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HEALING POTENTIAL OF NANOCARRIERS CONTAINING ESSENTIAL OILS: A LITERATURE REVIEW

POTENCIAL CICATRIZANTE DE NANOCARREADORES CONTENDO ÓLEOS ESSENCIAIS: UMA REVISÃO DA LITERATURA

Ruth Barin[1], Alencar Kolinski Machado[2], Ivana Zanella da Silva[2] e Aline Ferreira Ourique[2]

ABSTRACT

Essential oils are compounds of natural origin with numerous therapeutic properties, however, there are limitations regarding their stability, being easily degraded by processes of oxidation, volatilization, heating and light, characteristics that can be overcame with the use of nanotechnology. The aim of this study was to investigate the main types of nanocarriers used to carry essential oils and to assess their healing potential. A research was carried out in the Web of Science database, without a time limit, using the Boolean descriptors and markers: nano* AND essential oils AND wound healing. Articles published in Portuguese and English, with free access to the full article on the online platform, were included in the review. The research resulted in 168 articles, of which 22 were selected to include this review according to the proposed criteria. From the studies included in this review, it was possible to observe that nanocarriers such as nanoemulsions and nanofibers were able to activate the functionality of essential oils effectively and safely, achieving success in healing and antibacterial activity, demonstrating that nanotechnology is a promising alternative to develop nanotechnology-based formulations containing essential oils for wound healing.

Keywords: essential oils, nanocapsules, nanoemulsions, wound healing.

RESUMO

Os óleos essenciais são compostos de origem natural com inúmeras propriedades terapêuticas, porém, apresentam limitações quanto a sua estabilidade, sendo facilmente degradáveis por processos de oxidação, volatilização, aquecimento e luz, características estas que podem ser contornadas com o uso da nanotecnologia. O objetivo deste estudo foi investigar os principais tipos de nanocarreadores utilizados para carrear óleos essenciais com a finalidade de avaliar seu potencial cicatrizante. Uma pesquisa foi realizada na base de dados Web of Science, sem delimitação de tempo, utilizando os descritores e marcadores boleanos: nano AND essential oils AND wound healing. Artigos publicados em Português e Inglês, de acesso liberado ao artigo completo na plataforma online foram incluídos na revisão. A pesquisa resultou em 168 artigos, dos quais 22 deles foram selecionados de acordo com os critérios propostos. A partir dos estudos incluídos nesta revisão, foi possível observar que nanocarreadores, em destaque as nanoemulsões e nanofibras, foram eficazes em garantir a funcionalidade dos óleos essenciais de forma atóxica e segura, obtendo sucesso na atividade cicatrizante e antibacteriana, demonstrando que a nanotecnologia é uma alternativa promissora para desenvolver formulações de base nanotecnológica contendo óleos essenciais para a cicatrização de feridas.*

Palavras-chave: *cicatrização de feridas, nanocápsulas, nanoemulsões, óleos essenciais.*

1 Physiotherapist. Master's student at the Postgraduate Program in Nanosciences - Franciscan University (UFN), Santa Maria, RS, Brazil. E-mail: ruthbarin@hotmail.com

2 Collaborators. Professors of the Postgraduate Program in Nanosciences - Franciscan University (UFN), Santa Maria, RS, Brazil. E-mail: alencarkolinski@gmail.com; ivanazanella@gmail.com; alineourique@gmail.com

