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BRAZILIAN ORGANIC PROPOLIS IN THE PREVENTION AND TREATMENT OF ORAL MUCOSITIS: *in silico* STUDY OF BIOMOLECULES OF THIS PROPOLIS WITH ORAL MUCOSITIS TARGETS

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Dissertação apresentada como parte dos requisitos para obtenção do título de Mestre em Ciências Biológicas pela Universidade Federal de Alfenas. Área de concentração: Biologia Celular, Molecular e Estrutural das Doenças Agudas e Crônicas.

Orientador: Prof.ª Dr.ª Lívia Máris Ribeiro Paranaiba
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RESUMO

A mucosite oral (MO) é um processo inflamatório exacerbado da mucosa decorrente de terapia antineoplásica (*e.g.* radioterapia e/ou quimioterapia). A MO causa lesões ulcerativas, eritema e dor intensa, podendo afetar a fala, a alimentação, a eficácia e o tempo de tratamento, prolongar a hospitalização, diminuir a qualidade de vida e o aumento da mortalidade. Ainda não está claro o mecanismo pelo qual a MO se desenvolve, até o momento, acredita-se que haja ao menos 14 vias envolvidas na patogênese que se relaciona ao processo inflamatório, e com a liberação de espécies reativas de oxigênio (EROs). Essa falta de conhecimento, aliada a ausência de informações quanto às citocinas e quimiocinas específicas desse processo, dificulta o desenvolvimento de abordagens preventivas ou terapêuticas para a MO. Produtos naturais, como a própolis, têm sido investigados como possíveis fontes de biomoléculas para a atenuação da MO. A própolis é uma substância resinosa coletada de diversas plantas por abelhas que possui potencial antimicrobiano, anti-inflamatório, radioprotetor, anticancerígeno, antinociceptivo, entre outros. A própolis é capaz de modular a imunidade não específica, interferindo na produção de algumas citocinas pró-inflamatórias e neutralizar a produção de EROs. A própolis orgânica brasileira, especialmente do tipo 1 (PO1), possui uma alta atividade antioxidante e pode ser uma alternativa no tratamento da MO. Portanto, o objetivo do estudo é identificar os alvos moleculares relacionados à patogênese da MO, interagí-los com moléculas ativas identificadas e isoladas da PO1, por meio de estudo *in silico* de docking molecular e avaliar a biodisponibilidade das moléculas identificadas na PO1 pela 'regra dos 5' de Lipinski e absorção gastrointestinal, a partir do *website* SwissADME. Para o estudo de docking molecular, foram coletadas as informações químicas e estruturais dos alvos relacionados à patogênese da MO selecionados e das moléculas identificadas na PO1 (ligantes), que foram selecionadas na base Protein Data Bank (PDB) e PubChem, respectivamente. Neste estudo adotou-se duas estratégias metodológicas: I- Docking de 1 ligante e II- Docking de múltiplos ligantes. Utilizou-se como ferramentas os softwares AutoDock Vina® e MGLTools®, para a identificação e seleção dos sítios de ligação mais promissores; e o software Maestro© para a identificação dos sítios de ligação mais promissores e a identificação dos resíduos em que ocorreram as interações entre os alvos e os ligantes. Na estratégia I todos os sete ligantes identificados interagiram com todos os oito alvos, com a energia de ligação variando de -1,9 a -8,7 kcal.mol^{-1}. Na estratégia II observamos potencial atividade combinada de todos os 6 ligantes avaliados para com todos os 8 alvos, sendo que os ligantes demonstraram melhor atividade com a TNF-α. Também observamos que os resíduos dos alvos em que os ligantes interagiram são constituintes de enzimas proteases. Concluímos que todos os ligantes identificados na PO1, e analisados neste estudo, interagiram com todos os alvos de modo promissor, sugerindo uma possível atividade anti-inflamatória, multialvo e inibidora de proteases, sendo que estes ligantes são moléculas indicadas para estudos *in vitro* e *in vivo*.

Palavras-chave: *Docking* molecular; Alvos moleculares; Produto natural; Câncer oral; Bioinformática.

ABSTRACT

Oral mucositis (OM) is an exacerbated mucosal inflammatory process resulting from antineoplastic therapy (*e.g*. radiotherapy and/or chemotherapy). OM causes ulcerative lesions, erythema, and severe pain, which can affect speech, diet, efficacy, and duration of treatment, prolong hospitalization, decrease quality of life and increase mortality. The mechanism which OM develops is still unclear, so far, it is proposed that there are at least 14 pathways involved in the pathogenesis related to this condition, with the release of reactive oxygen species (ROS). This lack of knowledge and information regarding specific cytokines and chemokines related to this process makes it difficult to develop preventive or therapeutic approaches to OM. Natural products, such as propolis, have been investigated as possible sources of biomolecules for OM attenuation. Propolis is a resinous substance collected from several plants by bees that have antimicrobial, anti-inflammatory, radioprotective, anticancer, antinociceptive potential, among others. Propolis can modulate non-specific immunity, interfering with the production of some pro-inflammatory cytokines and neutralizing the production of ROS. Brazilian organic propolis, especially type 1 (PO1), has a high antioxidant activity and can be an alternative in the treatment of OM. Therefore, the study aims to identify the molecular targets involved in the pathogenesis of OM interacting them with active molecules identified and isolated from PO1, through an *in silico* study of molecular docking, and assess the bioavailability of the molecules identified in PO1 by Lipinski's 'rule of 5' and gastrointestinal absorption through the SwissADME website. For the study of molecular docking, chemical and structural information of selected OM pathogenesis related targets and molecules identified in PO1 (ligands) were collected, which were selected in the Protein Data Bank (PDB) and PubChem database, respectively. This study adopted two methodological strategies: I- 1-ligand docking and II- Multiple-ligand docking. The AutoDock Vina® and MGLTools® software were used to identify and select the most promising binding sites; and the Maestro© software for identifying the most promising binding sites and identifying the residues where interactions between targets and ligands occurred. In strategy I, all seven ligands interacted with all eight targets with binding energy ranging from -1.9 to -8.7 kcal.mol^{-1}. In strategy II, we observed potential combined activity of all 6 evaluated ligands for all 8 targets, the ligands showed better activity with TNF-α in general. We also observed that the residues from the targets where the ligands interacted were constituents of protease enzymes. We conclude that all ligands identified in PO1 and analyzed in this study promising interacted with all targets, suggesting a possible anti-inflammatory, multi-target, and protease inhibitory activity, and these ligands are suitable molecules for *in vitro* studies and *in vivo*.

Keywords: Molecular docking; Molecular targets; Natural product; Oral cancer; Bioinformatics.

LISTA DE TABELAS

LISTA DE ABREVIATURAS E SIGLAS

3D	Estrutura tridimensional
CCDC	Cambridge Crystallographic Data Centre
CRP	Protein C-Reactive/Proteína C Reativa
COX-2	Ciclooxigenase 2
CT/QT	Quimioterapia
DNA	Ácido desoxirribonucleico
EFG	Fator de crescimento epidermal
HMGB1	Proteína 1 do grupo de alta mobilidade
IF	Fator de impacto
IFN-γ	Interferon-gama
IL-1α	Interleucina um-alfa
IL-1β	Interleucina um-beta
IL-6	Interleucina-seis
IL-8	Interleucina-oito
INCA	Instituto Nacional de Câncer José Alencar Gomes da Silva
MO/OM	Mucosite oral/Oral mucositis
NF-κB	Fator nuclear kappa-B
PDB	Protein Data Bank
PDBe	Protein Data Bank in Europe
PUMA	P53 upregulated modulator of apoptosis/Modulador de apoptose regulado positivamente por P53
PO/OP	Própolis orgânica brasileira/Brazilian organic propolis
PPGCB	Programa de Pós-Graduação em Ciências Biológicas
ROS/ERO	Espécies reativas de oxigênio
RT	Radioterapia
TNF-α	Fator de necrose tumoral humana-alfa
UNIFAL-MG	Universidade Federal de Alfenas

SUMÁRIO

1 INTRODUÇÃO

O câncer oral é a sétima neoplasia de maior ocorrência mundial, ocupando a nona posição de mortes, sendo estimadas 359.000 mortes por ano *(BOSETTI et al., 2020)*. No Brasil o Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA) estima que a incidência do câncer para o triênio de 2020-2022 será de 387.980 novos casos em homens e 297.980 em mulheres, sendo que destes, 11.180 e 4.010 novos casos localizados na cavidade oral, em homens e mulheres, respectivamente *(INCA, 2020)*. Os tratamentos antineoplásicos visam a destruição das células cancerígenas, no entanto, os agentes quimio e radioterápicos não são seletivos, causando danos às células saudáveis, assim como às imunológicas *(BROWN; GUPTA, 2020)*.

Os tratamentos oncológicos, como a quimioterapia e a radioterapia na região de cabeça e pescoço, podem resultar em danos colaterais, como o aparecimento da mucosite oral *(CINAUSERO et al., 2017; JENSEN; PETERSON, 2014; SROUSSI et al., 2017)*. A mucosite oral (MO) consiste em uma reação inflamatória exacerbada *(KIM et al., 2005)*, causada por radioterapia e/ou quimioterapia na região de cabeça e pescoço. É caracterizada por lesões eritematosas e/ou ulcerativas, normalmente extremamente dolorosas, que podem: aumentar o tempo de internação, o uso de opióides para alívio da dor, e o risco de infecções oportunistas (*e.g.* locais e sistêmicas), contribuindo, portanto, para a diminuição da qualidade de vida dos sujeitos, do tratamento oncológico e encarecendo o tratamento *(RILEY et al., 2017; SONIS, 2004)*.

O desenvolvimento da MO se dá em 5 etapas: a de Iniciação, em que após o dano ao DNA induzido pelos tratamentos oncológicos há morte celular, produção de espécies reativas de oxigênio (ROS) e a ativação de diversos fatores de transcrição; esses fatores levam à etapa de Sinalização e Amplificação, em que há a ativação e regulação positiva de diferentes citocinas pró-inflamatórias, moléculas de adesão celular e respondedores de estresse, amplificando o dano celular; então, há a etapa de Ulceração, com o desenvolvimento de lesões acompanhadas por dor intensa e perda de apetite, podendo levar à internação do paciente; então, a partir de 2 a 4 semanas após a última dose do tratamento antineoplásico, há a última etapa do desenvolvimento da MO, que é a etapa de Cicatrização, onde há a cicatrização das lesões ulcerativas *(NICOLATOU-GALITIS et al., 2021; SONIS, 2004)*.

Apesar de ser um importante efeito adverso, a patogênese da MO permanece pouco

esclarecida *(HAN et al., 2013)*, assim como não há um tratamento eficaz, apenas preventivo (*e.g.* higiene bucal) e terapêutico, com eficácia limitada, sendo que o alívio da dor, o suporte nutricional e a prevenção de infecções secundárias são elementos-chave no tratamento do sujeito. A complexidade da patogênese da MO é evidenciada pela participação de 14 possível vias moleculares, como descrito na Tabela 1, sendo que não há na literatura, a relação de quais destas vias se desenvolve na MO induzida por radioterapia ou por quimioterapia *(SONIS; VILLA, 2018; VASCONCELOS et al., 2016)*.

