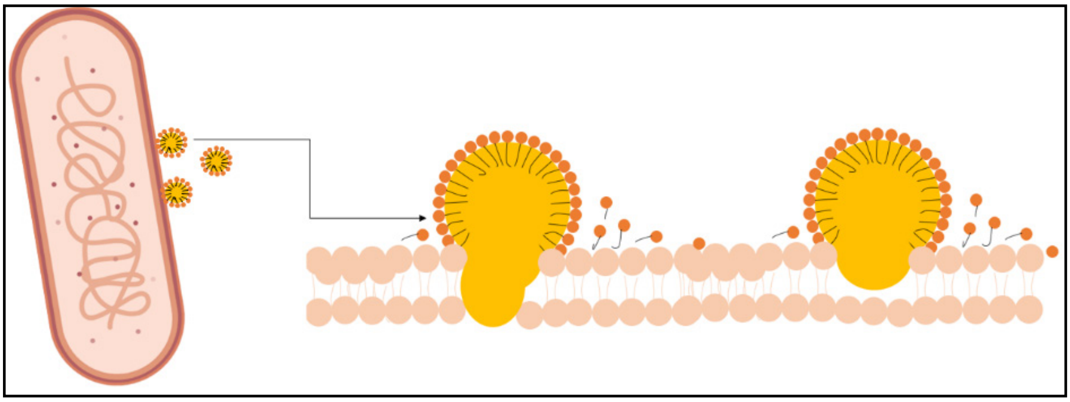
Traditional antiviral drugs are limited by their low solubility, rapid clearance profiles, low bioavailability, nonspecific targeting, and high toxicity (Shah, 2021). Nanoemulsions can overcome these limitations because these systems are adjustable, with versatile oil cores, improved encapsulation capacity, easy surface modification and flexible dosage forms (Delshadi *et al.* 2021).

2.4 Nanoemulsions as carriers of natural products and their mechanism of antimicrobial action

Most natural products have low solubility, posing one of the biggest obstacles to the development of usable drugs, such as antimicrobials. This causes extremely low bioavailability, high dosage level and low selectivity (Nielsen *et al.* 2004). For an antimicrobial compound to be effective, it must interact with the specific target and have minimal interactions with unwanted targets, to increase its potency and reduce adverse effects.

Several studies have sought to avoid these effects by encapsulating antimicrobials in colloidal delivery systems, such as nanoemulsions (Weiss *et al.* 2009; Acevedo-Fani *et al*. 2017b; Khaneghah *et al.* 2018). Encapsulation involves trapping substances within small micelles to enable their antimicrobial effect (El-Kader; Abu Hashish, 2020). Figure 4 represents the interaction of nanoparticles of a nanoemulsion with the microbial cell membrane through simple diffusion.

Figure 4 – Scheme of delivery of nanoemulsion nanoparticles to the microbial cell membrane



Source: Authors' private collection (February 2023)

The literature suggests that the internalization of substances present in nanoparticles into microbial cells occurs through simple diffusion, a process that is caused by the passive movement of nanoparticles from a more concentrated place to a less concentrated one, without energy expenditure (Harun *et al.* 2018; To *et al*. 2023).

Their use as drug carriers is promising because it allows the controlled release of an active principle at a specific place in the body for a longer period of time than conventional administration, maintaining the proper therapeutic concentration and avoiding the need for repeated administration (Park *et al*. 1999; Kumar, 2000; Kshisagar *et al.* 2005). Figure 5 shows a comparison of plasma drug levels achieved in conventional therapeutic administration and via controlled release administration.

The benefits include increased selectivity and reduced side effects (Kshisagar, 2005; Wang *et al.* 2008; Bedin *et al*. 2011), increased apparent solubility, biocompatibility and protection against physical and chemical degradation of the active principle, inducing increased pharmacological action and protection against toxicity, increased dispersibility in water, resistance to environmental conditions, and antimicrobial potency (Ray *et al*. 2016; Ferreira; Nunes, 2019).

The hydrophobicity of dispersants and surfactants together with the phytochemicals present in essential oils collectively contribute to the antimicrobial activities of nanoemulsions. These activities occur due to action on one or more binding targets in the microbial cell. Knowing the target of action is of fundamental importance to ensure that nanoemulsions have specificity for pathogens and that they will not bind to host cells causing unwanted effects.

Currently known antimicrobials act mainly on membrane and cell wall targets. In bacteria, the targets are inhibition of cell wall precursors, binding to ribosomes to prevent synthesis of essential proteins, inhibition of nucleic acid synthesis, inhibition of the metabolic pathway, and membrane disruption caused by inhibition of important cell membrane precursors (Purssel, 2019). In fungi, the most common mechanisms include inhibition of ergosterol biosynthesis (azole derivatives), inhibition of DNA replication and protein synthesis (5-fluorocytosine), binding to ergosterol present in the membrane creating pores that culminate in cell leakage (polyenes) and inhibition of the synthesis of 1,3-β-D-glucan, which constitutes the cell wall (echinocandins) (Ivanov *et al*. 2022).

Antifungal drugs usually have important cytotoxic effects due to the similarity of fungal and human cells (both are eukaryotic). Therefore, the search for compounds that have specific targets of action in fungal cells is a challenge.

Krishnamoorthy *et al*. (2021) presented evidence that a nanoemulsion inhibited the synthesis by *C. albicans* of chitin, an important polysaccharide that makes up the yeast wall. Microscopic images showed disruption of the yeast cell wall, probably caused by inhibition of cell wall polysaccharides. In turn, Pannu *et al*. (2009) reported that NB-002, a nanoemulsion with activity against filamentous fungi, dermatophytes and *C. albicans*, had a fungistatic effect, and microscopic images demonstrated that the compound caused rupture of the fungal wall of *T. rubrum*.

Similar to what occurs in fungi, in bacteria nanoemulsions cause membrane disruption. Several studies using micrographs obtained from scanning electron microscopy (SEM) and protein leak tests supported this evidence (Moghimi *et al*. 2016; Yang *et al*. 2022). This rupture causes irreversible damage to the bacterial membrane, culminating in cell lysis. This mechanism was observed in both gram-negative and gram-positive bacteria.

The physicochemical properties of surfactants influence the mechanism of action of nanoemulsions. In gram-negative bacteria, some surfactants can better translocate through the peptidoglycan outer membrane and accumulate in the inner membrane (Sharma *et al*. 2021). Cationic surfactants have better activity compared to nanoemulsions with anionic surfactants because this property provides an electrostatic interaction with the negative membrane of bacteria (Al-Adham *et al*. 2021).

3 CONCLUSIONS

Nanoemulsions loaded with essential oils and plant extracts from the different botanical species reported here showed *in vitro* antimicrobial activity against different microorganisms of medical importance, in addition to enhancing the antimicrobial effects of these bioproducts. Therefore, nanostructured antimicrobials with essential oils and plant extracts can be considered treatment options for microbial diseases. Due to their physicochemical properties, they will provide better delivery of natural products with good bioavailability, by reducing their toxicity and prolonging the useful life of natural antimicrobials, improving treatment of infectious human diseases.

However, more studies are needed regarding the methods and conditions for production of nanoemulsions, as well as their properties and safety, because of the limited understanding of their mechanisms and consequences on health. The consideration of all these factors is necessary for the production of nanoemulsions on an industrial scale, in turn for the development of products with better quality and safety and lower costs.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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