INTRODUCTION

The healing process of skin wounds is multifaceted, driven by sequential phases of inflammation, proliferation and remodeling (WANG *et al*., 2018). The basic principle of healing is the minimization of tissue damage by taking care of oxygenation and blood supply at the affected site, seeking to maintain local function and integrity, and avoiding contamination by microorganisms harmful to the dermis, causing a prolonged inflammatory process (HOU *et al*., 2020). To assist this process, it is commonly used in skin lesions such as burns, cuts, muscle perforations, among others, transdermally applied drugs that help in the regeneration of the dermis (JUNIOR; SHIOTA; CHIAVACCI, 2014). Complementary and alternative medicine (CAM) are attracting increasing interest for the treatment of a wide variety of diseases, such as essential oils (EOs), which are used to treat various comorbidities for being low cost, less harmful to health and with easier access in relation to allopathic medicines. EOs have a broad spectrum of biological activity, including antimicrobial (GÜNDEL *et al*., 2018; SUGUMAR *et al*., 2014), antioxidant, (BENEDEC *et al*., 2018; CELEBIOGLU; YILDIZ; UYAR, 2017) and healing effects (ALAM *et al*., 2017; RIZG *et al*., 2022). They are volatile products, originating from plants, in which the oil is extracted from the non-woody part (seeds, fruits, flowers, leaves and roots), and are composed mainly of terpenes and terpenoids, with aromatic and aliphatic constituents (SAPORITO *et al*., 2018). There are several EOs used for topical application with healing properties. As an example of this, *in vitro* studies can be cited for showing that the use of lavender and peppermint essential oil has the potential to accelerate wound healing (MORI *et al*., 2016; UNALAN *et al*., 2019).

However, when working with EOs, one must be aware of the limitations of these products, as they are volatile compounds that are unstable and easily degradable by oxidation, volatilization, heating and light. When combined with nanotechnology, its encapsulation can be useful to increase stability and improve its antibacterial activity, for example (SAPORITO *et al*., 2018).

In this context, the objective of this study was to analyze in the literature the main nanocarriers used to carry EOs with healing purposes.

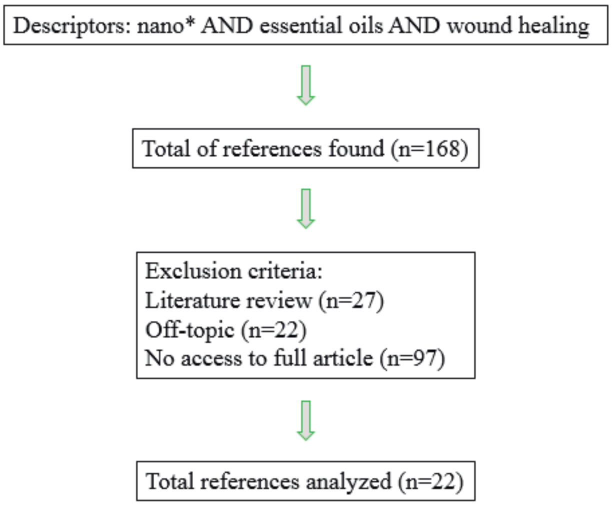
MATERIAL AND METHODS

This study is characterized as an exploratory, integrative literature review type. A research was carried out in the Web of Science database, without time limits, using the Boolean descriptors and markers: nano* AND essential oils AND wound healing.

The inclusion criteria used to select the articles were: articles published in Portuguese and English, with free access to the full article on the online platform, which used nanocarriers with essential oils with properties for wound healing. Literature review and off-topic articles were excluded. Articles that performed isolated evaluations, without proposing an *in vitro* or *in vivo* model to analyze healing properties were also excluded from the study.

After searching the database, titles and abstracts were evaluated, and those that met the inclusion criteria were selected to be read in full. The search resulted in 168 articles, of which 22 were selected to be included in the review, according to the proposed criteria. Figure 1 presents the flowchart with the selection strategy for the articles included. The articles that make up this study were published in the years between 2013 and 2022.

Figure 1 - Flowchart with article selection strategy.



RESULTS AND DISCUSSION

From the analyzed articles, it was observed that the nanocarriers containing essential oils for the purpose of evaluating wound healing were iron oxide nanoparticles, nanoemulsions, nanocapsules, lipid nanoparticles, nanostructured lipid carriers, electrospun nanofibers, cobalt nanoparticles, polymeric micelles, nanofibers with chitosan polymers and polyethylene oxide and zinc oxide nanoparticles, with nanofibers, nanoemulsions and inorganic nanoparticles being the most used (Table 1), representing 36%, 27% and 14%, respectively.

Table 1 - Publications that composed the study presented in chronological order.