Tabela 1- Vias moleculares relacionadas à MO

Vias moleculares que foram relacionadas à MO
Metabolismo de nitrogênio
Sinalização de receptor tipo Toll
Sinalização por NF-κB
Sinalização de receptor de células B (linfócitos B)
Sinalização P13K / AKT
Ciclo celular: receptor *checkpoint* de dano de DNA G2/M
Sinalização P38 MAPK
Sinalização Wnt/β-catenina
Sinalização do receptor de glutamato
Sinalização de integrina
Sinalização VEGF
Sinalização IL-6
Sinalização de receptor de morte
Sinalização SAPK/JNK

Fonte: *(SONIS et al., 2007)*

Há diversos tratamentos que têm sido propostos no controle da MO (*e.g.* crioterapia, laserterapia, uso de opioides, entre outros) *(BARBOSA et al., 2019a; SROUSSI et al., 2017)*, como o fármaco Benzidamina, que tem sido proposto, dentre os agentes anti-inflamatórios, como um possível agente preventivo e de tratamento contra a MO *(ELAD et al., 2020)*. Essa dificuldade em identificar um agente terapêutico adequado é devido ao fato de a MO ser uma doença multifatorial, ou seja, originária de diversas e complexas interações de fatores, como demonstrado pela Tabela 1 *(SALEHI et al., 2018)*.

A Associação Multinacional de Cuidados de Suporte em Câncer (*Multinational*

Association of Supportive Care in Cancer – MASCC) e a Sociedade Internacional de Oncologia Oral (*International Society for Oral Oncology – ISOO*) propõem o uso de agentes naturais e diversos *(YAROM et al., 2020)*. Produtos naturais são potenciais agentes terapêuticos, uma vez que possuem diversas biomoléculas que podem atuar em diferentes alvos *(FANG et al., 2020)*. Um destes produtos que têm sido amplamente estudado para controle e tratamento de doenças multifatoriais é a própolis, já que ela apresenta potenciais efeitos anti-inflamatórios, anticancerígenos, antimicrobianos, antioxidantes entre outros *(FRANCHIN et al., 2018; NANI et al., 2020; TIVERON et al., 2016)*. Em especial, Tiveron e colaboradores *(TIVERON et al., 2016, 2020)* estudaram a Própolis Orgânica, uma própolis brasileira (PO), que foi identificada e coletada nos estados do Paraná e Santa Catarina e classificada em 7 tipos (PO1 a PO7) como fonte de biomoléculas com atividades anti-inflamatória, antioxidante e antimicrobiana. Na PO1 foram identificadas sete estruturas pertencentes à classe de lignanas ou precursores de lignanas, denominadas de biomarcadores, uma vez que estavam presentes apenas neste tipo de própolis (PO1) e que apresentaram estas atividades biológicas em estudos *in vitro (NANI et al., 2020; TIVERON et al., 2016)*.

O *docking* molecular é um estudo racional prévio aos estudos *in vitro* e *in vivo* (pré-clínico e clínico), que poupa tempo dispendido, recursos financeiros, material, e principalmente a vida de animais em pesquisas *(FREIRES et al., 2017; SILVA et al., 2019)*. Esse modelo de estudo *in silico* busca melhorar a compreensão sobre o processo de reconhecimento entre duas ou mais moléculas, se baseando na teoria do ajuste induzido, que prevê que as enzimas e substratos podem sofrer variações conformacionais *(CZARNOTA et al., 2019)*. Ele também possibilita identificar os possíveis sítios de ligação, posição e afinidade entre um ligante, que é uma molécula pequena, e o receptor, que é a macromolécula, o que contribui para a compreensão do funcionamento do mecanismo de reconhecimento molecular *(ROCHE; BRACKENRIDGE; MCGUFFIN, 2015; TAO et al., 2020)*.

Para a ligação entre ligante e receptor é necessária que ocorra uma conformidade espacial e energética entre eles, nesse momento ocorrem alterações constantes no sítio de ligação até o estabelecimento de uma ligação estável. Há 3 tipos de *docking*: o rígido, onde tanto o receptor quanto o ligante permanecem sem alterações conformacionais, sendo indicado para grandes estruturas; o flexível, em que ambos, receptor e ligante, sofrem alterações estruturais; e o semi-flexível, com alterações estruturais apenas no ligante, sendo recomendado em estudos com ligantes de pequenas moléculas *(MORRIS et al., 2009; ROY et al., 2018; TAO et al., 2020)*, como é o caso deste estudo. Alguns dos *softwares* mais utilizados para esse tipo de estudo são o AutoDock (MGLTools) e o AutoDock Vina, que é mais veloz e tem maior

precisão *(TAO et al., 2020; TROTT; OLSON, 2010)*, sendo, portanto, os programas escolhidos para este estudo.

Devido aos potenciais efeitos anti-inflamatório e antioxidante, a PO1 é uma candidata promissora para um estudo como possível tratamento da MO *(TIVERON et al., 2020)*. Portanto, o objetivo deste estudo é estudar *in silico* a interação entre os alvos relacionados à patogênese da MO e as biomoléculas identificadas na PO1, por meio de *docking* molecular.

1.1 OBJETIVOS

1.1.1 Objetivo Geral

Identificar os alvos moleculares envolvidos na patogênese relacionada à MO, a partir de uma revisão da literatura e interagí-los com moléculas ativas isoladas da própolis orgânica, por meio de estudo *in silico*.

1.1.2 Objetivos Específicos

a) Identificar os alvos relacionados à patogênese da MO radioquimioinduzida;
b) Avaliar computacionalmente a biodisponibilidade das moléculas ativas identificadas da própolis orgânica tipo I;
c) Avaliar computacionalmente a interação entre as moléculas ativas identificadas da própolis orgânica e os alvos envolvidos na patogênese da MO individualmente, ou seja, adotando a estratégia de docking de apenas um ligante; e
d) Analisar computacionalmente a interação entre as moléculas ativas identificadas da própolis orgânica e os alvos envolvidos na patogênese da MO combinados, ou seja, adotando a estratégia de docking de múltiplos ligantes.

2 DESENVOLVIMENTO

2.1 *In silico* evaluation of the interaction of organic propolis molecules with pathogenesis targets of chemoradiotherapy-associated oral mucositis. [1]

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ABSTRACT

This study aims to identify potential inflammatory targets related TO OM pathogenesis from a review of literature, then to analyze their interaction with Brazilian Organic Propolis (OP1) molecules by bioavailability under Lipinski's rules; and also, to perform an *in silico* study of molecular docking through 2 strategies: I-Single ligand docking, and II-Multiple ligand docking. The chemical and structural information of selected OM targets and molecules identified in OP1 (ligands) were collected on suitable platforms; AutoDock Vina and MGLTools software was used to selecting promising binding sites; and Maestro software for analyzes of multiple ligands. In strategy I, all ligands interacted in a promising way with all targets. In strategy II, we observed combined interactions of ligands, demonstrating interactions with protease enzymes. In conclusion, the active molecules of OP1 interacted computationally with inflammatory targets related to the OM pathogenesis, with possible combined activity and inhibitory activity of proteases, suggesting several possible activities, which should be investigated.

Keywords: Molecular docking. Lignans. Bioinformatics. Natural product. Protease. Cancer.

[1] Este artigo foi submetido à revista Journal of Medicinal Chemistry, IF (2020): 7.446 (Anexo A)

Introduction

Mucositis consists of damage to the oral mucosa[1] and the oropharynx. It is characterized by inflammation in the oral cavity and damage to the mucosa[2]. Oral mucositis (OM) is a multifactorial condition that develops from antineoplastic treatment, such as radiotherapy (RT), in the head and neck region, and systemic chemotherapy (CT)[3]. The first symptom of OM is painful erythematous and/or ulcerative lesions, which can compromise nutrition causing weight loss. The degree of myelosuppression, as well as environmental factors represented by the oral microbial flora, saliva, and its protective components, added to the possible role of functional trauma, provide an important set of factors that impact the frequency, severity, and course of the disease[4,5]. This condition may also compromise the effectiveness by the need of treatment interruption associated or not to hospitalization with several complications, such as secondary infections and the progression of the underlying disease[6], which can increase mortality and influence the diagnosis of cancer[4].

RT and/or CT cause cellular damage releasing reactive oxygen species (ROS) which amplify this damage leading to cell death and the production of pro-inflammatory cytokines, intensifying mucosal lesions. Some inflammatory mediators or targets (*e.g.* cytokines and chemokines) that may be related to OM pathogenesis are TNF-α, IL-1β, IL-6[7–9], growth factors (EGF)[4,10,11], NF-κB[12], COX-2, IL-1α[7], IL-8[9], IFN-γ, and HMGB1[13–15].

Although benzydamine has been proposed as a preventive treatment for OM[16] there is no *standard* treatment for this condition[14]. Natural products such as honey and propolis have been widely studied as sources of molecules with biological activities, being, therefore, of pharmaceutical interest[17,18]. Propolis has a potential antibiotic effect[19], radioprotective, local anesthetic, immunomodulatory[20], anticancer[21], anti-inflammatory[17,21], and antioxidant activities[20–22] which can prevent, reduce, and treat OM radiochemical induced, as reduce the DNA damage.

Brazilian organic propolis (OP) is a special type of propolis classified into 7 types (OP1 up to OP7). Tiveron et al., (2020)[23] characterized the chemical composition of OP1, detecting bioactive products exclusive to natural products which can be used as chemical biomarkers. The seven compounds isolated from OP1 are: coniferyl alcohol, coniferyl aldehyde, (+)-lariciresinol, (-)-secoisolariciresinol, balajaponin D, (+)-pinoresinol, and (-)-matairesinol[23].

Natural products have been studied through *in silico* methodology (*e.g.* docking molecular), since understanding how ligand can recognize and interact with a macromolecule is extremely important for the development of new drugs[24]. Molecular docking aims to improve the understanding of the recognition process between two or more molecules[25], this allows the

identification of possible binding sites, position, and affinity between a ligand and the receptor, which contributes to the understanding of the functioning of the molecular recognition mechanism[26,27]. These aspects characterize docking as a rational study before *in vitro* and *in vivo* studies (preclinical and clinical), since predicting possible interactions can save time, investments, material, and especially the lives of animals and humans in research[28,29].

The objective of this study is to evaluate the bioavailability of OP1 isolated bioactive molecules, called ligands, and analyze the interaction of these ligands with inflammatory targets of OM, selecting candidates for anti-MO therapy.

Results and Discussion

Molecular targets related to the OM pathogenesis

Table 1 shows the pathogenesis targets OM-related that were selected by literature searches, the activity of these mediators in mucositis, the structure in the PDB platform, and the reference of the selected articles. All eight targets presented here were selected for the docking simulations.

Table 1. Selected pathogenesis targets related to OM.

Targets	Pharmacologic action	Structure	Reference
p53	Its deficiency causes blockade of apoptosis that occurs 3 to 6 hours after radiotherapy.	1AIE Chain: A Mutation: 0 https://www.rcsb.org/structure/1AIE	5,30–32
PUMA	Its deficiency blocks p53-activated apoptosis, hypoxia in tissues and cells and causing DNA damage. Works by activating caspase and causing mitochondrial dysfunction.	2M04 Chain: B Mutation: 0 https://www.rcsb.org/structure/2M04	5,30–32
TNF-α	Related to tissue damage. Under radiotherapy, it may be associated with the severity of mucositis. It is related to radio-induced and chemo-induced injuries.	1TNF Chain: A, B, C Mutation: 0 https://www.rcsb.org/3d-view/1TNF	10,30,31,33,34
IL-1β	Increases in chemotherapy and is related to tissue damage. Under radiotherapy, it may be associated with the severity of mucositis. When elevated, severe oral toxicity develops. It is related to radio-induced and chemo-induced injuries.	1ITB Chain: A Mutation: 0 https://www.rcsb.org/structure/1ITB	10,30,31,33,34
IL-6	Pro-inflammatory cytokine, up-regulated in OM, a potential therapeutic target. Under radiotherapy, it may be associated with the severity of	4ZS7 Chain: A Mutation: 0 https://www.rcsb.org/structure/4ZS7	4,10,31,33–35

	mucositis. When elevated, severe oral toxicity develops. Related to chemo-induced injuries.		
NF-κB	Up-regulated in OM, potential therapeutic target	1A3Q Chain: C [auth A] e D [auth B] Mutation: 0 https://www.rcsb.org/structure/1A3Q	4,30,33
EGF	Stimulates epithelial cell proliferation, which contributes to the worsening of mucositis	3NJP Chain: C, D Mutation: 0 https://www.rcsb.org/structure/3NJP	11,33
CRP	It is related to the degree of severity of radio-induced mucositis.	1B09 Chain: A, B, C, D, E Mutation: 0 https://www.rcsb.org/structure/1B09	36

The inflammatory targets studied in the literature more related to the pathogenesis of OM were selected (*e.g.* oral mucosa)[4,30,33,36], which are the same observed in systemic inflammatory processes[37]. In the literature, there are other inflammatory targets are related to other types of mucositis, such as gastrointestinal[38] and anal[39], which will not be addressed in this study.

