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"Júlio de Mesquita Filho"

Faculdade de Odontologia de Araraquara

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Avaliação da incorporação de Geraniol em nanoemulsões e micelas: caracterização, atividade antibiofilme e citotoxicidade

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Avaliação da incorporação de Geraniol em nanoemulsões e micelas: caracterização, atividade antibiofilme e citotoxicidade

Tese apresentada à Universidade Estadual Paulista, Faculdade de Odontologia de Araraquara, para a obtenção do Título de Doutor em Odontologia, Área de Implantodontia

Orientador: Profª Drª Denise M. P. Spolidorio

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Cristiano Silva Pontes

Avaliação da incorporação de Geraniol em nanoemulsões e micelas: caracterização, atividade antibiofilme e citotoxicidade

Comissão julgadora

Tese para obtenção do Título de Doutor em Odontologia, Área de Implantodontia

Presidente e Orientadora: Profª Drª Denise Madalena Palomari Spolidorio

2º Examinador: Profª Drª Janaína de Cássia Orlandi Sardi

3º Examinador: Prof. Dr. Marlus Chorilli

4º Examinador: Profª Drª Natália Leal Vizoto

Araraquara, 20 de junho de 2022.

Dedico esse trabalho a minha filha Mariana,
minha maior força nos momentos difíceis.

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“A vida é a arte do encontro, embora haja tanto desencontro pela vida”

Vinícius de Moraes[*]

[*] Moraes V. Samba da benção. Rio de Janeiro: Philips; 1971.

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Resumo

O objetivo deste trabalho foi sintetizar e caracterizar nanoemulsões lipídicas (NEs) e micelas (NMs) incorporadas com o composto natural geraniol (GE), e avaliar a atividade antimicrobiana e citotóxica *in vitro* destas nanopartículas sobre biofilmes de microrganismos periodontopatogênicos e células NOk-SI. A NE foi constituída de 10% de fase oleosa (colesterol), 10% de surfactantes [fosfatidilcolina de soja e polioxietileno 20-cetil éter (Brij 58®), 1:2] e 80% fase aquosa (tampão fosfato). A NM foi formulada com 5% de surfactantes (fosfatidilcolina de soja e Brij58®), 90 a 95% de fase aquosa e 1% de geraniol. A incorporação do geraniol foi realizada por sonicação e as características físico-químicas e estabilidade das nanopartículas foram analisadas após sua formulação e no período de 6 meses a 1 ano. Avaliou-se a atividade antimicrobiana das nanoemulsões contra cepas planctônicas de *Candida albicans* (ATCC 90028), *Streptococcus mutans* (ATCC 25175)*, Aggregatibacter actinomycetemcomitans* (JP2)*,* e a atividade antibiofilme de *C. albicans, S. mutans,* e biofilme misto de *C. albicans* e *Staphylococcus aureus* (ATCC 25923) sobre corpos de prova de Titânio. Os resultados foram submetidos à ANOVA 1-fator com correção de Welch e pós teste de Games-Howell, com nível de significância de 5%. O geraniol incorporado à nanoemulsão (GE-NE) e à micela (GE-NM) apresentaram tamanhos médios de 230 nm e 93 nm, PDI de 0,155 e 0,151, respectivamente, com boa estabilidade e homogeneidade após 6 meses a 1 ano de formulação. As concentrações acima de 300 µg/mL do GE e GE-NE foram citotóxicas e a GE-NM reduziu 4 vezes o efeito citotóxico do GE comparado ao composto puro. Os resultados indicaram uma atividade antimicrobiana das nanoemulsões contra *as cepas testadas,* mas apenas biofilmes de *C. albicans* sofreram redução significativa (6,3 Log_{10}) nas concentrações não-citotóxicas da GE-NE (< 300 µg/mL) e GE-NM (< 600 µg/mL).

Palavras-chave: Óleos voláteis. Nanotecnologia. Biofilmes. Peri-implantite. Estudos de viabilidade.

Pontes, CS**.** Evaluation of Geraniol incorporation in nanoemulsions and micelles: characterization, antibiofilm activity and cytotoxicity. [Tese de doutorado]. Araraquara: Faculdade de Odontologia da UNESP; 2022.