Year	Author	Nanocarrier	Essential oil
2013	Anghel *et al.*	Iron oxide nanoparticles	Savory *(Satureja hortensis)*
2014	Sugumar *et al.*	Nanoemulsion	Eucalyptus *(Eucalyptus globulus)*
2015	Hajiali *et al.*	Electrospun nanofibers	Lavender (*Lavandula angustifólia*)
2017	Alam *et al.*	Nanoemulsion	Clove *(Syzygium aromaticum)*
	Kalita *et al.*	PCL nanocapsules	Lemon grass *(Cymbopogon flexuous)*
2018	Alam *et al.*	Nanoemulsion	Eucalyptus *(Eucalyptus globulus)*
	Saporito *et al.*	Lipid nanoparticles	Eucalyptus (*Eucalyptus globulus)* or Rosemary (*Rosmarinus officinalis* L.)

	Khezri; Farahpour; Rad	Nanostructured lipid carriers	Rosemary *(Rosmarinus officinalis* L.)
2019	Shakeel *et al.*	Self-nanoemulsifying drug delivery system (SNEDDS)	Cubeba *(Piper cubeba)*
	Unalan *et al.*	Electrospun nanofiber mats	Clove *(Syzygium aromaticum)*
2020	Carbone *et al.*	Nanostructured lipid carriers	Lavender *(Lavandula x intermedia "Sumian")*
	Hou *et al.*	Cobalt nanoparticles	*Ziziphora clinopodioides*.Lam
2021	Hameed *et al.*	Nanofibers with chitosan polymers and polyethylene oxide	Clove *(Syzygium aromaticum)*
	Khan *et al.*	Electrospun nanofibers	Oregano (Carvacrol)
	Li *et al.*	Nanoemulsion	Oregano (Carvacrol)
	Melnikova *et al.*	Zinc oxide nanoparticles (ZnO NPs)	Lavender and thyme (thymol), betulin (B) or betulin diphosphate (BDP)
	Milanesi *et al.*	Electrospun nanofibers	Black pepper (*Piper nigrum*) ou limonene
	Sinsup *et al.*	Electrospun fiber membrane	Plai (*Zingiber cassumunar* Roxb.)
2022	Demir *et al.*	Electrospun nanofibers	Styrax Liquidus (*Liquidambar Orientalis Miller*)
	Hussein *et al.*	Nanofibrous scaffolds	Cinnamon e nanoceria (nCeO2)
	Kamel *et al.*	Nanoemulsion	*Deverra tortuosa* DC. e *Deverra triradiata* Hochst. ex Bioss
	Rizg *et al.*	Nanoemulsion	Geranium (*Pelargonium graveolens*) e pravastatin

Source: Prepared by the author on the total number of analyzed references from the Web of Science database.

LIPID SYSTEMS

Nanoemulsions

Nanoemulsions (NE) are stable formulations of two immiscible liquids, with an aqueous phase and an oil phase, in combination with a surfactant. Their droplet size ranges from 10 to 100 nm, and they offer greater bioavailability and efficacy to lipophilic compounds (PARK *et al*., 2019). In formulations containing essential oils, they are widely used for application in wounds for healing purposes, showing a response in increasing levels of collagen markers (ALAM *et al*., 2017; ALAM *et al*., 2018; KAMEL *et al*., 2022), in addition to anti-inflammatory and antimicrobial activity (SUGUMAR *et al*., 2014; LI *et al*., 2021; RIZG *et al*., 2022).

Alam *et al*. (2017) investigated the healing effects of nanoemulsions (NE) containing clove essential oil (OEC). The nanoemulsions were produced by the spontaneous emulsification method and presented an average droplet size around 29 nm. The healing potential was evaluated *in vivo* in female *Wistar* rats after oral administration of the treatment, which were divided into 4 groups: control, pure OEC, NE optimized with OEC (1% w/w of OEC) and gentamicin. The results showed better healing and higher leucine content (collagen estimation) in the groups treated with NE optimized with OEC and gentamicin, showing no signs of inflammatory cells, which indicates that the OEC nanoemulsion developed was safe and effective.