Ligand molecules

The ligands coniferyl alcohol, coniferyl aldehyde, and (-)-matairesinol presented the 'ideal' [$_{(I)}$] and 'representative' [$_{(R)}$] forms. This differentiation is due to the classification adopted by the PDBeChem website, which is the base for others, such as PDBe. The platform justified this differentiation with the following argument: ‘Model (representative) structures of ligands comes from a PDB entry the ligand was encountered for the first time. So their geometry can suffer from all sorts of artifacts (especially for the older ligands). Ideal coordinates are generated using Molecular Networks' Corina, and if there are issues, OpenEye's OMEGA. In some cases, *e.g.* complex ligands with ruthenium ions coordinates for certain atoms are not available, this is not the case for 'model' coordinates’.

Lipinski's ‘rule of 5’ and gastrointestinal absorption applied to ligands

In the results of Table 2, we can see that all the ligands under study, in both moments of evaluation, respected Lipinski's ‘rule of 5’. Therefore, all forms of the ligands showed good oral absorption (solubility and permeability) since they had a molecular weight (MWT) up to 500, MLogP up to 4.15, up to 10 of H-bonds receptors, and up to 5 H-bonds donors. All ligands are suitable candidates for drugs to be administered by this route. Due to the similar results for

all ligands, this criterion selected both 'ideal' [$_{(I)}$] and 'representative' [$_{(R)}$] forms for the continuity of the study.

In the gastrointestinal absorption analysis, all the seven ligands showed high absorption in this subject since they satisfy lipophilicity (MLogP) and polarity calculated by the predictive model BOILED-Egg.

Table 2. Lipinski and gastric absorption of ligands in the 'pre' and post-docking moments.

Moment	Ligand	G.I. Absorption*	Lipinski	MWT*[A]	MLogP*[B]	N or O*[C]	NH or OH*[D]
PRE-DOCKING	coniferyl alcohol$_{(I)}$ coniferyl alcohol$_{(R)}$ coniferyl aldehyde$_{(I)}$ coniferyl aldehyde$_{(R)}$ (+)-lariciresinol (-)-secoisolariciresinol balajaponin D (+)-pinoresinol (-)-matairesinol$_{(I)}$ (-)-matairesinol$_{(R)}$	HIGH	Yes, 0 violation	≤ 500	≤ 4.15	≤ 10	≤ 5
POST-DOCKING	coniferyl alcohol$_{(I)}$ (EGF;IL-1β;IL-6;NF-κB; P53;PUMA;TNF-α;CRP) coniferyl alcohol$_{(R)}$ (EGF;IL-1β;IL-6;NF-κB; P53;PUMA;TNF-α;CRP) coniferyl aldehyde$_{(I)}$ (EGF;IL-1β;IL-6;NF-κB; P53;PUMA;TNF-α;CRP) coniferyl aldehyde$_{(R)}$ (EGF;IL-1β;IL-6;NF-κB; P53;PUMA;TNF-α;CRP) (-)-matairesinol$_{(I)}$ (EGF;IL-1β;IL-6;NF-κB; P53;PUMA;TNF-α;CRP) (-)-matairesinol$_{(R)}$ (EGF;IL-1β;IL-6;NF-κB; P53;PUMA;TNF-α;CRP)	HIGH	Yes, 0 violation	≤ 500	≤ 4.15	≤ 10	≤ 5

*Gastrointestinal absorption; *[A]: molecular weight (MWT) up to 500; *[B]: MLogP up to 4.15; *[C]: up to 10 of H-bonds receptors; and *[D]: up to 5 H-bonds donors

To the best of our knowledge, this is the first study evaluating *in silico* the possible activities of lignans present in organic propolis, most of studies were *in vitro*[40].

In this study, all the seven ligands met all 4 of Lipinski's rules (Table 2), which may indicate good bioavailability since natural products normally meet only 3 of these rules[41]. All the ligands evaluated also met the criteria established for gastrointestinal absorption. Therefore,

it is possible to infer from this *in silico* study, that the ligands showed an excellent oral or gastrointestinal bioavailability[42,43]. In other studies, the ligands (+)-pinoresinol, (-)-matairesinol, (+)-lariciresinol, and (-)-secoisolariciresinol showed rapid absorption in the small intestine, having been identified in the bloodstream only one hour after ingestion[40,44].

Lignans are secondary plant metabolites pharmacologically active, constituted by the dimerization of phenolic compounds[45]. There are several 'subtypes' of lignans, and those that are converted to enterolignans and enterolactone can be absorbed by humans[46]. Lignans known to be precursors of enterolignans are the following compounds: (+)-lariciresinol, (-)-secoisolariciresinol, (+)-pinoresinol, and (-)-matairesinol[47]. The concentrations (in plasma, urine, and serum) of enterolignans are inversely proportional to the risk of breast cancer[48,49] having protective actions for several types of cancer[50,51] and cardiovascular diseases[52]. Also, enterolignans and (-)-secoisolariciresinol showed significant enterohepatic recirculation[40,44].

The literature shows that absorption of lignans varies from organism to organism (depending on intestinal bacteria, genetic factors) and that it occurs through the gastrointestinal tract[40]. All these properties are of interest to our study as OM is a multifactorial disease.

Analyze of the Strategy I: Single ligand docking

Initially, Strategy I was applied to benzydamine, a ligand used in this study as a control. It was simulated to analyze binding with the eight targets related to the pathogenesis of OM. The energetic variation between benzydamine and the targets ranged from -4.8 to -7.6 kcal.mol^{-1}, and the target that showed the best interaction was TNF-α (-7.6 kcal.mol^{-1}) (Table 3).

All seven ligands exhibited promising binding capabilities to the assessed targets (Table 3). Regarding TNF-α and CRP, the ligands that showed the best results were coniferyl alcohol, in the ideal [$_{(I)}$] and representative [$_{(R)}$] forms, coniferyl aldehyde, only in the $_{(R)}$ form, (+)-lariciresinol, (-)-secoisolariciresinol, balajaponin D, (+)-pinoresinol, and (-)-matairesinol, in $_{(I)}$ and $_{(R)}$ forms. Among the evaluated targets, TNF-α was the one that showed the greatest affinity with the ligands under study (Δ energetic -3.2 to -8.7 kcal.mol^{-1}).

The IL-6, IL-1β, P53, PUMA, EGF, and NF-κB targets showed similar results (Table 3). Among these, the lowest value of energy expenditure was -6.7 kcal.mol^{-1} for ligand (+)-lariciresinol with the IL-1β. The highest observed value of energy expenditure was -1.9 kcal.mol^{-1} to the PUMA with coniferyl aldehyde in the $_{(I)}$ form.

Regarding the TNF-α, Table 3 shows that the (+)-lariciresinol (-8.7 kcal.mol^{-1}), (-)-matairesinol, in the $_{(I)}$ (-8.0 kcal.mol^{-1}) and $_{(R)}$ forms (-7.9 kcal.mol^{-1}), (-)-secoisolariciresinol (-7.8 kcal.mol^{-1}), balajaponin D (-8.7 kcal.mol^{-1}), and (+)-pinoresinol (-8.5 kcal.mol^{-1}), showed

better interaction results than benzydamine (-7.6 kcal.mol^{-1}), considering that their results had lower binding energy.

In the CRP (Table 3), the interaction with benzydamine presented an energy expenditure of -6.9 kcal.mol^{-1}, while the ligands (+)-lariciresinol (-7.7 kcal.mol^{-1}), balajaponin D (- 7.2 kcal.mol^{-1}), (+)-pinoresinol (-7.6 kcal.mol^{-1}), and (-)-matairesinol in the $_{(I)}$ (-7.6 kcal.mol^{-1}) and $_{(R)}$ (-7.2 kcal.mol^{-1}) forms, presented numerically lower results than benzydamine.

Regarding the P53 (Table 3), benzydamine presented an energy expenditure of -6.0 kcal.mol^{-1} of interaction, and the ligands (+)-lariciresinol (-6.1 kcal.mol^{-1}), (-)-matairesinol in the $_{(R)}$ form (-6.3 kcal.mol^{-1}), and (+)-pinoresinol (-6.1 kcal.mol^{-1}) presented results numerically smaller or similar to benzydamine.

For the IL-1β (Table 3), benzydamine presented an interaction energy expenditure of -6.0 kcal.mol^{-1}. However, the (+)-lariciresinol (-6.7 kcal.mol^{-1}), (-)-secoisolariciresinol (-6.2 kcal.mol^{-1}), balajaponin D (-6.2 kcal.mol^{-1}), (+)-pinoresinol (-6.2 kcal.mol^{-1}), and (-)-matairesinol in the $_{(I)}$ (-6.4 kcal.mol^{-1}) and $_{(R)}$ forms (-6.2 kcal.mol^{-1}), presented numerically smaller or similar results to benzydamine.

Table 3. Results of strategy I: the affinity between targets and ligand (kcal.mol^{-1}).

Ligand	**Inflammatory targets**							
	IL-6	**IL-1β**	**P53**	**PUMA**	**TNF-α**	**EGF**	**NF-κB**	**CRP**
Benzydamine $_{(control)}$	-5.7	-6.0	-6.0	-4.8	-7.6	-5.6	-5.9	-6.9
coniferyl alcohol $_{(I)}$	-4.6	-4.4	-4.4	-3.4	-5.6	-4.5	-4.3	-5.3
coniferyl alcohol $_{(R)}$	-5.0	-4.3	-4.8	-3.7	-6.0	-4.8	-5.1	-5.2
coniferyl aldehyde $_{(I)}$	-3.1	-2.5	-3.5	-1.9	-3.2	-2.8	-2.9	-3.0
coniferyl aldehyde $_{(R)}$	-5.1	-4.4	-4.6	-3.8	-6.1	-4.8	-5.0	-5.5
(+)-lariciresinol	-6.0	-6.7	-6.1	-5.0	-8.7	-5.7	-6.6	-7.7
(-)-secoisolariciresinol	-6.1	-6.2	-5.5	-4.6	-7.8	-5.8	-5.9	-6.6
balajaponin D	-6.2	-6.2	-5.7	-5.4	-8.7	-5.9	-6.1	-7.2
(+)-pinoresinol	-6.5	-6.2	-6.1	-5.2	-8.5	-5.8	-6.2	-7.6
(-)-matairesinol $_{(I)}$	-6.1	-6.4	-5.9	-4.2	-8.0	-6.3	-6.0	-7.6
(-)-matairesinol $_{(R)}$	-5.6	-6.2	-6.3	-4.8	-7.9	-6.5	-5.7	-7.2

(I) ideal and (R) representative forms of ligand

Analyzing the images of the results between the seven ligands under study and benzydamine (supporting information, Table 1S[2]) we detected ligands that interacted at the same site as benzydamine and others at different sites, as described below (Table 4).

