

NANOSTRUCTURED SYSTEMS CONTAINING ESSENTIAL OIL OF LAVENDER: CURRENT OVERVIEW AND FUTURE PERSPECTIVES

SISTEMAS NANOESTRUTURADOS CONTENDO ÓLEO ESSENCIAL DE LAVANDA: VISÃO ATUAL E PERSPECTIVAS FUTURAS

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ABSTRACT

The wide variety of aromatic plants and their use represent great economic value worldwide, due to the numerous therapeutic properties available. The *Lavandula* genus stands out in the world economy, mainly due to the production of essential oil, which can be extracted from its leaves or flowers, being widely used in the cosmetic, food and pharmaceutical industries. However, the therapeutic properties of this essential oil can be impaired due to its low aqueous solubility, high volatility and low physical-chemical stability. The association of essential oil with nanostructured systems can be a promising and efficient alternative to overcome these limitations, providing greater stability of the active compounds, protection against oxidation, photodegradation and thermal degradation processes, and thus, promoting a potential enhancement of efficiency. Thus, the objective of the study was to carry out a review of the literature about the available research that uses nanostructured systems to encapsulate the essential oil of different lavender species. The search was carried out in April 2020, in the electronic databases Web of Science, PubMed and ScienceDirect. The descriptors and keywords used were: nano *, lavender, *Lavandula*, followed by the Boolean operators AND; OR, and the year of publication of the articles was not defined. Eight articles were found that adequately met the inclusion criteria, which were published between the years 2017 to 2020. From the results found, it is believed that nanotechnology can be a promising alternative to protect the active compounds of lavender essential oil against factors that can impair their stability, as well as, guarantee or even increase their effectiveness, with the possibility of decreasing dose and consequently side effects.

Keywords: Essential oils; *Lavandula*; Nanotechnology; Natural products.

RESUMO

A grande variedade de plantas aromáticas e seu uso representam grande valor econômico mundial, devido às inúmeras propriedades terapêuticas disponíveis. O gênero Lavandula se destaca na economia mundial, principalmente, pela produção de óleo essencial, que pode ser extraído de suas folhas ou flores, sendo amplamente utilizado nas indústrias cosmética, alimentícia e farmacêutica. Entretanto, as propriedades terapêuticas desse óleo essencial podem ser prejudicadas devido à sua baixa solubilidade aquosa, alta volatilidade e baixa estabilidade físico-química. A associação de óleo essencial com sistemas nanoestruturados pode ser uma alternativa promissora e eficiente para superar essas limitações, proporcionando maior estabilidade dos compostos ativos, proteção contra processos de oxidação, fotodegradação e degradação térmica, promovendo assim um potencial aumento de eficiência. Dessa forma, o objetivo do estudo foi realizar uma revisão da literatura sobre as pesquisas disponíveis que utilizam sistemas nanoestruturados para encapsular o óleo essencial de diferentes espécies de lavanda. A busca foi realizada em abril de 2020,

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nas bases de dados eletrônicas Web of Science, PubMed e ScienceDirect. Os descritores e palavras-chave utilizados foram: nano *, lavender, Lavandula, seguidos dos operadores booleanos AND; OR, e não foi definido o ano de publicação dos artigos. Foram encontrados oito artigos que atenderam adequadamente aos critérios de inclusão, os quais foram publicados entre os anos de 2017 a 2020. Pelos resultados encontrados, acredita-se que a nanotecnologia pode ser uma alternativa promissora para proteger os compostos ativos do óleo essencial de lavanda contra fatores que podem prejudicar sua estabilidade, bem como, garantir ou mesmo aumentar sua eficácia, com possibilidade de diminuição da dose e conseqüentemente efeitos colaterais.

Palavras-chave: Óleos essenciais; Lavandula; Nanotecnologia; Produtos naturais.

INTRODUCTION

The use of plants and their active compounds in traditional medicine has been prescribed for decades for the treatment of various disorders and diseases (SILVA; FERNANDES, 2010; SHOKRI *et al.*, 2017). One of these promising natural compounds are essential oils (EOs), produced from the secondary metabolism of plants, and have different therapeutic properties, such as antibacterial, anti-fungal, antiviral, antioxidant, anticancer, immunomodulatory activities, in addition to analgesic and anti-inflammatory actions. inflammatory (BAKKALI *et al.*, 2008; BONA *et al.*, 2016). According to the International Organization for Standardization (ISO), the term “essential oil” is defined as a “product obtained from a natural raw material of vegetable origin, by steam distillation, by mechanical processes of the citrus fruit epicarp or by distillation. dry, after separation of the aqueous phase - if any - by physical processes” (ISO 9235, 2013), and to be used in the health area, they must comply with national pharmacopoeias (BILIA *et al.*, 2014).

EOs are volatile liquids, fat-soluble and soluble in organic solvents, with a density generally lower than that of water (BURT, 2004). They can be synthesized by all the organs of the plant, that is, buds, flowers, leaves, stems, branches, seeds, fruits, roots, wood or bark, and are stored in secretory cells, cavities, channels, epidermal cells or glandular trichomes (KAMATOU *et al.*, 2008; SELL, 2010). Its composition is directly related to planting conditions, altitude, soil, fertilization and rainfall volume (PROBST, 2012), in addition to the plant organ, age and stage of the vegetative cycle (ANGIONI *et al.*, 2006), factors that may present differences in composition in EOs in plants of the same species (PROBST, 2012).