In another study by the same group (ALAM *et al*., 2018), they proposed the development of nanoemulsions containing eucalyptus essential oil (OEE), and evaluated the *in vivo* potential in wound healing compared to gentamicin. The OEE concentration ranged from 12-28% (w/w) and the S_{mix} concentration (specific mass ratio of surfactant to co-surfactant) was constant at 24% (w/w). The different nanoformulations were prepared using the aqueous phase titration method, identified by the construction of phase diagrams and characterized by various physicochemical parameters. Based on such parameters, as minimum droplet diameter (32.45 nm), minimum PDI (0.153), ideal zeta potential value (-34.25 mV), ideal refractive index value (1.335) and maximum percentage value of transmittance (99.1%), and the E1 formulation (containing 12% of OEE) was optimized and selected to evaluate the healing activity in rats. The optimized nanoemulsion showed significant healing activity in rats compared to pure OEE after oral administration, and was similar with gentamicin. The significant increase in collagen after E1 nanoemulsion administration was also similar to gentamicin-treated animals. This study demonstrated the healing potential of the optimized nanoemulsion containing OEE orally, suggesting efficacy and non-toxicity, as it does not show signs of inflammatory cells.

Sugumar *et al.* (2014) also developed nanoemulsions containing 16% eucalyptus essential oil (OEE) and evaluated their antimicrobial activity. Through the sonication process, the most stable nanoemulsion obtained had an average droplet diameter of 3.8 nm. In addition, the developed formulation showed *in vitro* antimicrobial properties against *Staphylococcus aureus*. Furthermore, the wound healing potential and skin irritation activity of the nanoemulsion was analyzed *in vivo* in rats, and its effect was non-irritating and the wound contraction rate was higher compared to the control treatment and neomycin treatment.

Another study dedicated to evaluating the antimicrobial activity of nanoemulsions was from Li *et al.* (2021), who developed nanoemulsions using gelatin stabilized by photocrossing with riboflavin (vitamin B2) as a photocatalyst and *carvacrol* (the main constituent of oregano essential oil). *In vitro* tests showed antimicrobial activity against drug-resistant bacterial biofilms (*P. aeruginosa* CD-1006, methicillin-resistant *S. aureus* [MRSA] CD-489, *Escherichia coli* CD-2 and *Enterobacter cloacae* CD-1412 complex). The results, which were also observed in a murine model, were shown to improve wound healing in mice, both in size and degree of purulence.

Rizg *et al.* (2022) formulated a nanoemulsion (NE) based on geranium oil (Gr) with pravastatin (PV), optimized by the Box-Behnken project, as a nanoplatform for wound healing. Among the formulations developed were: optimized Gr-PV-NE (A), Gr-NE (B), PV-NE (C), PV-Gr mixture (D) and normal saline solution (E), which presented droplet size from 61 to 138 nm, zeta potential of -17.3 ± 1.2 mV and acceptable polydispersity index ranging from 0.09 to 0.40. In the experimental design, better efficiency of formulation A (NE-Gr-PV) was observed, with droplet size of 95 ± 2.4 nm, resulting in better antibacterial and anti-inflammatory activity. In an *in vivo* transdermal analysis, over 16 days, the wounds of the rats had a decrease of up to 4 times in the average diameter of the burn, also reducing the serum level of interleukin-6, evidencing the superiority of formulation A in combating inflammation compared to the other formulations tested.

In the same year, Kamel *et al*. (2022) evaluated the healing potential, topically, of several nanoemulsions (NE) containing different concentrations of *Deverra tortuosa* DC essential oil. and *Deverra triradiata* Hochst. ex Bioss. Using the supercritical fluid extraction (SFE) method, the EN were divided into: group I (control); group II and III: NE of *D. tortuosa* 1 and 2%; group IV and V: NE of *D. triradiata* 1 and 2%; group VI: standard control (Mebo ® ointment). The pH characterization values ranged from 4.5 ± 0.082 to 5.1 ± 0.183, droplet size for blank and oil loaded formulations ranging from 224.43 ± 5.77 to 407.7 ± 7.27 nm, polydispersity index did not exceed 0.41 ± 0.02 and zeta potential 15.8 ± 0.36 mV at 21.2 ± 0.25 mV. The antioxidant and anti-inflammatory activity markers increased significantly ($p < 0.0001$) for the two oil species, especially the group containing *D. tortuosa* (2%). Regarding healing potential, topical application of NE from *D. tortuosa* and *D. triradiata* (1% or 2%) in rats exhibited nearly 100% wound contraction within 16 days of treatment, and a significant increase in vascular endothelial growth factors and levels of hydroxyproline, an indicator of collagen renewal.