For the PUMA (Table 4), all seven ligands interacted at the same site as benzydamine, while for the P53, all of them presented a possible multitarget behavior, interacting at different

[2] O material suplementar, Table 1S está no APÊNDICE A

sites than the benzydamine site. In the IL-1β, only the coniferyl aldehyde in the ideal form interacted at a different site compared to benzydamine, whereas in the IL-6 only the (+)-lariciresinol interacted at the same site as benzydamine. In the NF-κB, only the (+)-lariciresinol and (-)-secoisolariciresinol interacted at the same site as benzydamine.

In the CRP (Table 4), the coniferyl alcohol in ideal [$_{(I)}$] and representative [$_{(R)}$] forms, coniferyl aldehyde in $_{(I)}$ form, (+)-pinoresinol, and (-)-secoisolariciresinol interacted at the same site as benzydamine, while the coniferyl aldehyde in $_{(R)}$ form, (+)-lariciresinol, balajaponin D and (-)-matairesinol in $_{(I)}$ and $_{(R)}$ forms, interacted at different sites compared to benzydamine.

In the EGF (Table 4), the ligands coniferyl aldehyde in the forms $_{(I)}$ and $_{(R)}$, coniferyl alcohol in the form $_{(R)}$, (-)-matairesinol in the form $_{(I)}$ and $_{(R)}$, and (+)- pinoresinol interacted at the same site as benzydamine, while the coniferyl alcohol in the form $_{(I)}$, (+)-lariciresinol, balajaponin D, and (-)-secoisolariciresinol interacted at different sites than benzydamine.

Finally, regarding the TNF-α (Table 4), only the coniferyl aldehyde, in $_{(I)}$ and $_{(R)}$ forms, and coniferyl alcohol, in $_{(I)}$ and $_{(R)}$ forms, interacted at different sites than benzydamine.

Table 4. Ligands that dispute, or do not dispute, the binding site with the benzydamine.

Targets	Ligands that have bonded to the same site	Ligands that have not bonded to the same site
CRP	coniferyl aldehyde$_{(I)}$ coniferyl alcohol($_I$ and $_R$) (+)-pinoresinol (-)-secoisolariciresinol	coniferyl aldehyde$_{(R)}$ (+)-lariciresinol balajaponin D (-)-matairesinol($_I$ and $_R$)
EGF	coniferyl aldehyde($_I$ and $_R$) coniferyl alcohol$_{(R)}$ (+)-matairesinol($_I$ and $_R$) (+)-pinoresinol	coniferyl alcohol$_{(I)}$ (+)-lariciresinol balajaponin D (-)-secoisolariciresinol
IL-1β	balajaponin D coniferyl alcohol($_I$ and $_R$) coniferyl aldehyde$_{(R)}$ (+)-lariciresinol (-)-matairesinol($_I$ and $_R$) (+)-pinoresinol (-)-secoisolariciresinol	coniferyl aldehyde$_{(I)}$
IL-6	(+)-lariciresinol	coniferyl alcohol($_I$ and $_R$) coniferyl aldehyde($_I$ and $_R$) (-)-secoisolariciresinol balajaponin D (+)-pinoresinol (-)-matairesinol($_I$ and $_R$)
NF-κB	(+)-lariciresinol (-)-secoisolariciresinol	coniferyl alcohol($_I$ and $_R$) coniferyl aldehyde($_I$ and $_R$) balajaponin D (+)-pinoresinol (-)-matairesinol($_I$ and $_R$)
P53	-	coniferyl aldehyde($_I$ and $_R$) coniferyl alcohol($_I$ and $_R$)

		(+)-lariciresinol (-)-secoisolariciresinol balajaponin D (+)-pinoresinol (-)-matairesinol(I and R)
PUMA	coniferyl aldehyde(I and R) coniferyl alcohol(I and R) (+)-lariciresinol (-)-secoisolariciresinol balajaponin D (+)-pinoresinol (-)-matairesinol(I and R)	-
TNF-α	balajaponin D (+)-lariciresinol (-)-matairesinol(I and R) (+)-pinoresinol (-)-secoisolariciresinol	coniferyl aldehyde(I and R) coniferyl alcohol(I and R)

(I) ideal and (R) representative forms of ligand

Based on the analysis of the results obtained in this strategy, in the ligands that presented the 'ideal' [$_{(I)}$] and 'representative' [$_{(R)}$] forms the difference in conformity between these forms were detected, which was confirmed through the visualization of the complex ‘inflammatory target + ligand'. Therefore, it is of interest for this study to adopt both forms for future analyzes.

This molecular docking study was carried out to assess whether the bioactive molecules of Brazilian organic propolis (OP1), identified as belonging to the chemical group of lignans or lignans precursors (the ligands studied) and the control ligand benzydamine would demonstrate possible interactions with the selected targets related to OM pathogenesis (eight) (Table 3). We observed, *in silico*, that all ligands interacted with all targets related to the inflammatory process occurring in OM (Table 3).

Benzydamine, a non-steroidal anti-inflammatory drug, has also been shown in the literature to inhibit TNF-α and IL-1β targets[53,54]. Morgan and collaborators (2018)[53] reported that the difficulty in identifying an inhibitor for this target is due to the bell shape of the active site, where benzydamine interacts. Therefore, as noted in this article, this reinforces the possible inhibitory action of the ligands we studied that interacted at the same site as benzydamine concerning TNF-α (Table 4).

There are no small molecule TNF-α inhibitors approved by FDA[53], which makes the ligands (+)-lariciresinol, (-)-secoisolariciresinol, balajaponin D, (+)-pinoresinol, and (-)-matairesinol promising molecules in the inactivation of this pro-inflammatory cytokine, since, in addition to having presented lower interaction energy expenditure for this target, compared to benzydamine, these molecules are components of propolis, which is classified as a safe and effective food (GRAS) by the FDA[55].

Regarding benzydamine, several ligands not interact at the same binding site with this drug (Table 4), presenting, therefore, possible different interaction sites with the targets evaluated here. Ligands that interacted at the same site as benzydamine can demonstrate a possible site-specific capacity for certain targets.

Ligands that did not compete for the same site (possible multi-target behavior) can be evaluated for treatments in conjunction with this drug since natural products can also interact with drugs, increasing their therapeutic activity. The combination of 'natural products + drugs' has been strongly proposed, considering that, it can contribute to reducing treatment costs, drug-resistant strains, and increasing treatment efficacy[56].

In agreement with the data obtained in this study, the literature reports that the ligand (-)-matairesinol has promising anti-inflammatory activity, *in vitro*, acting in several inflammatory mediators (*e.g.* NF-κB, in the regulation of TNF-α, NO, and COX-2), either by decreased activation or the negative regulation of the production of these cytokines[57]. Iqbal and collaborators (2013)[58] demonstrated that the increased release of TNF-α contributes to the development of several diseases of inflammatory origin. TNF-α is an interesting target in the search for OM treatment, as it is regulated by the NF-κB pathway, one of the most important in the development of this condition since it also regulates IL-6 and IL-1β[59]. Therefore, it is of interest to search for compounds that decrease the production of this cytokine or others involved in the same process.

In an *in vitro* evaluation of the modulation of the inflammatory response of several lignans, such as (-)-secoisolariciresinol, (+)-pinoresinol, (+)-lariciresinol, and (-)-matairesinol, it was observed that ligand (+)-pinoresinol demonstrated the highest anti-inflammatory activity among these, especially concerning the inflammatory cytokines IL-6 and PGE-E2 derived from COX-2, while ligand (-)-matairesinol increased PGE-E2 derived from COX-2, however, the study highlighted that this ligand had presented a high degree of impurities[60].

The ligand coniferyl alcohol is a phenolic precursor of lignans and lignins that have several biological roles and is also found in pheromones of queen bees of the genus *Apis mellifera*[61]. Sun and collaborators (2014)[50] demonstrated that the ligand coniferyl alcohol has a weak inhibitory effect of TNF-α, induced by NF-κB, however, the weak inhibitory activity was justified by the possibility that the benzene ring present in the ligand coniferyl alcohol was replaced in the C-3 methoxy group of 1-(-3-hydroxy-propen-1-yl) phenyl[50]. In our study, this ligand interacted with TNF-α, which did not appear to result in weak activity.

Also following that observed in Strategy I, the ligand coniferyl aldehyde demonstrated

anti-inflammatory activity by inhibiting the cytokines TNF-α, IL-1β, and IL-6[51].

Regarding the CRP inflammatory protein, studies in the literature have shown that the ingestion of food containing a lignan complex reduce the release of this pro-inflammatory protein[62,63]. In addition, the intake of lignan capsules reduced the levels of p53 and PUMA[64]. However, for the inflammatory targets p53, PUMA and EGF, studies are still needed specifically evaluating the seven lignans object of this study.

According to the study that identified the seven ligands of OP1[23], all of them showed a strong antioxidant capacity for the radical peroxyl (ROO•), and this capacity was stronger in the subfractions than in the isolated compounds, which indicates a possible synergistic activity of these ligands[23]. Knowing that propolis components exhibit better biological activities together, instead of isolates[65] the next strategy, in this study, assessed whether the 7 ligands would act synergistically.

Analyze of strategy II: Docking of multiple ligands

In this analysis the balajaponin D ligand was fixed to all inflammatory targets for the docking of multiple ligands since this molecule met the criteria previously established: 1) best result obtained in Strategy I, that is, the position model with the lowest energy expenditure; 2) the non-overlap of the selected model with the models of the other ligands; and 3) greater free radical scavenging power (antioxidant activity), indicated in a previous study of OP123.

Therefore, we evaluated all eight targets on the ‘inflammatory target + balajaponin D’ complex against the remaining six ligands.

From the data obtained (Table 5), it is possible to report that the ligands interacted with the target, with the interaction energy ranging from -8.66 to 0.24 kcal.mol^{-1}. The inflammatory target that presented the best overall result, that is, the interactions with the lowest energy expenditure were in TNF-α, with the energy Δ of -8.66 kcal.mol^{-1} for the ligand (-)-secoisolariciresinol and -2.52 kcal.mol^{-1} for the ligands coniferyl alcohol in ideal [$_{(I)}$] and representative [$_{(R)}$] forms.

From the data obtained (Table 5), the ligands (-)-secoisolariciresinol (Δ energetic -8.66 to -3.35 kcal.mol^{-1}), (+)-lariciresinol (Δ energetic -8.26 to -3.65 kcal.mol^{-1}), (+)-pinoresinol (Δ energetic -7.57 to -3.62 kcal.mol^{-1}), and (-)-matairesinol, in both forms, (Δ energetic -7.59 to -3.47 kcal.mol^{-1}) showed the best interaction potential in general. Therefore, these ligands showed the greatest potential for combined interaction, considering that these interactions involved the ‘inflammatory targets + balajaponin D' complex.

The ligand coniferyl aldehyde in the $_{(I)}$ and $_{(R)}$ forms showed weak interaction with the

targets when compared to the other ligands (Table 5). The values of these interactions varied between its forms ($\Delta_{(I)}$ energetic -4.92 to -3.90 kcal.mol^{-1} and $\Delta_{(R)}$ energetic -4.66 to -2.92 kcal.mol^{-1}). The ligand coniferyl alcohol in $_{(I)}$ and $_{(R)}$ forms showed the worst interaction in general, having the lowest interaction value for the IL-1β (-1.08 kcal.mol^{-1}) and the highest interaction value for the NF-κB (0.24 kcal.mol^{-1}).

Table 5. Results of strategy II: the affinity between the complex target + balajaponin D' and ligands (kcal.mol^{-1}).