They are characteristically formed by a mixture of dozens of complex and aromatic chemical compounds that are capable of attributing a great diversity of performance (CALO *et al.*, 2015). The components of EOs can be divided into two large groups: terpene components (alcohol, esters, acids, aldehydes, ketones, amines, epoxides and sulfides) and aromatic components (PALMEIRA-DE-OLIVEIRA *et al.*, 2009; CALO *et al.*, 2015).

Among the EO worldwide surveyed, highlight the genus of Lavandula, which belongs to the *Lamiacea* family and is prominent in the world economy, being used in the perfumery, cosmetics

(BOMBARDA *et al.*, 2008), food and pharmaceutical industries (TSURO *et al.*, 2000; CASSELLA; CASSELLA; SMITH, 2002; SILVEIRA *et al.*, 2012) due to their sedative, (LIN *et al.*, 2007), anxiolytic properties (LEHRNER *et al.*, 2005; CHEN *et al.*, 2015) analgesics (OLAPOUR *et al.*, 2013) and neuroprotective (WANG *et al.*, 2012). Among the most known species of *Lavandula* are *L. angustifolia* (also known as *L. officinalis*), *L. latifolia*, *L. stoechas*, *L. dentata*, and there is also the commercialization of hybrid forms (CUNHA *et al.*, 2003; LORENZINI; MATOS, 2008; TAKAHASHI *et al.*, 2011; WORONUK *et al.*, 2011), as well as in extract form, which has shown antibacterial activity (TEIXEIRA; CORREIA; VASCONCELOS, 2012), anticholinesterase inhibition and antioxidant capacity (FERREIRA *et al.*, 2006).

Despite all the characteristics and potentialities, EOs have some limitations, such as easy degradation of their constituents, due to oxidation, isomerization, cyclization or dehydrogenation reactions, triggered enzymatically or chemically (SCOTT, 2005), which can be influenced by conditions during processing and storage, after distillation and in the course of subsequent manipulation of the EO itself (SCHWEIGGERT; CARLE; SCHIEBER, 2007). In addition, these products have high volatility, and can easily decompose, due to direct exposure to heat, humidity, light or oxygen (TUREK, 2013).

As a way of protecting the active compounds against external factors, as well as guaranteeing their effectiveness, we highlight the association of EOs with nanometric structures, which due to their subcellular size can increase absorption mechanisms and, consequently, bioefficiency (BILIA, 2014; GONZÁLEZ *et al.*, 2014). There are several types of nanostructured systems, such as liposomes (CHATZIKLEANTHOUS *et al.*, 2020), nanoemulsions (ZHAO *et al.*, 2010; SHOKRI *et al.*, 2017) lipid nanoparticles (RASHED *et al.*, 2019), polymeric nanoparticles (FLORES *et al.*, 2019) and inorganic nanoparticles (KANWAR, 2012; PARVEEN; MISRA; SHOO, 2012).

The association of EOs with nanosystems seems to be efficient to control the release of active compounds, increase the physical stability of active substances, protect them from interactions with the environment, decrease volatility, reduce toxicity and thus, increase cellular absorption mechanisms (RAVI, 2000; BILIA *et al.*, 2014). The authors Ziani *et al.*, (2011) and Donsi *et al.*, (2011) believe that EOs incorporated in nanoemulsions promote an increase in permeability in the membrane, due to the increase in its surface area, which makes it possible to reduce the concentration of the constituents to obtain an equivalent or even greater effect than in conventional emulsions (LIANG *et al.*, 2012; SALVIA-TRUJILLO *et al.*, 2013).

Based on information from studies on the different and important effects provided by the lavender EO, as well as the possibility of increasing its stability and guaranteeing or enhancing its effect when associated with nanometric systems, it is necessary to search the current literature for studies that use nanotechnology as a way to improve the performance of lavender EO and allow its use in the clinic safely and effectively, which was the objective of the present study.

METHODOLOGY

This study is characterized as exploratory, of the literature review type. The search for the studies took place in April 2020, in the electronic databases Web of Science, PubMed, ScienceDirect. The keywords and keywords used were: nano*, lavender, *Lavandula*, followed by the Boolean AND operators; OR, the year of publication of the articles was not defined.

The selection of studies included in this review was carried out in three distinct stages. The first consisted of searching the selected databases, in the second step, a critical reading of the abstracts of the studies selected in the previous step was carried out, to confirm whether they met the inclusion criteria, and the third step consisted of a complete reading of the selected studies in the previous steps. All stages of the methodological quality analysis of the articles were carried out by two independent and blind evaluators.