In a study by Shakeel *et al*. (2019) wound healing by self-nanoemulsifying drug delivery system (SNEDDS) containing Piper cubeba essential oil (PCEO) was evaluated. SNEDDS are systems capable of self-emulsification with gastrointestinal fluids by oral administration. The PCEO SNEDDS formulations were developed by the spontaneous emulsification method through the construction of phase diagrams. The formulation that proved to be stable (F1) presented as droplet size, polydispersity index and viscosity 7.53 ± 0.56 nm, 0.119 and 12.80 ± 1.09 cp, respectively. Zeta potential registered -28.98 mV. Healing potential was assessed by wound contraction in rats after oral administration of pure PCEO and SNEDDS F1 compared to standard treatment with gentamicin. Both pure PCEO and SNEDDS F1 significantly increased wound contraction up to day 24 compared to control, however there was no statistical difference compared to gentamicin ($p>0.05$). In collagen content, leucine levels of animals treated with SNEDDS F1 increased significantly on day 10 compared to animals treated with pure PCEO and negative control ($p<0.05$).

Solid lipid nanoparticle and nanostructured lipid carrier

Solid lipid nanoparticles (SLN) are particles formed by solid lipids in their core, integrating bioactives, surrounded by a layer of surfactant (WEISS *et al*., 2008). They are capable of carrying lipophilic compounds, what increases their stability, controls their release, and capability of being biodegradable and of low cytotoxicity (GOKCE *et al*., 2012). As a second generation of the same technology, nanostructured lipid carriers (NLC) are a mixture of solid lipids and oils, and overcome SLN limits, with greater drug loading capacity and sustained release (CIMINO *et al*., 2021). Such systems were developed using essential oils in publications by Saporito *et al*. (2018); Khezri; Farahpour; Rad (2019) and Carbone *et al*. (2020) with healing purpose.

In the study published by Saporito *et al*. (2018), lipid nanoparticles containing eucalyptus or rosemary essential oils were developed. The formulations were prepared by high shear homogenization followed by ultrasonication. The nanoparticles loaded with eucalyptus oil showed greater stability by nanostructured lipid carrier (NLC), good bioadhesion, cytocompatibility and healing properties in fibroblasts, associated with antimicrobial properties. Subsequently, the *in vivo* results in a burn model showed the ability of these NLC loaded with eucalyptus or rosemary oil to enhance the healing process.

Khezri; Farahpour; Rad (2019), investigated the effects of rosemary essential oil (*Rosmarinus officinalis* L.) (REO) on nanostructured lipid carriers on antibacterial activity for wound healing, both *in vitro* and *in vivo*. Nanocarriers containing REO were prepared by hot melt homogenization, their zeta potential was -15.7 mv, particle size from 100 to 250 nm with PDI = 0.335. The nanocarriers showed antibacterial properties *in vitro* and *in vivo*, accelerated the healing process of infected wounds in animal models, reducing the period of inflammation and increasing neovascularization and wound contraction rate.

Carbone *et al*. (2020) evaluated the use of nanostructured lipid carriers with *lavandula x intermedia "Sumian"* combined with ferulic acid (LEO-FA), substances already reported to be beneficial for the wound healing process. The use of ferulic acid increased the stability of the nanoparticles in relation to the use based on synthetic isopropyl myristate. Nanoparticles showed a polydispersion index of less than 0.2, average size around 150 nm, encapsulation efficiency greater than 85%, and high antioxidant potential evaluated by the *in vitro* assay using the DPPH radical. Due to its greater cytocompatibility, it was observed that nanoparticles with LEO-FA resulted in a more efficient formulation in promoting fibroblast migration and wound closure compared to the one that used only AF, proving to be a promising treatment for wound healing.

POLYMERIC SYSTEMS

Nanocapsules

Polymeric nanoparticles, including nanocapsules and nanospheres, are drug carrier systems. Nanocapsules have an oily core surrounded by a biodegradable polymeric wall, have a diameter smaller than 1 μm and are used therapeutically with advantages such as protecting the active from degradation and controlled drug release, improving its performance (SCHMALTZ; SANTOS; GUTERRES, 2005).