Ligand	**Target + balajaponin D**							
	IL-6	**IL-1β**	**P53**	**PUMA**	**TNF-α**	**EGF**	**NF-κB**	**CRP**
coniferyl alcohol$_{(I)}$	-0.32	-0.89	0.23	-0.75	-2.52	-0.41	0.24	-1.08
coniferyl alcohol$_{(R)}$	-0.32	-0.89	0.23	-0.75	-2.52	-0.41	0.24	-1.08
coniferyl aldehyde$_{(I)}$	-3.90	-4.92	-4.28	-4.04	-4.28	-4.28	-4.47	-4.71
coniferyl aldehyde$_{(R)}$	-3.97	-4.02	-4.32	-2.92	-4.66	-4.00	-3.96	-4.49
(+)-lariciresinol	-5.26	-5.70	-5.06	-3.65	-8.26	-5.64	-5.32	-6.58
(-)-secoisolariciresinol	-5.05	-5.42	-5.17	-3.35	-8.66	-6.05	-5.58	-6.54
(+)-pinoresinol	-5.07	-4.95	-4.62	-3.62	-7.57	-4.49	-5.24	-5.36
(-)-matairesinol$_{(I)}$	-4.85	-5.29	-4.50	-3.47	-7.59	-4.05	-4.25	-6.56
(-)-matairesinol$_{(R)}$	-4.85	-5.29	-4.50	-3.47	-7.59	-4.05	-4.25	-6.56

(I) ideal and (R) representative forms of ligand

Analyzing the images of the results between the six ligands and the balajaponin D fixed to the eight selected targets (supporting information, Table 2S[3]) we observed positional convergence between some of the evaluated ligands and the balajaponin D.

Regarding CRP, EGF, IL-1β, and p53, all six ligands interacted in the same region as balajaponin D.

Regarding the IL-6, only coniferyl aldehyde in the ideal form [$_{(I)}$] did not interact at the same site as balajaponin D, while in the PUMA only the coniferyl aldehyde in the $_{(I)}$ and representative forms [$_{(R)}$] did not interact at the same site as balajaponin D.

In the NF-kB, only the (+)-lariciresinol and (+)-pinoresinol ligands interacted at the same site as balajaponin D. In the TNF-α only the coniferyl aldehyde in the $_{(R)}$ form did not

[3] O material suplementar, Table 2S está no APÊNDICE B

interact in the same site as balajaponin D.

Finally, it was observed that the residues in which the interactions between the selected targets and the ligands evaluated in this study occurred are protease enzymes (supporting information, Table 3S[4]). The residues identified were Ala, Arg, Asn, Asp, Cyx, Glu, Gln, Glh, Gly, Hie, His, Ile, Leu, Lys, Met, Phe, Pro, Thr, Trp, Tyr, Ser, Val

To the best of our knowledge, this is the first *in silico* study evaluating the interaction between lignans combined with other lignans and their precursors with OM-related targets.

The interactions observed in this *in silico* study (Table 5) are suggestive of beneficial interactions (additive or synergistic) of anti-inflammatory and antioxidant biological activities. These interactions observed here are confirmed in the study conducted by Tiveron and collaborators (2016)[23], who detected these same seven lignans in Brazilian organic propolis type 1 and related the anti-inflammatory and antioxidant activities with the synergy of the compounds present in the chemical profile of this propolis[23].

In multifactorial diseases (*e.g.* cancer and OM) there is a regulation by different molecular targets, and natural products are known to be able to act on different targets simultaneously[66], which is the requirement for the classification of a multi-target drug[67]. Therefore, not only the chemical characterization of natural products has been of great interest in studies, but also the evaluation of possible combined activities (additive, synergistic or antagonistic) of the compounds of these products has also been proposed as essential for the elucidation of the effects biological, and potential therapeutic effects. Furthermore, the biological activities of a product can be derived from such synergistic interactions[66].

The combined active compounds are less likely to develop resistance by the body[66]; increases treatment efficiency, as it is not specific to a single target; reduces toxicity and side effects[68]. The use of combined natural products to enhance the effects of their compounds is secular, being traditional in older cultures such as Chinese, Japanese, Indian, among others[56]. However, the validation of the interaction hypothesis of the compounds presented here by an *in silico* study should, in the future, be designed in non-clinical and clinical models.

Furthermore, residues in which interactions between targets and ligands occurred are present in proteases of the five classes found in humans: aspartic, serine, cysteine, threonine, and metallo. These enzymes act in several physiological processes (*e.g.* digestion, differentiation, cell signaling, immune defense, and apoptosis)[69] therefore, the regulation of

[4] O material suplementar, Table 3S, está no APÊNDICE C

proteases is of great importance for the organism's homeostasis[70].

Therefore, inhibitors of such proteases have been investigated as potential therapies for inflammatory, immunological, cancer, neurodegenerative diseases, among other conditions. Inhibitors must have minimal peptide character, long life in the bloodstream and cells, be highly stable to non-selective proteolytic degradation, permeable to the membrane, must be highly selective, difficult to eliminate, and of good bioavailability (preferably by the oral administration). Most inhibitors are flexible molecules with energy expenditure to bind to proteases[69]. Among the different mechanisms of protease activation, there is one that consists in the interruption of specific interactions and substitution by other proteases[70], therefore, as observed in this *in silico* study, the activation may have been interrupted by the interaction with the residues of the identified biomolecules of Brazilian organic propolis type 1 (ligands)[23].

The ligands that we studied, in addition to having demonstrated a possible good bioavailability based on the detected chemical interactions and the residues that the inflammatory targets interacted with the propolis molecules, can maintain their biological functions and are interacting with proteases that act directly in inflammatory processes, immunological diseases, and cancers.

Conclusion

The seven ligands showed site-specific interactions or not to benzydamine, which is the recommended drug for the prevention and treatment of oral mucositis, demonstrating that the interaction of these ligands in this *in silico* study has a great possibility of acting alone or in association in interfering with the process multifactorial aspect of oral mucositis.

All seven molecules of type 1 organic propolis (ligands) have satisfactorily bounded to inflammatory targets related to oral mucositis, which reinforces the possible anti-inflammatory activity of these molecules: coniferyl alcohol, coniferyl aldehyde, (+)-laricіresinol, (-)-secoisolariciresinol, balajaponin D, (+)-pinoresinol, and (-)-matairesinol. We also noticed the possible synergistic action of all the seven molecules, identifying that such compounds can have potential protease inhibitory activity. Therefore, the seven lignans studied *in silico* are strong candidates for *in vitro* and *in vivo* studies, for complete verification of such activities in oral mucositis and other inflammatory pathological processes.

Experimental section

The methodology that was adopted for this *in silico* study comprised the definition of the inflammatory targets involved in oral mucositis (OM), that is, the possible targets; the

compounds identified in organic propolis type 1 (OP1), called ligands; obtainment the three-dimensional (3D) structures of the targets and ligands; Lipinski's 'rule of 5' for the assessment of oral bioavailability (analyzing the parameters of solubility and permeability) and gastrointestinal absorption; and the choice of the operating system, the software and the strategies adopted to perform the docking of a ligand and multiple ligands.

Inflammatory targets of OM

Adopting the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) strategy[71], the targets and ligands were selected. The inflammatory targets involved in the manifestation of OM were selected through research in the online databases PubMed/Medline and Google Scholar. The search filter (supporting information, Table 4S[5]) was built based on the PubMed/Medline platform, containing two levels of research: (i) clinical condition (oral mucositis) and (ii) inflammatory mediators (inflammatory targets). For this, standardized descriptors and keywords were used based on the Medical Subject Headings (MeSH) database. The search filters were built associating the descriptors, Boolean operators (AND/OR/NOT) and the search algorithms [MeSH Terms] and [TIAB][72].

The studies were accessed in full text and included in the eligibility analysis, in which well-defined inclusion and exclusion criteria were adopted. Studies addressing inflammatory targets related to mucositis (*e.g.* cytokines, chemokines, and growth factors) caused by radiotherapy and/or chemotherapy were considered to be potentially relevant. The following studies were excluded: (i) not available in full text; (ii) gray literature (not indexed and not published in formal scientific review journals); (iii) studies that do not address the outcomes of interest; (iv) secondary studies (*e.g.* letters to the editor, conference summaries, comments, notes, and books); (v) studies that do not have at least one control group; (vi) studies with self-control and (vii) studies with multiple interventions that hinder access to the relationship between mucositis and related targets.

The reference lists of the selected articles were also verified, emphasizing that they contributed to the collection of several targets73. The selected targets are eight: TNF-α, IL-1β, IL-6, p53, PUMA[14,31], NF-κB[12], EGF, and CRP[74].

Ligand molecules

The ligand molecules were those referenced by Tiveron et al., (2020)[23] identified from

[5] O material suplementar, Table 4S está no APÊNDICE D

OP1. These molecules belong to the chemical category of lignans and lignans precursors and have been considered as the chemical markers of OP1. Thus, the binding molecules that were evaluated in this study are seven: coniferyl alcohol, coniferyl aldehyde, (+)-lariciresinol, (-)-secoisolariciresinol, balajaponin D, (+)-pinoresinol, and (-)-matairesinol.

Three-dimensional structure (3D) of inflammatory targets and ligands

The three-dimensional (3D) structures of inflammatory targets related to OM used for molecular docking were obtained on the database Protein Data Bank (https://www.rcsb.org/)[75] (supporting information, Table 5S[6]).

The 3D structures of the ligand molecules were collected on the PubChem platform (https://pubchem.ncbi.nlm.nih.gov/), Cambridge Crystallographic Data Center (CCDC) (https://www.ccdc.cam.ac.uk/), and Protein Data Bank in Europe (PDBe) (https://www.ebi.ac.uk/pdbe/) (supporting information, Table 6S[7]).

Lipinski's 'rule of 5' and gastrointestinal absorption applied to ligands

Lipinski's 'rule of 5' and gastrointestinal absorption of ligands was analyzed in the 'pre' and 'post' docking moments, with this last one being applied only for those ligands that presented the 'ideal' and 'representative' forms[42]. Lipinski's values were analyzed to determine whether the ligands under study showed good oral availability, that is, whether they meet the criteria of solubility and permeability of drugs under administration by this route[41].

Lipinski's 'rule of 5' has four experimental and computational parameters, namely: 1) molecular weight up to 500 (MWT); 2) MLogP (octanol/water partition coefficient) up to 4.15; 3) up to 10 H-bond receptors (N or O); and 4) up to 5 H-bond donors (NH or OH)[42].

Gastrointestinal absorption was determined based on the prediction model BOILED-Egg (Brain Or Intestinal Estimated permeation). This model is based on the lipophilicity and polarity of the molecules for the evaluation of passive gastrointestinal absorption and access to the brain by passive diffusion[76].

At the pre-docking moment, the SMILES of the selected ligands were obtained from the platforms where the 3D structure of the ligands was downloaded. For the post-docking analysis, the *OPENBABEL-Chemical file format converter* website was used to obtain the SMILES of the structures generated from the docking. To obtain the values of Lipinski and gastrointestinal

[6] O material suplementar, Table 5S está no APÊNDICE E

[7] O material suplementar, Table 6S está no APÊNDICE F

absorption, the website SwissADME was used (http://www.swissadme.ch/)[43].

In case of identical values between 'ideal' [(I)] and 'representative' [(R)] forms of ligands in the pre-docking moment, the criteria adopted was based on the results in the post-docking moment, with the Lipinski rule being a determinant for choosing the form that would follow in the study.

To obtain the values of Lipinski and gastrointestinal absorption, the SwissADME website was used[43].

The SMILES of the compounds in the 'pre' and 'post' docking moments are found in supporting information, Table 7S and Table 8S[8], respectively.

Molecular docking assay

The docking study between inflammatory targets and ligands was based on the semi-flexible type with structural changes only in the ligands since they are small molecules. The best approach is the one that adopts the prediction of conformational changes only in the ligands[27,77,78].

For this research, we adopted two methodological strategies: Strategy I - docking of a single ligand, and Strategy II - docking of multiple ligands.

The operating systems used were Linux Ubuntu 20.04 (Strategy I) and Windows 2010 (Strategy II) for the operationalization of the software Maestro, to carry out docking simulations according to the strategies adopted.