Abstract

The objective of this work was to synthesize and characterize lipid nanoemulsions (NEs) and micelles (NMs) incorporated with the natural compound geraniol (GE), and to evaluate the in vitro antimicrobial and cytotoxic activity of these nanoparticles on biofilms of periodontopathogenic microorganisms and NOk-SI cells. The NE consisted of 10% oil phase (cholesterol), 10% surfactants [soy phosphatidylcholine and polyoxyethylene 20-cetyl ether (Brij 58®), 1:2] and 80% aqueous phase (phosphate buffer). NM was formulated with 5% surfactants (soy phosphatidylcholine and Brij58®), 90 to 95% aqueous phase and 1% geraniol. The incorporation of geraniol was performed by sonication and the physicochemical characteristics and stability of the nanoparticles were analyzed after their formulation and in the period from 6 months to 1 year. The antimicrobial activity of the nanoemulsions was evaluated against planktonic strains of *Candida albicans* (ATCC 90028), *Streptococcus mutans* (ATCC 25175), *Aggregatibacter actinomycetemcomitans* (JP2), and the antibiofilm activity of *C. albicans*, *S. mutans*, and mixed biofilm of *C. albicans* and *Staphylococcus aureus* (ATCC 25923) on Titanium specimens. The results were submitted to 1-factor ANOVA with Welch correction and post-Games-Howell test, with a significance level of 5%. The geraniol incorporated into the nanoemulsion (GE-NE) and the micelle nanoemulsion (GE-NM) presented average sizes of 230 nm and 93 nm, PDI of 0.155 and 0.151, respectively, with good stability and homogeneity after 6 months to 1 year of formulation. Concentrations above 300 µg/mL of GE and GE-NE were cytotoxic and GE-NM reduced 4 times the cytotoxic effect of GE compared to the pure compound. The results indicated an antimicrobial activity of the nanoemulsions against the tested strains, but only *C. albicans* biofilms suffered a significant reduction (6.3 Log 10) in the non-cytotoxic concentrations of GE-NE (< 300 µg/mL) and GE-NM (< 600 µg/mL).

Keywords: Oils, volatile. Nanotechnology. Biofilms. Periimplantitis. Feasibility studies.

SUMÁRIO

1 INTRODUÇÃO

Os implantes dentários revolucionaram a reabilitação protética de pacientes edêntulos parciais e totais, e novos materiais e designs possibilitaram uma taxa de sobrevida de 94% no período superior a 13 anos[1,2]. Entretanto, a peri-implantite (PI) é a principal doença infecciosa que compromete sua estrutura de suporte biológica, com prevalência de 9,25% a 19,83% baseada em implantes e sujeitos, respectivamente[3,4], acarretando a perda dos implantes e suas próteses. O desenho e as superfícies rugosas destes implantes e conectores protéticos podem representar um ambiente propício para adesão de microrganismos orais e formação de biofilme. Bactérias proteolíticas, anaeróbias[5-8], espécies de *Streptococcus*[9,10], e *Candida albicans*[5,6] estão envolvidos na modulação da virulência de biofilmes bacterianos em estágios iniciais e tardios de PI.

Os métodos utilizados para o tratamento das doenças periimplantares como o debridamento mecânico e uso de antimicrobianos podem danificar as propriedades de superfície dos implantes ou promover a resistência bacteriana[11]. A clorexidina é considerada o padrão-ouro na redução dos microrganismos periodontopatogênicos e possui um excelente desempenho no controle químico, entretanto, acarreta na alteração da coloração dos dentes, descamação da mucosa oral, sensibilidade e alteração do paladar[12]. Além disso, não há consenso para o tratamento de infecções periimplantares devido à heterogeneidade dos estudos e à variabilidade dos tipos de superfícies de implantes[13-15].

Diante disso, pesquisas vêm sendo desenvolvidas no intuito de se desenvolver novos fármacos e diferentes produtos naturais estão sendo estudados como agentes alternativos na tentativa de suprimir a destruição dos tecidos periodontais e periimplantares, auxiliando na remoção do biofilme de superfície, prevenção e tratamento periodontal[16]. Os produtos naturais apresentam características notáveis, como excelente diversidade química, propriedades químicas e biológicas e menor toxicidade[17].

O geraniol (GE) é o constituinte comum de vários óleos essenciais, como a citronela, e é amplamente usado como um produto químico em fragrâncias cosméticas e uso no lar[18]. Além de apresentar baixa toxicidade, suas propriedades efetivas como repelente e inseticida para o controle de pragas, apresentaram boa atividade quimiopreventiva, assim como propriedades antimicrobianas, antioxidantes

e anti-inflamatórias[19-22]. Portanto, as propriedades promotoras do GE incentivam estudos a fim de explorar e viabilizar formulações de produtos contendo este composto. Contudo, possui elevada volatilidade exacerbada com o aumento da temperatura, curto tempo de ação e grande hidrofobicidade.