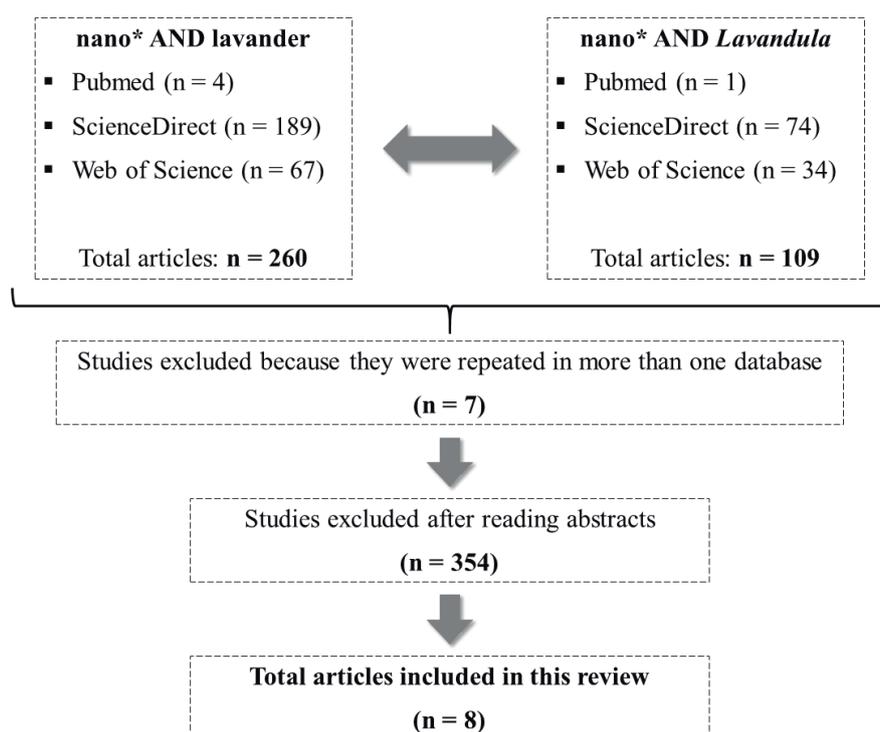
Full articles were included in this review, which addressed the use of nanostructured systems in the encapsulation of lavender EO. Literature review studies and pilot studies were excluded from the sample, as well as studies that used lavender EO in the same nanostructured system together with some active compound. The following characteristics of publications were recorded: year of publication, name of the author (s), nanocarrier, major component of the lavender EO and objective of the study.

RESULTS AND DISCUSSION

It is noteworthy that the objective of the study was to search the literature for research that used nanotechnology as a way to improve the functional performance only of the lavender OE, without any other associated compound, as explained previously in the inclusion criteria. In addition, it is noteworthy that other articles that used nanotechnology to encapsulate lavender in the form of extract were identified in the current literature (PEREIRA *et al.*, 2015), as well as studies that associated the lavender EO with other compounds, such as Silver (AgNPs) (BELOVA *et al.*, 2019; ELEMIKE *et al.*, 2017), gold (AuNPs) (JADCZAK *et al.*, 2019), clotrimazole (CARBONE *et al.*, 2019) and ferulic acid (CARBONE *et al.*, 2020).

Thus, the studies found in the present literature review that used nanotechnology as a way to improve the functional performance of only the lavender EO are shown in the flowchart below (Figure 1).

Figure 1 - Flowchart of research and analysis of articles.



The publications that comprised the sample of the present study were published between the years 2017 to 2020, and are shown in Table 1.

Table 1 - Studies included in the present literature review.

Author (s) (Year)	Nanocarrier	Species (majority compound)	Objective of the study
Shokri et al. (2017)	Nanoemulsion	<i>L. angustifolia</i> (1,8-cineol)	To investigate the antileishmaniasis effects of EO and nano-emulsions containing <i>L. angustifolia</i> , as well as, of EO and nanoemulsions containing <i>R. officinalis</i> in <i>L. major</i> .
Velmurugan et al. (2017)	Nanospheres	<i>L. angustifolia</i> (linalol)	Develop nanospheres containing <i>C. sinensis</i> EO, as well as nanospheres containing <i>L. angustifolia</i> EO and evaluate its effectiveness when they are infused into the leather.
Carbone et al. (2018)	Nanostructured lipid carriers (NLC)	<i>L. intermedia</i> (linalol)	Develop NLC as distribution systems for Mediterranean EOs, (<i>R. officinalis</i> L., <i>L. intermedia</i> , <i>O. vulgare subsp. Hirtum</i> and <i>T. capitatus</i>) developed separately.
Bayramzadeh et al. (2019)	Nanocapsules	<i>L. angustifolia</i> (acetato de linalil)	Synthesize nanocapsules containing <i>C. cyminum</i> EO and nanocapsules containing <i>L. angustifolia</i> EO, as well as to evaluate its toxicity by fumigation in contaminants of stored products.
Flores et al. (2019)	Nanocapsules	<i>L. dentata</i> (1,8-cineol)	Develop and validate an analytical method for simultaneous quantification of the main free and nanoencapsulated EO monoterpenes of <i>R. officinalis</i> and <i>L. dentata</i> and verify their antioxidant action.
Rashed et al. (2019)	Nanoemulsion	<i>L. angustifolia</i> (linalol)	Produce nanoemulsions of <i>L. angustifolia</i> EO and evaluate its functional properties.

Garzoli <i>et al.</i> (2020)	Nanoemulsion	<i>L. intermediaria</i> (linalol) and Hydrolate de <i>L. intermediaria</i> (1,8-cineol)	Develop nanoemulsions containing <i>L. intermediaria</i> EO and nanoemulsions containing <i>L. intermedia</i> hydrolate and evaluate their properties and effectiveness.
Rashed <i>et al.</i> (2020)	Nanoemulsion	<i>L. angustifolia</i> (linalol)	To evaluate the synergistic effects of amorphous starch modified by octenyl succinic anhydride (OSA-MS) and sunflower oil (RBD-SFO) in the manufacture of nanoemulsions containing <i>L. angustifolia</i> EO.