Strategy I: Single ligand docking

Each of the eight inflammatory targets and each of the seven ligands was treated with the software MGLTools® 1.5.6[27,77,78] and AutoDock Vina® 1.1.2[79], where the most promising binding site on the target was identified based on the lowest energy binding expenditure, that is, of better affinity[80]. Details of this methodology adopted in this strategy are available in supporting information, Table 9S[9]. The AutoDock Vina® software selected the nine best position models in which these connections occurred, called position model 1 to position model 9, with model 1 being the one with the lowest energy expenditure. This procedure to identify the connection with the lowest energy expenditure was repeated 20 times[75].

To enrich the understanding of docking simulations between targets and ligands, we also

[8] O material suplementar, Table 7S e Table 8S está no APÊNDICE G e H, respectivamente

[9] O material suplementar, Table 9S está no APÊNDICE I

included in this strategy the performance of docking using the drug benzydamine, which has been proposed as a preventive and therapeutic treatment for OM[16]. Benzydamine will be used as a comparison parameter (control) with the seven ligands proposed in this study.

Strategy II: Multiple ligands docking

One ligand was fixed to all the eight inflammatory targets to assess the interaction between the other ligands. The fixed ligand was selected according to the following criteria: 1) best result obtained in Strategy I, that is, the position model with the lowest energy expenditure; 2) the non-overlap of the selected model with the models of the other ligands; and 3) greater free radical scavenging power (antioxidant activity), indicated in a previous study of OP1[23].

For the verification of the non-overlap of the ligand fixed with the other ligands, as in the criterion previously established, the methodology described[81,82] was modified in this study to visualize the interaction between multiple ligands, using the software MGLTools® and Maestro© 12.8 (Schrodinger, Nova York, USA). The inflammatory targets and ligands were selected in the complex 'target + fixed ligand' and 'target + other ligands'. So, both molds were read to confirm the non-overlap between the ligands, using the Maestro© software[83].

The antioxidant activity was determined as a biological criterion since one of the possible development mechanisms of OM is the release of oxidizing agents, which generate free radicals[7,14,15].

To carry out the docking, we adopted the methodology described by the company Schrodinger, developer of the Maestro software[84]. The inflammatory targets were prepared using the Receptor Grid Generation tool according to the described protocol: the size of the target was determined; the fixed ligand was detected, as well as the chemical interactions and regions where it interacted with the inflammatory target, to be disregarded in the docking.

To prepare the ligand, the LigPrep[85] tool was accessed, specifying the conditions for carrying out the docking. In addition, the ligand preparation identifies all the possible positions that the ligand can adopt. Therefore, the number of positions resulting from the docking is dependent on the positional capacity of the ligand detected in this preparation step. Details of this methodology adopted in this strategy are available at[84].

After preparing the inflammatory targets and ligands, the docking was performed with the Ligand Docking tool, which generates the results of the docking and interactions obtained by the software. From the results observed, only the position of lowest energy expenditure was selected.

Supporting Information

Detailed results; additional experimental details, materials, and methods, including photographs and videos of the experimental setup.

Abbreviations Used

OM, oral mucositis; OP1, organic propolis type 1; EGF, epidermal growth factor; $_{(i)}$, ideal form; $_{(R)}$, representative form.

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3 CONSIDERAÇÕES FINAIS

As sete biomoléculas identificadas na Própolis Orgânica Brasileira tipo 1 (PO1) avaliadas neste estudo *in silico* demonstraram possível atividade inibitória para com os alvos inflamatórios IL-6, IL-1β, P53, PUMA, TNF-α, EGF, NF-κB e CRP, que são citocinas relacionadas ao processo inflamatório da mucosite oral (MO). Também, todas as sete biomoléculas identificadas na PO1 sugerem possível atividade combinada (multialvo). A capacidade multialvo é de grande interesse no tratamento de doenças multifatoriais, como a MO e câncer. Por fim, essas biomoléculas também apresentaram potencial atividade inibitória em resíduos de enzimas proteases. Devido a todas essas promissoras atividades detectadas *in silico*, temos que todas as sete biomoléculas da PO1 são candidatas promissoras para estudos *in vitro* e *in vivo* na busca por agentes adequados à prevenção e ao tratamento da MO.

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APÊNDICE A – Ligantes que interagiram ou não no mesmo sítio que a Benzidamina

Table 1S. Comparison of binding site between ligands and benzydamine.

TARGET	LIGAND	LINK*
CRP	coniferyl alcohol$_{(I)}$	https://drive.google.com/drive/folders/1uufgv6wKy876Jx0gizXxrGbzX500wYME?usp=sharing
	coniferyl alcohol$_{(R)}$	https://drive.google.com/drive/folders/1k-1GB_V-SUMkOm_F9tJSDiE3IAESC1TW?usp=sharing
	coniferyl aldehyde$_{(I)}$	https://drive.google.com/drive/folders/1ONj39FLqBR14ShKl4811r-F6frSttK5y?usp=sharing
	coniferyl aldehyde$_{(R)}$	https://drive.google.com/drive/folders/1uuabdDj84qnKgiQbh_TjBbvy8bwgrWg4?usp=sharing
	(+)-lariciresinol	https://drive.google.com/drive/folders/1RoM-RzbWdtdxzgVMVnQBH9RU6D5HunXN?usp=sharing
	(-)-secoisolariciresinol	https://drive.google.com/drive/folders/1yVqrQpXuNjKunKXYWuMxqiVIArPdY0oN?usp=sharing
	balajaponin D	https://drive.google.com/drive/folders/13ag1IA1-5Py5LLT3XyTNMuQwMk33lSp8?usp=sharing
	(+)-pinoresinol	https://drive.google.com/drive/folders/1mFgBNGMFyQhgMkcEzZcv3sm9xi3PDeu_?usp=sharing
	(-)-matairesinol$_{(I)}$	https://drive.google.com/drive/folders/16rO7vHp5m8elVcoP86QP_c6usYa0XoEh?usp=sharing
	(-)-matairesinol$_{(R)}$	https://drive.google.com/drive/folders/1T628cELU-i8isOCvZWiuqi3fQBWriZYk?usp=sharing
EGF	coniferyl alcohol$_{(I)}$	https://drive.google.com/drive/folders/1lY_3zCVhSHuV1ZIjN3NPEs0h-5CtDLj4?usp=sharing
	coniferyl alcohol$_{(R)}$	https://drive.google.com/drive/folders/1nHV5Xn1sFbIBBBq5MF6vU-4731PNlKLf?usp=sharing
	coniferyl aldehyde$_{(I)}$	https://drive.google.com/drive/folders/1Dv-KHlNMjicQH1CpvSrJ-tS0ZCGnyPyc?usp=sharing
	coniferyl aldehyde$_{(R)}$	https://drive.google.com/drive/folders/13grV77mB7DT5dJFyDGSsDIdkgUjBEGAc?usp=sharing
	(+)-lariciresinol	https://drive.google.com/drive/folders/1rHSynFjDMq5BPx4FxN5mUbCSa8DZJZ76?usp=sharing
	(-)-secoisolariciresinol	https://drive.google.com/drive/folders/15bQIG7qZUH3xh6QDiC3-u-yDktJAFtAP?usp=sharing
	balajaponin D	https://drive.google.com/drive/folders/1tivu_HwbhmJXozyMbEPl-ZGdJNjvNKm2?usp=sharing
	(+)-pinoresinol	https://drive.google.com/drive/folders/1vUVwf0h-rKKRws_FWL6RFci97khzsI15?usp=sharing
	(-)-matairesinol$_{(I)}$	https://drive.google.com/drive/folders/1wDkXz7p3cECKAYlrJgiN7u4Ltfak61dS?usp=sharing
	(-)-matairesinol$_{(R)}$	https://drive.google.com/drive/folders/1W8AkwuSfGhd98ferRFL2i6E6mO_9nQ7E?usp=sharing
IL-1β	coniferyl alcohol$_{(I)}$	https://drive.google.com/drive/folders/1U5HN3GWow23k8CyKg4Je5zpFR10ab6b2?usp=sharing
	coniferyl alcohol$_{(R)}$	https://drive.google.com/drive/folders/1DtxwP412n3vocyQtsMQ44ZH_W_Q1-6RS?usp=sharing
	coniferyl aldehyde$_{(I)}$	https://drive.google.com/drive/folders/1O0AZnpwqFFshHLx-MN9sHG3pyEfoMltm?usp=sharing
	coniferyl aldehyde$_{(R)}$	https://drive.google.com/drive/folders/1XJjer6QlpG5f_AMpdMl3eMErb-hZ5boj?usp=sharing
	(+)-lariciresinol	https://drive.google.com/drive/folders/1eNx3cHYfmDHWKBq3lLXVKvGz0bfQIuV2?usp=sharing
	(-)-secoisolariciresinol	https://drive.google.com/drive/folders/1ekiUiVDd4cN3gT3FB99HTq0WgbUVUR2o?usp=sharing
	balajaponin D	https://drive.google.com/drive/folders/1EW4j8VU_55UsoIRtfu7QDNabnGmt2JKi?usp=sharing
	(+)-pinoresinol	https://drive.google.com/drive/folders/1pWCCKksNFTsL7ekVIqvQrksJ9q2z_lGm?usp=sharing
	(-)-matairesinol$_{(I)}$	https://drive.google.com/drive/folders/1d2h3BRTIysp1DfBsVgRmCrkc0Q0kIYgv?usp=sharing
	(-)-matairesinol$_{(R)}$	https://drive.google.com/drive/folders/1im9NCx0K4YvJZCvpPQpnf7YxTrO7eNm3?usp=sharing
IL-6**	coniferyl alcohol$_{(I)}$	https://drive.google.com/drive/folders/1GeJM-bPyZfwZ3yofRuyflH9VKxBTJo6r?usp=sharing
	coniferyl alcohol$_{(R)}$	https://drive.google.com/drive/folders/1yABZYQCObWZZtekHuHY6FejDCn6Gk4CO?usp=sharing
	coniferyl aldehyde$_{(I)}$	https://drive.google.com/drive/folders/1uAzA44iys1_cd5V9CaXxkpS9BNFcpZF9?usp=sharing
	coniferyl aldehyde$_{(R)}$	https://drive.google.com/drive/folders/1OP_FUpzboGcsygMaBrYmUPEplVLpUuSo?usp=sharing
	(+)-lariciresinol	https://drive.google.com/drive/folders/1xDsvQx4AeoLUHcqA6LyzsbM0cyR56Xsh?usp=sharing