Kalita *et al*. (2017) used lemongrass essential oil to produce poly (ε-caprolactone) (PCL) and chloramphenicol (CAM) nanocapsules. The resulting particle size was 124.8 nm and a zeta potential of -22.4 mV. Such formulation exhibited significantly improvement *in vitro* antimicrobial activity and was able to penetrate burn wounds demonstrating pronounced wound healing ability in burns coinfected by methicillin and *Candida* sp. in mice by reducing significantly the pathogen load. They also helped to increase cell proliferation and collagen synthesis in the wound area, with a reduction in inflammatory cytokines, showing to be promising to treat chronic wound infections.

Nanofibers

Nanofibers (NF) are polymeric filaments, both natural and synthetic, with at least one of their dimensions less than 1µm, with a high area-to-volume ratio and high porosity (MOHITI-ASLI; LOBOA, 2016). They present great stability, targeting and biocompatibility, being commonly adopted in therapeutic treatments such as tissue regeneration (KENRY; LIM, 2017). In its development, the electrospinning technique stands out, the most used to carry drugs for controlled release (MORIE *et al*., 2014), which was used in the studies by Hameed *et al*. (2021), Unalan *et al*. (2019), Hajiali *et al*. (2015), Khan *et al*. (2021), Sinsup *et al*. (2021), Milanesi *et al*. (2021), Demir *et al*. (2022) and Hussein *et al*. (2022).

In the study by Hameed *et al*. (2021), clove essential oil (CEO) was encapsulated in chitosan and polyethylene oxide polymers for the development of nanofibers (NFs). The CEO load was 1%, while the percentage yield was 79%, with an average diameter of 154 ± 35 nm. NFs were developed by electrospinning technique, and showed good release at pH 5.5 (acid) and 7.4 (physiological) in a biphasic manner, in which approximately 60% of the nanostructured compound was initially released, followed by a sustained release. The prepared nanofiber dressing was tested *in vitro*, and showed significant antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*, in addition, it did not show cytotoxicity against human fibroblast lines, demonstrating potential antibacterial and healing activity of NFs with CEO.

Another study that also used clove essential oil was that of Unalan *et al*. (2019) in which they produced electrospun poly (ε-caprolactone) (PCL) - gelatin (GEL) nanofibers containing CEO. The nanofiber mats produced contained various concentrations of CEO (1.5%, 3% and 6% v/v), and were manufactured using glacial acetic acid as a “benign” (non-toxic) solvent, by the electrospinning process, to antibiotic-free wound healing applications. The use of CEO increased the surface wettabililty of nanofiber mats (PCL-GEL) and their fiber diameter was from 241 ± 96 to 305 ± 82 nm. Encapsulation efficiency increased when comparing concentrations of 1.5% to 3% and 6% v/v, exhibiting maximum encapsulation efficiency of 73 ± 3%. PCL-GEL nanofibers loaded with OEC had no cytotoxic effects on healthy human dermal fibroblasts, and exhibited antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*., proving to be promising biomaterials for wound healing without the use of antibiotics.

Hajiali *et al*. (2015) also used the electrospinning process to produce bioactive nanofibrous dressings using sodium alginate (SA) and lavender essential oil (LEO), at a concentration of 5%, for application in skin burns induced by ultraviolet radiation (UVB) medium range. By the electrospinning process, using Polyethylene Oxide (PO), the nanofibers presented an average diameter of 91±21 nm for SA-PO and 93±22 nm for SA-PO/LEO. In *in vitro* results, SA-PO/LEO nanofiber dressings showed antimicrobial and anti-inflammatory activity, inhibiting *Staphylococcus aureus* proliferation and production of pro-inflammatory cytokines, respectively. In an *in vivo* test, UVB burns in rats treated with SA-PO and SA-PO/LEO nanofibrous dressings showed no visible burn marks on the animals' skin after 24 hours of injury, with erythema disappearing completely within 48 hours, corroborating with the antimicrobial and anti-inflammatory properties shown *in vitro*.