Source: Elaborated by the authors.

The lavender EO due to its biological properties and attractive aroma (KIVRAK, 2018) has been used in complementary medicine for many years, through aromatherapy, therapeutic massage (WELSH 1995), as an active ingredient for many pharmaceutical and cosmetic products (MUYIMA *et al.*, 2002), as well as in the food industry (PREEDY, 2015; KIVRAK, 2018). However, its effectiveness may be compromised due to its limited solubility in water and low physical-chemical stability (CARBONE *et al.*, 2018). Nanotechnology represents a viable and efficient alternative to overcome these inconveniences, as it can provide stability to the active compounds (MARTINS; KHALIL; MAINARDES, 2017), protection against oxidation (WORANUCH; YOKSAN, 2013), retention of volatile compounds and reduction of side effects (MISHRA; PATEL; TIWARI, 2010; WORANUCH; YOKSAN, 2013).

Flores *et al.* (2019) developed polymeric nanoparticles to encapsulate the EOs of *Rosmarinus officinalis* and *Lavandula dentata*, separately, as they argue for an efficient way to retain their antioxidant effects. They aimed to validate an analytical method by gas chromatography with a flame ionization detector (GC-FID) by direct injection for simultaneous quantification of the main free and nano-encapsulated oil monoterpenes of *R. officinalis* and *L. dentata* for future topical application as an antioxidant agent. The nanocapsules containing the EOs (225 mg) were prepared according to the nanoprecipitation method developed by Fessi *et al.*, (1989) and the Eudragit EPO was used as a polymer, because due to its cationic nature, it allows a greater interaction with the skin as a result of electrostatic interaction (SINGH *et al.*, 2015).

Major constituents of *R. officinalis* EO were identified as camphor (39.46%) and 1.8-cineol (14.63%), and *L. dentata* EO was 1.8-cineol (68.59 %) and β -pinene (11.53%). The average diameter of the nanoparticles was 226 nm, polydispersity index of 0.197 and zeta potential of 54 mV for nanocapsules containing *R. officinalis* and 235 nm, polydispersity index 0.214 and zeta potential 50 mV for nanocapsules containing *L. dentata* OE. Both formulations showed homogeneous size distribution and remained stable for 8 weeks at 25 ± 2 °C. The encapsulation efficiency was determined by GC-FID and presented values of 59% and 41% of the total EO of *R. officinalis* and *L. dentata*, respectively.

The authors believe they have developed a simple, repeatable and reproducible method, being an analytical tool for the simultaneous quantification of the main components of EO loaded in an

Eudragit EPO nanocapsule, as well as a monitoring tool for biological assays. However, it is important to emphasize that the encapsulation of a complex natural product, such as OE, is a process that represents greater difficulty compared to the encapsulation of a drug and requires studies to optimize the encapsulation of the EO (EPHREM *et al.*, 2014).

Shokri *et al.* (2017) opted to develop nanoemulsions containing *Lavandula angustifolia* EO and nanoemulsions containing *Rosemary officinalis* EO, and investigated the anti-leishmaniasis effects against *Leishmania major* of oils in the free form, as well as in the nanoemulsified form. The minimum concentration required to inhibit 50% (IC₅₀) values were calculated in the promastigote and amastigote stages in the macrophage (J774) compared to Meglumine Antimoniate (MA), which was used as a positive control. In addition, the effects of cytotoxicity on macrophages (J774) of free and nanoemulsified EOs were evaluated. The oil-in-water (o/w) nanoemulsions were prepared using EO (1% w/w) and produced using the Ultrasound Cavitation Homogenization technique (Sonicator 4000).

Both nanoemulsions were stable for 6 months at temperatures of 4 °C and 25 °C. The average droplet diameter, polydispersity index and zeta potential of the nanoemulsion containing *L. angustifolia* EO was 104.2 nm, 0.312, -15.8 mV and the nanoemulsion containing *R. officinalis* EO was 98.7 nm, 0.298, - 17.3 mV. The main constituents of the EO of *L. angustifolia* were 1,8-cineol (22.29%), linalool (11.22%) and camphor (7.88%), and the EO of *R. officinalis* were 1,8- cineole (15.96%), α-pinene (13.38%) and camphor (7.87%).

The *in vitro* anti-leishmanial activities of the nanoemulsions of *L. angustifolia* and *R. officinalis*, as well as of EOs, were investigated against the standard strain of *L. major*. For the free and nanoemulsified *L. angustifolia* EO, the effective concentration was reached with IC₅₀ = 0.11 μL/mL. For the free *R. officinalis* EO the concentration was effective with IC₅₀ = 0.26 uL/mL and when nanoemulsified it presented IC₅₀ = 0.08 μL/mL. In addition, during the amastigote stage assay, *L. angustifolia* and *R. officinalis* EOs and both nanoemulsions were effective at 0.12 μL/mL and 0.06 μL/mL, respectively, in infected macrophages. The results were compared with MA, with IC₅₀ = 197 mg/mL and demonstrated that the EOs and the nanoemulsions of *L. angustifolia* and *R. officinalis* are more effective than the MA. In addition, the cytotoxicity assay employing macrophages did not reveal toxicity in the host cells at the mentioned concentrations of IC₅₀.