	(-)-secoisolariciresinol	https://drive.google.com/drive/folders/1mKYYCStrIe_RPk11IBAY05AT7BKwvww2?usp=sharing
	balajaponin D	https://drive.google.com/drive/folders/1Gq4KZKezisWvm7GAW8eFT933Vn9lepGI?usp=sharing
	(+)-pinoresinol	https://drive.google.com/drive/folders/1x7HF-VyMmxR8JYfOx1G7hEX_K9jvYh2o?usp=sharing
	(-)-matairesinol$_{(I)}$	https://drive.google.com/drive/folders/1nCEKuxMRqTtYoN5VnMFx5lhEhX5Z8Tc6?usp=sharing
	(-)-matairesinol$_{(R)}$	https://drive.google.com/drive/folders/1gGle7bK7Dq40lftZbPSOepOeX1PSu58W?usp=sharing
	coniferyl alcohol$_{(I)}$	https://drive.google.com/drive/folders/1YuMwYUfYQDt0xOz-0Nxt_pYVuTbQQZpc?usp=sharing
	coniferyl alcohol$_{(R)}$	https://drive.google.com/drive/folders/1TKu6qbtegCzFk1AlMj3Zkn9XhyVH-bhk?usp=sharing
	coniferyl aldehyde$_{(I)}$	https://drive.google.com/drive/folders/17_JZArXmnJxF5VMp7sacYjdtcShtDaOs?usp=sharing
	coniferyl aldehyde$_{(R)}$	https://drive.google.com/drive/folders/1KKimQuXNJN7OtUVPZXtH-QtVBZqiHu0Z?usp=sharing
NF-κB	(+)-lariciresinol	https://drive.google.com/drive/folders/1Y6Lq3IwjdX2-UMEImA92mCHjXgSS65bM?usp=sharing
	(-)-secoisolariciresinol	https://drive.google.com/drive/folders/1isq5SWVaAIxWUNgVlvImO3TPnnVlE_xD?usp=sharing
	balajaponin D	https://drive.google.com/drive/folders/1IUu58EcV6EhjMVN2mYrbrJmg3v2CQOD6?usp=sharing
	(+)-pinoresinol	https://drive.google.com/drive/folders/1TYcJRuHnzU5kbc2dKGyUUPc8sAIGZ74s?usp=sharing
	(-)-matairesinol$_{(I)}$	https://drive.google.com/drive/folders/1JT2r9QeZa8TkfFn-XnPoAGeLZaT_YjBR?usp=sharing
	(-)-matairesinol$_{(R)}$	https://drive.google.com/drive/folders/1R0i3dTQ2P63gQycK9kqCETO3xpWYYzbB?usp=sharing
	coniferyl alcohol$_{(I)}$	https://drive.google.com/drive/folders/1fbYRXb8Tbj4fNHJ-uS51Jz2UYHEoQDuQ?usp=sharing
	coniferyl alcohol$_{(R)}$	https://drive.google.com/drive/folders/1iflXKKXNHhruzDA7P-u_ii3FSS2-8rX1?usp=sharing
	coniferyl aldehyde$_{(I)}$	https://drive.google.com/drive/folders/14zHU25A9ivJei_yoB5ASv-DfoJCoPb_i?usp=sharing
	coniferyl aldehyde$_{(R)}$	https://drive.google.com/drive/folders/1Zwmnh7Iqioc9k9rMTV3nVHW34DohEMeC?usp=sharing
P53	(+)-lariciresinol	https://drive.google.com/drive/folders/1Vl9KV7HhEb6dM3WQSFB-py0YSYC8TF0z?usp=sharing
	(-)-secoisolariciresinol	https://drive.google.com/drive/folders/1lxcEXpkEQvNy5fGFs_QqNbuBxtViBJxM?usp=sharing
	balajaponin D	https://drive.google.com/drive/folders/1xHoHL20QK_-udOI1fOx3Xo6KGDNxlpAh?usp=sharing
	(+)-pinoresinol	https://drive.google.com/drive/folders/10blZ8_NlX6coNB2fWfB5Ms256kQDLaUR?usp=sharing
	(-)-matairesinol$_{(I)}$	https://drive.google.com/drive/folders/1NeuO3Hd6faGRZUSt8wmF5iHDcDijAbw5?usp=sharing
	(-)-matairesinol$_{(R)}$	https://drive.google.com/drive/folders/1z5mSu2HulpOJgm7oF0WB4yfmkBE5C-GS?usp=sharing
	coniferyl alcohol$_{(I)}$	https://drive.google.com/drive/folders/1T3cmWADu5ZIuaGkwDNHZrtQlhT5EOG-b?usp=sharing
	coniferyl alcohol$_{(R)}$	https://drive.google.com/drive/folders/11THqCMvRMTHmZop_f3ecDONXklteEKBc?usp=sharing
	coniferyl aldehyde$_{(I)}$	https://drive.google.com/drive/folders/15snolrsRrAlNnvFbPfvPezhtUE6nU16O?usp=sharing
	coniferyl aldehyde$_{(R)}$	https://drive.google.com/drive/folders/1X6dc05i8ZWszDIZFdKI4DsI3S-aTm2ux?usp=sharing
PUMA	(+)-lariciresinol	https://drive.google.com/drive/folders/1xKm_eNGFAMxdzzBz3qJ9JgNEUdcYhmgZ?usp=sharing
	(-)-secoisolariciresinol	https://drive.google.com/drive/folders/13E1umjOHl79NBonHOFhPMw1wJPFCjwCS?usp=sharing
	balajaponin D	https://drive.google.com/drive/folders/1V7mMgOXA_iThxW2tLCXDqBj63Fkl6EQS?usp=sharing
	(+)-pinoresinol	https://drive.google.com/drive/folders/1Pg7YRopqv_Be8z0PRi6ymQr3vUCjnVCj?usp=sharing
	(-)-matairesinol$_{(I)}$	https://drive.google.com/drive/folders/1DMulsZdiDP1biYS-sS9LH-Yajt3gSdpP?usp=sharing
	(-)-matairesinol$_{(R)}$	https://drive.google.com/drive/folders/1tyXnjW2ILJfrnisH6xbcpnM31Y1oIMcp?usp=sharing
	coniferyl alcohol$_{(I)}$	https://drive.google.com/drive/folders/1zPyWdJbbrZV-pYo6vAERPiQgSbPeWuuJ?usp=sharing
	coniferyl alcohol$_{(R)}$	https://drive.google.com/drive/folders/1MEBC3FukMuEl41Qd1_DS02Cu16QgmNaG?usp=sharing
	coniferyl aldehyde$_{(I)}$	https://drive.google.com/drive/folders/1weuODuaoGzT2lmqsyS5cxQr0PS5xlthG?usp=sharing
TNF-α	coniferyl aldehyde$_{(R)}$	https://drive.google.com/drive/folders/1HVpc7hUHcm4tuEjtCAV7UpgLZK6GVzF5?usp=sharing
	(+)-lariciresinol	https://drive.google.com/drive/folders/1FfdP7AjVObAeVeWfHPGOnqADpnkpUTv1?usp=sharing
	(-)-secoisolariciresinol	https://drive.google.com/drive/folders/1KoYYho2xBrLgKKhbMTDDYcAoLNKCEUrt?usp=sharing

balajaponin D	https://drive.google.com/drive/folders/1SjTCWxnKVC7u20sed6QwrHrVhy-tPIPP?usp=sharing
(+)-pinoresinol	https://drive.google.com/drive/folders/1daF5qAnfGtqz5VlmN0BRldDLE_Jl8zJM?usp=sharing
(-)-matairesinol$_{(I)}$	https://drive.google.com/drive/folders/1ZeYkqsVQ6Y0oiU9sVmcaBhszTIlVFX8p?usp=sharing
(-)-matairesinol$_{(R)}$	https://drive.google.com/drive/folders/1nKsdsQboq443q4sI_po6QJSIqTixwqh9?usp=sharing

$_{(I)}$: ideal form; $_{(R)}$: representative form

* The link leads to a folder containing two files: the structure of each inflammatory target with benzydamine and the evaluated ligand, and a video showing the target with benzydamine, then the ligand to be evaluated is added.

** The Maestro software mistakenly detected some IL-6 residues as ligands therefore this classification should be ignored.

APÊNDICE B – Ligantes que interagiram na região da balajaponina D (Estratégia II)

Table 2S. Comparison of binding site between ligands and balajaponin D.

TARGET	LIGAND	LINK*
CRP	coniferyl alcohol$_{(I)}$	https://drive.google.com/drive/folders/1P-jnzf70NnFpHozI7jN8lkhUShQ0XSIn?usp=sharing
	coniferyl alcohol$_{(R)}$	https://drive.google.com/drive/folders/1Fea5DybgKcwP1IsSGSEWv_fJamq_g-nL?usp=sharing
	coniferyl aldehyde$_{(I)}$	https://drive.google.com/drive/folders/1byblVE3S1a741tNhKEqMmiOWpQxdih1q?usp=sharing
	coniferyl aldehyde$_{(R)}$	https://drive.google.com/drive/folders/1FffCZWKWpN-TX0myPGI2JDgKNl0sJYoB?usp=sharing
	(+)-lariciresinol	https://drive.google.com/drive/folders/1G6QuMBhCq2B6bJDd0vesbA34I8X8H0oS?usp=sharing
	(-)-secoisolariciresinol	https://drive.google.com/drive/folders/1HylFkwvyPzKGM4VWpRAowVceWZ0LVwI_?usp=sharing
	(+)-pinoresinol	https://drive.google.com/drive/folders/1yvhXhrSPbeWGc6zX5HkjDw1mLcBlC5dS?usp=sharing
	(-)-matairesinol$_{(I)}$	https://drive.google.com/drive/folders/1RXBJKTrAyrYIh90_Ln1tjOghq_5GbBNp?usp=sharing
	(-)-matairesinol$_{(R)}$	https://drive.google.com/drive/folders/1ECR-skDJ-tKsYEagGlI9-D7d6iLeHpto?usp=sharing
EGF	coniferyl alcohol$_{(I)}$	https://drive.google.com/drive/folders/1DRmeLIE1HcYez5Bl1BYY0Q7Tl5MFQCRZ?usp=sharing
	coniferyl alcohol$_{(R)}$	https://drive.google.com/drive/folders/1diHZYxWGAOASD-mKYTaV924LF_wX4Pnv?usp=sharing
	coniferyl aldehyde$_{(I)}$	https://drive.google.com/drive/folders/1gJiC-ECAqvo2oRpumyxqCf7tHn2EZuSx?usp=sharing
	coniferyl aldehyde$_{(R)}$	https://drive.google.com/drive/folders/1Q6z3pFdEeACVttwa9pGrHgcBphudWUXA?usp=sharing
	(+)-lariciresinol	https://drive.google.com/drive/folders/1fQNKfp5bZDTEqBfX1ZcoTr9eI9ynD4BK?usp=sharing
	(-)-secoisolariciresinol	https://drive.google.com/drive/folders/1ogGqe185uEYh4mdD0tJ-Kr4T8xMNYrh0?usp=sharing
	(+)-pinoresinol	https://drive.google.com/drive/folders/1pmueFfcTQZxVMH4yyhxYVvsUMtjy7N0Q?usp=sharing
	(-)-matairesinol$_{(I)}$	https://drive.google.com/drive/folders/1QVokI0PkORg27pbUJJWO_NTlFzaEK47f?usp=sharing
	(-)-matairesinol$_{(R)}$	https://drive.google.com/drive/folders/1rDJDhqEzI47c_oVSntQRvLexKaYREQUX?usp=sharing
IL-1β	coniferyl alcohol$_{(I)}$	https://drive.google.com/drive/folders/1RAmqasDVTB0IgSDvLCt3w3gd1QXcKUDp?usp=sharing
	coniferyl alcohol$_{(R)}$	https://drive.google.com/drive/folders/16E3ZnLsNtYUu0j90JsSWVtSHqkiKhmNp?usp=sharing
	coniferyl aldehyde$_{(I)}$	https://drive.google.com/drive/folders/14mTehFiB9Vn2fABNHurY9_loVhAU9v19?usp=sharing
	coniferyl aldehyde$_{(R)}$	https://drive.google.com/drive/folders/1RDOzgQjIjCgrEnjSeWGT-s6-Alln4z9L?usp=sharing
	(+)-lariciresinol	https://drive.google.com/drive/folders/1wLZRc4PY-4csNLajv787P5OcUscEgb7f?usp=sharing
	(-)-secoisolariciresinol	https://drive.google.com/drive/folders/1tu64loTvOJrmESyEYd1MpAjHG5s6vSAd?usp=sharing
	(+)-pinoresinol	https://drive.google.com/drive/folders/1CY1eYHRkiCx0kjK364zKQyBlsy-MZgzf?usp=sharing
	(-)-matairesinol$_{(I)}$	https://drive.google.com/drive/folders/1VHuM_LFS3-QUfDjWC2pNZT8i-1DH8jtl?usp=sharing
	(-)-matairesinol$_{(R)}$	https://drive.google.com/drive/folders/1FNMWOPJd1PWsBRUkImJurUCdGwA9QOqh?usp=sharing
IL-6	coniferyl alcohol$_{(I)}$	https://drive.google.com/drive/folders/1zCVu9yPg8QAxMKEWTlB537EbZJ2I3PhU?usp=sharing
	coniferyl alcohol$_{(R)}$	https://drive.google.com/drive/folders/1pgI7FNmK-v5Sb-fkmnOqeJViWyPa_3a5?usp=sharing
	coniferyl aldehyde$_{(I)}$	https://drive.google.com/drive/folders/19v5lvuJBPzBncQVucVZAy7fcP179zMe3?usp=sharing
	coniferyl aldehyde$_{(R)}$	https://drive.google.com/drive/folders/1tYPeHI43YBjzH3YfRmPB78dcUPWkAz4e?usp=sharing
	(+)-lariciresinol	https://drive.google.com/drive/folders/1dVm7cAqVJFFt8ZiJXrt1Fq3VqGSA7Gl0?usp=sharing
	(-)-secoisolariciresinol	https://drive.google.com/drive/folders/16aWucU4bMjhdRdeMfnucv2hONHaamHj7?usp=sharing