Khan *et al*. (2021) formulated a multifunctional core-shell membrane composed of electrospun nanofibers (NF) loaded with zinc oxide nanoparticles (ZnO NP) and oregano essential oil (OEO) for application in diabetic wounds. The physicochemical characterization results were adequate, and the NF-ZnO NP-OEO membrane showed good biocompatibility and non-toxicity in cell count assay Kit-8 (CCK-8), showing cell growth within 7 days. The healing potential was evaluated in wounds of diabetic rats, with significant closure of 89.7% of the wound within 15 days with the use of fiber containing ZnO NP and OEO. Anti-inflammatory property was observed in quantitative fluorescence polymerase chain reaction (FQ-PCR) test in IL-6 and MMP-9 (pro-inflammatory) genes.

In the same year, Sinsup *et al*. (2021) used essential oil of Plai (*Zingiber cassumunar* Roxb.) embedded in a poly (lactic acid)/poly (ethylene oxide) electrospun fiber membrane for its application as an antibacterial dressing. The fiber mixture showed antibacterial activity against *S. aureus* and *E. coli* and controlled release when tested by (E)-1-(3,4-dimethoxyphenyl) butadiene (DMPBD), a molecule indicative of anti-inflammatory activity. The *in vitro* cytotoxicity analysis was performed using the MTS assay in human dermal fibroblast cells (HDFa) and keratinocyte cells (HaCat), showing no toxicity, with promising results for application in dressings.

In the study by Milanesi *et al*. (2021) was also used poly (lactic acid) (PLA) to develop nanofibers electrospun with essential oils (EOs) of black pepper (EO-BP) or limonene (L) 10% w/w. A chitosan coating was added to the fibers to improve hydrophilicity, biocompatibility, antibacterial property and cell proliferation. No statistical difference in fiber size was observed before and after coating. Antibacterial tests, performed on *S. aureus*, *S. epidermidis*, *E. coli* and *P. aeruginosa*, proved the synergistic effect of chitosan and greater antibacterial activity of fibers containing EOs compared to pure PLA fibers. The combination of essential oils and chitosan also promoted good results for cell adhesion and proliferation in fibrous membranes in MTT assay in normal human dermal fibroblasts, showing complete cell colonization in 7 days of culture compared to uncoated fibers, healing potential in wound treatment.

The work published by Demir *et al*. (2022) also used a polyester to develop nanofibers. These were electrospun based on poly (ε-caprolactone) (PCL) and Styrax Liquidus (*Liquidambar Orientalis Miller*) and after that, their cytocompatibility was evaluated *in vitro*. The fibers with styrax, analyzed at different concentrations, presented diameters of 192.70 ± 58.33, 316.11 ± 102.29 and 371.27 ± 108.61 nm for PCL25%, PCL50% and PCL100%, respectively. By the DPPH method, the higher the concentration of PCL nanofiber analyzed, the greater was its antioxidant activity, while for antimicrobial activity, PCL50% and PCL100% were effective ranging from 16 to 64 μg/mL against gram negative bacteria, and from 16 to 128 μg/ mL for gram positive bacteria. Cell viability tested in mouse embryonic fibroblasts was higher for PCL100% nanofiber compared to the control group. The incorporation of styrax gave the nanofibers hydrophilic, antimicrobial character and greater cell adhesion, promising for wound treatment.

A recent study by Hussein *et al.* (2022), developed with the aim of wound healing in diabetics, produced nanofibrous (NF) scaffolds of Polyurethane (PU) and polyvinyl alcohol-gelatin (PVA/Gel), containing cinnamon essential oil (CNEO) and nanoceria (nCeO2), known for their antibacterial and antioxidant properties, respectively. Antibacterial activity and biocompatibility were higher when CNEO was incorporated in relation to NF-nCeO2 and pure NF-PU/PVA/Gel, showing better distribution and higher growth rate of adipose-derived mesenchymal stem cells (ADMSC) in the nanofibers produced NF-nCeO2/ OEC. Based on *in vitro* results, NF-nCeO2/CNEO are promising for application in diabetic wounds.

INORGANIC NANOPARTICLES

Inorganic nanoparticles are biocompatible, protect bioactive from degradation, with a size that can vary according to the core material used (MOHAMMADPOUR *et al*., 2019). Metallic and semiconductor nanoparticles such as iron oxide (ANGHEL *et al*., 2013), cobalt (HOU *et al*., 2020) and zinc oxide (MELNIKOVA *et al*., 2021) were used incorporating essential oils to assess healing potential.