The nanoemulsions of both EOs were more effective than EOs in free form, both in infected macrophages and in the amastigote stage. However, there was a small difference in the concentration of 0.25 μL/mL, where the *R. officinalis* nanoemulsion was more effective than *L. angustifolia* in this concentration (13.33% versus 37.33%). Thus, the study authors believe that these formulations can be used in combination therapy with MA to reduce healing time, but recommend further investigations to evaluate the effect of these medicinal plants in *in vivo* models.

Nanoemulsions containing *L. angustifolia* EO were also developed in the study by Rashed *et al.* (2019) with the aim of improving the functional technical performance, as well as the sustainable

applications. The authors investigated the antibacterial activity of EO *L. angustifolia* in free and nano-emulsified form, against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram-negative bacteria (*Escherichia coli* and *Salmonella enterica*). The formulations were produced using a High Speed Homogenizer (Ultra Turrax) and refined, bleached and deodorized sunflower oil (RBDSFo) was used as a type of unsaturated lipid vehicle, and as a biodegradable wall material, whey protein (WPI) was used. The *L. angustifolia* EO was used in the proportions of 1: 0.5, 1: 1, 1: 1.5 and 1: 2, (w/w). The encapsulation efficiency (EE) was determined by GC-FID and the oil was extracted by Clevenger distillation.

The average droplet diameter was 129 nm, the polydispersity index was 0.151 and the zeta potential - 42 mV. The formulation showed a slight change in the droplet size, polydispersity index and zeta potential after 28 days of storage at ambient temperature. The nanoemulsion was stable against the aggregation and coalescence processes in thermal destabilizing stresses similar to those that can be exposed in commercial storage conditions (5, 25 and 45 °C) at neutral pH, and presented 95.53% efficiency of encapsulation. The main constituents of the *L. angustifolia* EO were linalool (31.01%), linalyl anthranilate (15.60%) and lavandulil acetate (15.01%).

The results obtained in the study demonstrated that the thermal stability of the *L. angustifolia* EO can be improved through the process of encapsulation in edible biopolymers using WPI and BDSFo. In addition, the *L. angustifolia* EO nanoemulsion demonstrated high efficacy in inhibiting gram-positive and negative pathogenic bacteria compared to free *L. angustifolia* oil. Similar data were also found in the studies by Aytac *et al.* (2017a, b) and Lyu *et al.* (2017), as well as in the study by Mazarei and Rafati (2018). The antibacterial potential is probably attributed to the constituent linalool (ZHOU *et al.*, 2016). Thus, the authors believe that nanoemulsions containing *L. angustifolia* EO demonstrate a great potential to be used in order to improve the release of bioactive components, as well as enhance the activity against pathogenic bacteria.

The same research group, Rashed *et al.* (2020), continued to develop nanoemulsions containing *L. angustifolia* EO, however, with the objective of evaluating the synergistic effects of amorphous starch modified by octenylsuccinic anhydride (OSA-MS) (2%), (as an emulsifying agent and wall material) and sunflower oil (RBD-SFO) (1%) as an unsaturated lipid carrier in the manufacture of nanoemulsions. In addition, the authors investigated the integrated effect on the physicochemical properties of the particles, with two combined techniques (Ultrasound Cavitation Homogenizer and High Speed Homogenizer - Ultra Turrax). The authors also evaluated the effectiveness of nanoemulsions in antioxidant activity and as lipid peroxidation agents.

The main components identified in the nanoemulsions NE-1 (OSA-MS + ADD) + (RBD-SFO: *L. angustifolia* EO) in the proportion of 1:1 and NE-2 (OSA-MS + ADD) + (RBD-SFO: *L. angustifolia* EO) in the proportion of 1:2 were the following: linalool (22.25 and 26.68%), linalyl acetate (12.55 and 16.28%), lavandulol (9.33 and 3.91 %), neryl acetate (7.24 and 8.28%), respectively. NE-2 had

the highest percentage of linalool (26.68%) and linalyl acetate (16.28%), while NE-1 had the highest percentage of lavandulol (9.33%). These results indicated that the extraction processes in two phases (NE-2) are highly efficient in the improvement of the qualitative and quantitative parameters of *L. angustifolia* EO.

The average droplet size of the CON group (OSA-MS + deionized distilled water - ADD) was 709 nm with a polydispersity index of 0.511, while the average droplet size (with a polydispersity index) for each of the NE-1, NE-2, and NE-3 (OSA-MS + ADD) + (RBD-SFO: *L. angustifolia* EO) in a 2:1 ratio were as follows: 126 nm (0.183), 130 nm (0.214) and 151 nm (0.272), respectively. These results showed that the formulations (NE-1, NE-2 and NE-3) produced based on *L. angustifolia* EO, RBD-SFO (as carrier material) and amorphous OSA-MS (as wall material) in synergy with the technique used in the preparation of nanoemulsions, they contributed to the production of droplets of nanometric size with spherical distribution and polydispersity index ≤ 0.300 . The results of this study provide a new concept on the synergistic effects of amorphous starch modified by OSA and the unsaturated lipid vehicle as macromolecules of safe degree for the production of nanoemulsions containing *L. angustifolia* EO. In addition, the application of the phenomenon of ultrasound cavitation proved to be effective in reducing the diameter of the droplets, in addition to improving the polydispersity index and the electrokinetic potential of nanoemulsions.