A nanotecnologia é um campo multidisciplinar da ciência com inúmeras aplicações, e tem proporcionado uma alternativa promissora para a pesquisa e desenvolvimento de sistemas de liberação de fármacos através do seu encapsulamento em sistemas nanométricos propiciando uma melhor estabilidade e proteção aos extratos voláteis contra a degradação ambiental, e permitindo uma melhor distribuição do composto ao seu local de ação, fator que proporciona uma série de benefícios ao paciente, como aumento da eficácia terapêutica, redução de doses, menor número de administrações e diminuição dos efeitos colaterais[17,23,24].

Inúmeras nanopartículas vêm sendo utilizadas como sistemas de transporte de fármacos[25], e os sistemas coloidais possuem vantagens devido à sua capacidade de proteção e encapsulamento de soluções bioativas insolúveis (lipofílicas ou hidrofílicas)[26]. As nanoemulsões são sistemas constituídos de uma fase contínua e uma fase dispersa e podem ser formadas por dispersão do óleo na água ou água em óleo, permitindo a incorporação de diferentes substâncias ativas. Possuem facilidade de preparação, composição simples, estabilidade termodinâmica e baixo custo de produção, proporcionando uma vantagem substancial a essa tecnologia como carreadora de substâncias hidrofóbicas[27-29].

Os surfactantes são compostos orgânicos anfifílicos que contêm grupos hidrofóbicos e hidrofílicos que podem organizar-se sob condições ambientais específicas em estruturas organizadas denominadas micelas. Estas são formadas por um núcleo hidrofóbico interno, no qual fármacos pouco solúveis em água podem ser aprisionados e por uma casca hidrofílica externa que isola a droga encapsulada do meio externo[30-33]. Possuem tamanho aproximado de 5 a 200 nm e se formam dependendo da concentração micelar crítica (CMC) das moléculas anfifílicas, podendo ser utilizadas como sistema de distribuição de compostos de tamanho nanométrico, fornecendo maior solubilidade e estabilidade aos fármacos hidrofóbicos[34], além de evitar a eliminação precoce via filtração glomerular com consequente melhoria da absorção celular.

Portanto, os sistemas nanoestruturados surgem como alternativas eficazes e seguras à incorporação do GE com objetivo de aumentar o seu tempo de ação,

permitindo a sua liberação de forma mais lenta, garantindo um espalhamento nas superfícies[35]. Além disso, possibilitam uma melhor biodegradabilidade, tolerabilidade e biodisponibilidade do fármaco a fim de orientar sua ação para o local específico de interesse[36].

Em vista do problema exposto, há grande interesse em desenvolver novas estratégias de tratamento e controle da PI. Isso inclui a busca de novas fontes de moléculas bioativas com capacidade antimicrobiana, eficiência farmacológica e baixos níveis de efeitos colaterais. Este projeto propõe avaliar a incorporação do geraniol em nanoemulsões e o seu efeito em biofilmes microbianos envolvidos na iniciação e progressão da Peri-implantite.

7 CONCLUSÃO

- O geraniol incorporado à nanoemulsão (GE-NE) e à nanoemulsão micelar (GE-NM) apresentaram tamanhos médios de 230 nm e 93 nm, PDI de 0,155 e 0,151, respectivamente, com boa estabilidade e homogeneidade após 6 meses a 1 ano de formulação;
- Os resultados indicaram uma atividade antimicrobiana do geraniol contra *S. mutans* e *A. actinomycetemcomitans,* mas em concentrações citotóxicas;
- Apenas biofilmes de *C. albicans* sofreram redução significativa (6,3 Log_{10}) nas concentrações não-citotóxicas da GE-NE (< 300 µg/mL) e GE-NM (< 600 µg/mL);
- A utilização do GE, GE-NE e GE-NM em biofilmes mistos de *Sthaphilococcos aureus* e *Candida albicans* em corpos de prova de Titânio diminuíram significativamente a quantidade das leveduras e sua transição para a forma de hifas;
- A incorporação do geraniol em nanoemulsões GE-NE (> 300 µg/mL) e GE-NM (> 1200 µg/mL) foram consideradas citotóxicas sobre células de queratinócitos orais humanos (NOK-SI);
- A incorporação do geraniol nas nanoemulsões como sistemas de entrega de fármacos melhoraram sua atividade antimicrobiana em comparação com seu extrato simples. Baseados nos resultados desse estudo e nas atividades biológicas das formulações desenvolvidas, novos estudos *in vitro* e *in vivo* são necessários para a sua utilização na prática clínica.

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