In a study by Anghel *et al*. (2013), a dressing coating containing iron oxide nanoparticles and *Satureja hortensis* essential oil (SHEO) was manufactured as a way to prevent the development of fungal biofilm by *Candida albicans*, a fungal colonization that is often the cause of local infections, hindering proper wound healing. The chemical composition of the EO was established by gas chromatography coupled to mass spectroscopy, and the analysis of the colonized surfaces using scanning electron microscopy revealed that the adhesion of *C. albicans* and the subsequent development of the biofilm are strongly inhibited by the dressing coated with the nanoparticles, compared to regular uncoated materials. The average size of the obtained nanoparticles was 10 nm. Therefore, the nanocoated dressings exhibited antimicrobial activity, with fibers resistant to fungal cell adhesion and biofilm development.

Hou *et al*. (2020) produced cobalt nanoparticles (NPCo) from the aqueous extract of *Ziziphora clinopodioides*.Lam. In characterization, an average diameter of 29.08 nm of the biosynthesized nanoparticles was observed by scanning electron microscopy and transmission electron microscopy. Previous *in vivo* tests showed high antibacterial and antifungal effects. The DPPH free radical scavenging test revealed similar antioxidant potential for NPCo and butylated hydroxytoluene. The results obtained from the application in rat models was that the use of NPCo ointment in the treatment groups substantially increased ($p \leq 0.01$) wound contracture compared to the other groups, proving to be a possible substance to be used for the treatment of various types of skin wounds in humans.

Melnikova *et al*. (2021) studied the behavior of terpenoid-protected zinc oxide nanoparticles (ZnO NPs) in the normalization of redox imbalance in burns. Hydrophilic and oleophilic gel dispersions have been developed, incorporating terpenoids from lavender and thyme oil (thymol), and betulin triterpenoids (B) or betulin diphosphate (BDP), due to their known anti-inflammatory and antioxidant properties. After characterizing and evaluating the stability of the formulations, in an *in vivo* test, it was observed that all formulations had better healing results than untreated wounds, with hydrophilic dispersions showing better results, due to better penetration into the epidermis. The hydrophilic NP-ZnO with lavender (5%) and thymol (5%) in 21 days of experiment showed greater signs of maturation and epithelialization of the dermis, and decreased levels of oxidative stress, increasing superoxide dismutase (SOD) and catalase in 13- 26% and 18-21%, respectively, with redox balance restoration parameters.

PERSPECTIVES

An issue to be explored is which nanoformulations maintained the stability of essential oils and provided controlled release, leading to a better dressing/dermal solution for application with healing potential. Among the reviewed articles, nanofibers and nanoemulsions can be noted as the most used nanoformulations in studies aimed at the treatment of wounds and burns. Regarding the essential oils evaluated, lavender, eucalyptus and clove were the ones that most had their properties analyzed, in concentrations ranging from 1-5%. Regarding the *in vivo* forms of administration, the topical route was used (MELNIKOVA *et al*., 2021; HOU *et al*., 2020; KHAN *et al*., 2021; HAJIALI *et al*., 2015; KALITA *et al*., 2017; KHEZRI; FARAHPOUR; RAD, 2019; SAPORITO *et al*., 2018; KAMEL et al., 2022; RIZG *et al*., 2022; LI *et al*., 2021; SUGUMAR *et al*., 2014) and oral (SHAKEEL *et al*. , 2019; ALAM *et al*., 2017; ALAM *et al*., 2018).

The results found in this review are promising, in which better healing can be observed, as well as antimicrobial and anti-inflammatory activities from the incorporation of essential oils in the developed nanoformulations. However, further studies are still needed on the techniques used and the great diversity of oils with healing properties that can be administered with greater therapeutic efficacy.

CONCLUSION

From the present literature review, it was possible to observe that the main nanocarriers containing essential oils with the purpose of wound healing were nanofibers, nanoemulsions and inorganic nanoparticles, followed by nanostructured lipid carriers, nanocapsules and polymeric micelles. In the analyzed articles, the nanocarriers containing essential oils ensured their functionality, in a non-toxic and effective way, as, while maintaining their properties, they presented potential healing and antimicrobial activities. It demonstrates that nanotechnology is a promising tool to expand the use of different species of essential oils for healing purposes.

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