The authors Garzoli *et al.* (2020) also developed nanoemulsions, but chose to study another species of lavender (*L. intermediaria*), both in the form of oil and in the form of hydrolate. The nanoemulsions were produced by the solvent displacement technique that involves the spontaneous emulsification of an organic phase, added to an aqueous phase, under magnetic stirring. More specifically, the organic phase consisted of 125 μL of EO from *L. intermediaria*, 30 mg of soy phosphatidylcholine and 4 mg of benzalkonium chloride dissolved in a solvent mixture composed of 9.5 mL of acetone and 0.5 mL of ethanol. The nanoemulsion containing the hydrolate was produced following the same procedure described for *L. intermedia* EO, however 10 mL of *L. intermedia* hydrolate was used as the organic phase. A control nanoemulsion was also prepared with the same procedure, but using Labrafac as the oil phase.

The formulations were evaluated by solvent-free gas chromatography coupled with the mass spectrometry (GC-MS) method, to determine the chemical composition of the vapor phase of the *L. intermediaria* EO and the hydrolate of *L. intermediaria* in free and nanoemulsified form. Nanoemulsions were also evaluated for antibacterial activity against *E. coli* (G -) and *B. cereus* (G +).

The average droplet diameter of the nanoemulsion containing the *L. intermediaria* EO was 479.1 nm with a polydispersity index of 0.110, the zeta potential was not reported in the study. The formulation remained physically stable for more than a month after preparation, but it was not informed at which storage temperature. The average droplet diameter of the nanoemulsion containing the *L. intermedia* hydrolate was 225.4 nm with a polydispersity index of 0.098, which is lower than that obtained

in the nanoemulsion, a fact that is justified because the hydrolate contains a small amount of EO components dissolved in water, therefore, when it was used for the preparation of the nanoemulsion, a very low volume ratio between EO and water was present in the system.

In relation to the main constituents of the *L. intermediaria* EO were linalool (35.8%) and 1.8-cineole (19.8%), followed by α -pinene (8.7%) and linalyl acetate (7, 5%). When nanoemulsified, the percentage of linalool reached 54.7%, linalyl acetate 21.8% and 1.8-cineole (7.3%) being the third most abundant component, thus demonstrating that the active components of *L. intermediaria* EO remained in the nanoemulsion, but with a different trend. Regarding the main constituents of *L. intermediaria* hydrolate were 1,8-cineole (52.9%), followed by camphor (19.6%) and linalool (12.6%). When nanoemulsified also had the same components, with a different trend, where camphor (32.9%) was the most abundant constituent, followed by linalool (20.6%) and 1.8-cineole (18.6%). It is observed that the most volatile compounds were reduced during the preparation procedure of both formulations.

Both nanoemulsions proved to be effective when tested against *E. coli* and *B. cereus*, and a potentiation of antimicrobial activity was observed when the *L. intermediaria* EO was in the nanoemulsified form. As for the *L. intermediaria* hydrolate, the results were even more promising, since only the nanoemulsified hydrolate showed antibacterial activity against the strains mentioned, while the free form was inactive. Therefore, the authors concluded that nanoemulsions are interesting vehicles for improving the biological activity of the *L. intermediaria* EO, especially of the hydrolate of *L. intermediaria*, expanding its potential for application in the pharmaceutical, cosmetic and food fields.

Bayramzadeh *et al.* (2019) developed nanocapsules containing *L. angustifolia* EO and nanocapsules containing *Cuminum cyminum* EO, using the Solvent Evaporation Emulsion method, using Polyethylene Glycol (PEG) as a polymer. Fumigation toxicity was investigated against three important pests, *Tribolium castaneum* (Herbst), *Sitophilus granarius* (L.) and *Oryzaephilus surinamensis* (L.). The diameter of the nanocapsules of *C. cyminum* and the nanocapsules of *L. angustifolia* were 127.59 nm and 542.20 nm, respectively, the values of polydispersity index and zeta potential were not reported in the study. The analysis of the compositions of the *C. cyminum* EO and of the *L. angustifolia* EO analyzed by GC-MS demonstrated that α -Pinene (44.63%) and linalyl acetate (61.74%) were the main components, respectively. The encapsulation efficiency was verified by ultraviolet absorption, in a spectrophotometer and the results were slightly higher in *C. cyminum* EO (89.95%) in relation to *L. angustifolia* EO (88.42%), suggesting that the EO content can influence encapsulation efficiency.

The results indicated that *C. cyminum* EO was more effective than *L. angustifolia* EO in relation to toxicity after 24 h of treatment in the three mentioned pests. The mean lethal concentration values (LC_{50}) for the 48-hour treatment revealed that in most cases there were no differences between EOs and insect susceptibility, except for *O. surinamensis*. However, when nanoencapsulated, *C. cyminum* was more toxic to *O. surinamensis* and *T. castaneum* after 24 hours of exposure, however there was no difference in toxicity and susceptibility in the nanoencapsulated oils tested in 48 hours. The fumigation

toxicity of free and nanoencapsulated EOs showed that *C. cyminum* and *L. angustifolia* were toxic to pests. Among the three stored pests, the highest and the lowest susceptibility were observed after 24 hours of exposure of *S. granarius* and *T. castaneum* to the tested oils, respectively. In addition, the authors tested toxicity by sublethal fumigation to decrease the concentrations of nanoencapsulated EO and phosphine gas. In this bioassay, the mixture of *C. cyminum* oil and phosphine gas nanocapsules caused synergistic effects in the three pests. In addition, the combination of *L. angustifolia* and phosphine EO nanocapsules promoted additive effects in *S. granarius* and *T. castaneum*.

The results obtained prove that the union of phosphine with nanoencapsulated EO resulted in a decrease in lethal concentrations to achieve higher mortality rates compared to treatments with phosphine alone. The study authors believe that the combination of the nanoencapsulated form of EO with reduced amounts of phosphine could be used as an ideal method for pest control of stored products.

The authors Carbone *et al.* (2018) opted to research another species of lavender and develop nanostructured lipid carriers (NLC) as delivery systems for Mediterranean EOs, more specifically the oils of *Rosmarinus officinalis*, *Lavandula intermedia*, *Origanum vulgare* and *Thymus capitatus*, selected based on their antioxidant and anti-inflammatory activities. The NLC were produced by Phase Inversion Temperature (PIT) and High Pressure Homogenization (HPH), using two different emulsifying systems. The particles were characterized from the average size, polydispersity index and zeta potential, morphology and chemical interactions. The best NLC formulations were obtained with Kolliphor/Labrafil as surfactants and using *R. officinalis*, *L. intermedia* and *O. vulgare* as EOs (polydispersity index between 0.126 and 0.141, size < 200 nm).

Accelerated stability studies were also performed to estimate the effect of the production method and the composition of the surfactant on the long-term stability of NLC loaded with EOs. The biological cell viability *in vitro* and the anti-inflammatory activity were evaluated in macrophage cells, while the antioxidant activity *in vitro* was verified by the DPPH assay. The nanostructured lipid carriers containing *L. intermedia* and *R. officinalis* proved to be the most biocompatible formulations up to a concentration of 0.1% (v/v), while being able to induce a dose-dependent anti-inflammatory activity in the order *L. intermedia* > *R. officinalis* ≥ *O. vulgare*. The authors observed that only the *O. vulgare* EO showed significant antioxidant activity, it is worth mentioning that the use of *O. vulgare* as a component of the NLC system matrix did not alter its antioxidant activity.

The antioxidant capacity in eliminating DPPH radicals depends on the specific composition of the oil, which is affected by a huge number of different factors, such as geographical location, plant variety, climatic and seasonal variations, nutrition and addition of fertilizers in addition to stress during growth (BONA *et al.*, 2016). It is possible that the presence of high amounts of terpenes in *L. intermedia* (linalool 30% and linalyl acetate 38%) and *R. officinalis* (1.8 cineol > 50%), with a very low amount of phenolic compounds, is responsible for the lack of antioxidant activity observed for these tested Mediterranean EOs (CARBONE *et al.*, 2018).

Thus, the authors concluded that Mediterranean EOs can be successfully used as components of the NLC matrix prepared by the laboratory scale PIT method. In addition, NLC maintained the same physicochemical properties after being produced. The results of in vitro biological experiments allowed us to infer that Mediterranean EOs, due to their relevant anti-inflammatory activity, can be proposed as active ingredients and oily components of NLC, increasing biocompatibility and reducing the cytotoxicity of pure oils (CARBONE *et al.*, 2018).

In the study by Velmurugan *et al.* (2017), it was decided to produce nanospheres containing *Citrus sinensis* EO and nanospheres containing *L. angustifolia* EO with the aim of infusing the leather. The concentration of non-ionic surfactant (Triton X-100) ranged from 0.2 to 1 (1%). The authors used chitosan and acrylic acid as wall material using the emulsion polymerization technique, established by the same research group in previous studies (PUNITHA *et al.*, 2015). Nanospheres were characterized and leathers infused with EOs were studied for physical and organoleptic properties, morphology, washability test, perception and porosity assessment.

The nanospheres containing *C. sinensis* or *L. angustifolia* EOs exhibited a bimodal and trimodal size distribution with an average of 213.6 nm and 273.8 nm and with the polydispersity index of 0.69 and 1, respectively. The major components of *L. angustifolia* EO were linalool and linalyl acetate and *C. sinensis* was pinene, followed by sabinene and myrcene.

The authors observed that *L. angustifolia* EO nanospheres maintain better EO content and content than encapsulated nanospheres with *C. sinensis* EO. In contrast, the nanospheres loaded with oil of *C. sinensis* have a higher oil load compared to the nanospheres loaded with oil of *L. angustifolia*. This is believed to be due to the greater loss/volatility of *C. sinensis* oil during the encapsulation process (LI *et al.*, 2005).

The authors observed that both droplets of EOs dispersed evenly and presented a distinct spherical shape surrounded by the wall material, which can be identified by the contrasting nature of the oil and the wall material. On the other hand, the encapsulated *L. angustifolia* EO showed surface imperfections with different shapes and sizes, presenting nanospherical agglomeration, which may corroborate with the trimodal distribution. It was observed that the organoleptic properties, such as softness, fullness and smoothness, are better in leather infused with *C. sinensis* EO than in leather infused with *L. angustifolia* EO, whereas the color uniformity has not changed in leather.

When performing the thermogravimetric analysis, it was identified that the moisture loss (initial degradation) for both is 248 °C. The loss of residual oil and its constituents was observed at 457 °C. The degradation of the core material and the complete evaporation of the oil were recorded above 550 °C, thus demonstrating that the wall material plays a predominant role in oil retention at high temperatures (above 100 °C) and can be applied in thermal coatings. The EOs used in this study also showed antimicrobial efficacy, and the nanosphere containing *L. angustifolia* has greater antimicrobial activity against certain bacteria such as *Bacillus cereus* and *Bacillus subtilis* and fungi such

as *Rhizoctonia solani*, *Macrophomina phaseolina* and *Aspergillus fumigatus*, respectively, when compared to nanosphere containing the *C. sinensis* EO. The authors also observed a synergistic effect of chitosan with EOs, increasing the antimicrobial efficacy of nanospheres, a fact that becomes important since leather is generally prone to fungal attack.

When carrying out this review of the studies that associated the lavender EO to nanostructured systems, it can be observed that among the main nanocarriers used, nanoemulsions stand out, followed by nanocapsules. Only one study developed nanostructured lipid transporters and another nanospheres. Regarding the applications suggested by the authors, topical administration stands out, justified by the healing, anti-inflammatory, antioxidant and antibacterial properties evidenced in the EO of lavender associated with nanostructured systems. Two other interesting applications were the use of these nanosystems to control pests in stored products, as well as to incorporate lavender EO into the leather fabric, again highlighting its antimicrobial activity. There was consensus among the authors the capacity of the nanosystems to increase biological activity, as well as the stability of the lavender EO, enabling an expansion of its use, in the pharmaceutical, cosmetic and food fields.

Among the methods used to develop the nanosystems, most studies used the High Speed Homogenizer technique, followed by the Ultrasound Cavitation Homogenizer technique, one study combined both techniques and another study joined the High Pressure Homogenization technique (HAP) with Phase Inversion Temperature (PIT), to produce nanostructured lipid carriers and nanoemulsions, respectively. One study used the Solvent Evaporation Emulsion technique to produce nanocapsules and another opted for the same technique to produce nanoemulsions, only one study used the Emulsion Polymerization technique to produce nanospheres.

The diameter of the nanoparticles between the studies ranged from 104 nm to 479 nm, the smallest diameter being obtained in the research by Shokri *et al.* (2017), who developed nanoemulsions containing *L. angustifolia* EO, using the Homogenization technique by Ultrasound. The largest diameter, on the other hand, was observed in the study by Garzoli *et al.* (2020), which also produced nanoemulsion, but used the species of *L. intermediaria* using the Solvent Displacement technique. Regarding the polydispersity index, the values ranged from 0.110 to 1, with the largest polydispersity index observed in the study by Velmurugan *et al.* (2017), which produced nanospheres containing *L. angustifolia* EO, which showed surface imperfections with different shapes, sizes and nanospherical agglomeration, as well as trimodal distribution. It is known that the polydispersity index values should be in the range of 0.15 to 0.3 to indicate homogeneity and stability (MOHANRAJ; CHEN, 2006), results not found in the study by Velmurugan *et al.* (2017). The values for zeta potential were negative in most studies, ranging from -42 mV to -15.8 mV, only in one study the zeta potential value was positive (50 mV), due to the use of the Eudragit EPO polymer that has cationic characteristics (SINGH *et al.*, 2015).

Regarding the lavender species used in the studies, the *L. angustifolia* species was the most researched, followed by *L. intermedia* and *L. dentata*. The major component in studies that used

L. angustifolia EO was linalool, followed by linanil acetate and 1,8 cineol. For the species of *L. dentata* and *L. intermediate*, it was 1,8-cineol and linalool, respectively. It is believed that most authors chose to use the *L. angustifolia* species because there are several studies that prove different activities of its major component, linalool, such as anti-inflammatory (PEANA *et al.*, 2002), antimicrobial (PARK *et al.*, 2012) and antioxidant (LIU *et al.*, 2012), as well as sedative (SUGAWARA *et al.*, 1998), anxiolytic (SOUTO-MAIOR *et al.*, 2011), anticonvulsant (ELISABETSKY *et al.*, 1999), analgesic (LI *et al.*, 2016) and local anesthetic (ZALACHORAS *et al.*, 2010). Food supplements containing linalool showed efficacy in the treatment of anxiety disorders, through clinical trials (KASPER *et al.*, 2010). In addition, the preparation of capsules containing *L. angustifolia* EO has been licensed in Germany for the treatment of anxiety disorders (UEHLEKE *et al.*, 2012).

CONCLUSION

It can be concluded with this review that the research that associated lavender EO to nanostructured systems obtained an increase in the effectiveness of EO, as well as a decrease in toxicity and greater physical-chemical stability of its components. The main species of lavender used was *L. angustifolia*, which due to its major component linalool, has shown great therapeutic efficacy. Regarding nanosystems, it was observed that most studies produced nanoemulsions, as they believe to be a promising nanocarrier to be associated with the lavender EO, with the aim of improving the release of bioactive components, as well as increasing its effectiveness. Therefore, it is believed that nanotechnology can be a promising alternative to protect the active compounds against external factors, as well as to guarantee or even increase their effectiveness, with the possibility of reducing the dose and consequently of the side effects. It is also worth noting that the nanostructured formulations are water-based, and thus, they can enable the use of these by-products in the clinic.

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