	(+)-pinoresinol	https://drive.google.com/drive/folders/1LD8onNuWXh4ja6IjPC3_AbW8hhrcw-jw?usp=sharing
	(-)-matairesinol$_{(I)}$	https://drive.google.com/drive/folders/1JJYcikxv66W6Xt1gvreAFEEGk4OWWJUh?usp=sharing
	(-)-matairesinol$_{(R)}$	https://drive.google.com/drive/folders/1TlZLKpHzMrsVQb-taNf0oOZuNDrNgIge?usp=sharing
NF-κB	coniferyl alcohol$_{(I)}$	https://drive.google.com/drive/folders/1toyRuUViHOgjD0dRC-p3n-w1yoojMlIC?usp=sharing
	coniferyl alcohol$_{(R)}$	https://drive.google.com/drive/folders/1tnoNlHIAN-VwccCD8FVUKOegmP17OHRM?usp=sharing
	coniferyl aldehyde$_{(I)}$	https://drive.google.com/drive/folders/1am2I9dipRjjiHYwbVTtFhV_YJVfC_dzl?usp=sharing
	coniferyl aldehyde$_{(R)}$	https://drive.google.com/drive/folders/1i-nY7OZoYJwsZVRNrLmB672GNXspLfSc?usp=sharing
	(+)-lariciresinol	https://drive.google.com/drive/folders/1mq_Dv03ScNOALUEpusFYWVlFb8dd_PZa?usp=sharing
	(-)-secoisolariciresinol	https://drive.google.com/drive/folders/1Z--hqcaA2lota2JMpTe_QVAnnO28UFL1?usp=sharing
	(+)-pinoresinol	https://drive.google.com/drive/folders/1fqimaCLYUtFWBak72YAarTsMZVbN9Bl-?usp=sharing
	(-)-matairesinol$_{(I)}$	https://drive.google.com/drive/folders/1AW2-81Q5agj-IJpN0Zu6nYYX-aGDjvPD?usp=sharing
	(-)-matairesinol$_{(R)}$	https://drive.google.com/drive/folders/1MkaR7dOgxQfK_kqoducrrq0sZMrHaUsb?usp=sharing
P53	coniferyl alcohol$_{(I)}$	https://drive.google.com/drive/folders/1VhLL-GFxTybfk8mfeaUZd5Zi4bFcbEet?usp=sharing
	coniferyl alcohol$_{(R)}$	https://drive.google.com/drive/folders/1q9f4eH8tUx9WIBSBjlA6Q91zio2NMSnC?usp=sharing
	coniferyl aldehyde$_{(I)}$	https://drive.google.com/drive/folders/1jYY_ZLnZ37H7HK5FU-kLrVhMvUs5APo3?usp=sharing
	coniferyl aldehyde$_{(R)}$	https://drive.google.com/drive/folders/1wQhklWvJBvHntVkdF-asXB9VAOO642BQ?usp=sharing
	(+)-lariciresinol	https://drive.google.com/drive/folders/1fh23LPfDI0oXfflqlQZcqAAIxgfio1hn?usp=sharing
	(-)-secoisolariciresinol	https://drive.google.com/drive/folders/16bpodr93yq1dvsQmc-hlwz9ns9kkw_wT?usp=sharing
	(+)-pinoresinol	https://drive.google.com/drive/folders/19FrhHE_oXdRmkISzT4thI5tNJkfC3ltX?usp=sharing
	(-)-matairesinol$_{(I)}$	https://drive.google.com/drive/folders/1zYzjok5LHUutzFEU3VJgLoy7D-ADb1b6?usp=sharing
	(-)-matairesinol$_{(R)}$	https://drive.google.com/drive/folders/1Xpc2zXV7i1GQaOon4qHAanCFgwF_b4mc?usp=sharing
PUMA	coniferyl alcohol$_{(I)}$	https://drive.google.com/drive/folders/15UGRl8hh48C3HrYOOnEUNRAy71xAIouc?usp=sharing
	coniferyl alcohol$_{(R)}$	https://drive.google.com/drive/folders/185SwYx3e7JipF43PgI0Y0OX0FUd9VmNC?usp=sharing
	coniferyl aldehyde$_{(I)}$	https://drive.google.com/drive/folders/1PHh6w4IcOSBVxx28OgPlrjwpvKSCb9Lq?usp=sharing
	coniferyl aldehyde$_{(R)}$	https://drive.google.com/drive/folders/1rKSU4d7D2QFdjegkJIfMEq96BwVjkRHf?usp=sharing
	(+)-lariciresinol	https://drive.google.com/drive/folders/1YzylDsWvEDF0RiRhpGTFHrLCPWy6HKbb?usp=sharing
	(-)-secoisolariciresinol	https://drive.google.com/drive/folders/1828w5nzgTRAhPQRJX22GQtZy1x2mgAjw?usp=sharing
	(+)-pinoresinol	https://drive.google.com/drive/folders/1rNwqOg5kWHbckUQnFUp4K8bOjVvbGZ2l?usp=sharing
	(-)-matairesinol$_{(I)}$	https://drive.google.com/drive/folders/1u54M2hYhQJhQBvhSjT0BMbs7iRDmBWXL?usp=sharing
	(-)-matairesinol$_{(R)}$	https://drive.google.com/drive/folders/1vEm-aC2wlDsiEu447VBGgJTXwTs8iqux?usp=sharing
TNF-α	coniferyl alcohol$_{(I)}$	https://drive.google.com/drive/folders/1ZAqdnS-SC2-RxTjmfjVqgCFhTqweM6Qz?usp=sharing
	coniferyl alcohol$_{(R)}$	https://drive.google.com/drive/folders/1C2sfN0aTTTKJVx1E8iOmmXNRx16Ir0FO?usp=sharing
	coniferyl aldehyde$_{(I)}$	https://drive.google.com/drive/folders/1Ehcz0G0yKgrPs9OzeMhfBvH82FZtXm-E?usp=sharing
	coniferyl aldehyde$_{(R)}$	https://drive.google.com/drive/folders/1DZvT6yz9kivBdh0Oukg1y4lzlgHUmxP3?usp=sharing
	(+)-lariciresinol	https://drive.google.com/drive/folders/1WRUhRZ06KScuzMKW9-ptkCusipPX4ng7?usp=sharing
	(-)-secoisolariciresinol	https://drive.google.com/drive/folders/1hMWkYpUlR_AYY3RP15iYqgDlx8p3zT0f?usp=sharing
	(+)-pinoresinol	https://drive.google.com/drive/folders/1w8VkhYUb50f0FIxtd6rUggxBJdXjo2rN?usp=sharing
	(-)-matairesinol$_{(I)}$	https://drive.google.com/drive/folders/1F7svGRBDf8QJELn87BkbGaLM1d4fmJ75?usp=sharing
	(-)-matairesinol$_{(R)}$	https://drive.google.com/drive/folders/1AuhNU3exjumtd8uHyir0w30E0f4-NSZ2?usp=sharing

$_{(I)}$: ideal form; $_{(R)}$: representative form

* The link leads to a folder containing two files: the structure of each inflammatory target with a fixed balajaponin D and the evaluated ligand; and a video showing the target with a balajaponin D, in dark green color, then the ligand to be evaluated is added.

APÊNDICE C – RESÍDUOS DOS ALVOS NO COMPLEXO ‘ALVO INFLAMATÓRIO + balajaponina D’ EM QUE OCORRERAM AS INTERAÇÕES COM OS SEIS LIGANTES

Table 3S. Residues in the 'inflammatory target + balajaponin D’ complex where interactions occurred.

TARGET	LIGAND	RESIDUES	LINK*
CRP	coniferyl alcohol$_{(I)}$	ARG 188; ARG 188; ASN 160; ASN 186; GLY 178; PRO 182; PRO 182; SER 181	https://drive.google.com/drive/folders/1YDbMR5FNVJNpxRR9QLCl3vLyG0zvduOb?usp=sharing
	coniferyl alcohol$_{(R)}$	ARG 188; ARG 188; ASN 160; ASN 186; GLY 178; PRO 182; PRO 182; SER 181	https://drive.google.com/drive/folders/19LzaNHsT7PtdByM6xg_uBR2BhfDm2215?usp=sharing
	coniferyl aldehyde$_{(I)}$	No residues	https://drive.google.com/drive/folders/1UM09kG25zct2VUgbVY4OJtzKu68h0uVW?usp=sharing
	coniferyl aldehyde$_{(R)}$	GLY 178; ILE 174; PHE 180; TRP 162	https://drive.google.com/drive/folders/1VyMq38NQMCLM6__hW6C5K5bS3ZVnw3Cr?usp=sharing
	(+)-lariciresinol	ARG 188; ARG 188; ASN 156; ASN 160; ASN 186; ASN 186; GLN 203; GLY 177; HIE 38; HIE 38; HIE 38; ILE 174; ILE 174; PHE 180; PRO 182; PRO 206; SER 181	https://drive.google.com/drive/folders/1Fuz5OAa_NqaOI64rqJy6dOdy2fRDkkSg?usp=sharing
	(-)-matairesinol$_{(I)}$	ARG 188; ASN 158; HIE 38; HIS 95; PHE 180; PHE 180; TYR 175	https://drive.google.com/drive/folders/1SHLfZ3htXlEPEIZ_YJwrmSQ6RFWXsANZ?usp=sharing
	(-)-matairesinol$_{(R)}$	ARG 188; ASN 158; HIE 38; HIS 95; PHE 180; PHE 180; TYR 175	https://drive.google.com/drive/folders/1idEFYWVtBeJwbl82B5jgkzosb3bIKghy?usp=sharing
	(+)-pinoresinol	ARG 188; ASN 158; GLY 177; GLY 177; HIE 38; HIE 38; ILE 174; ILE 174; PRO 206 TYR 175	https://drive.google.com/drive/folders/1PJemj8rHsI9MBLSXE9EzrqXptG5KssFb?usp=sharing
	(-)-secoisolariciresinol	ARG 188; ARG 188; GLN 203; GLY 177; GLY 178; GLY 177; HIE 38; HIE 38; ILE 174; PRO 206; TRP 162; TYR 175	https://drive.google.com/drive/folders/1z43zsqx9DrbSghG7pI74kFWoUoP7rSz4?usp=sharing
EGF	coniferyl alcohol$_{(I)}$	ASP 11; ASP 11; CYX 6; CYX 14; CYX 14; CYX 20; GLU 5; GLU 5; GLY 12; GLY 12; GLY 18; HIE 10; VAL 19	https://drive.google.com/drive/folders/1SfWTIezBZ26fQRTCF0IqghN7fMnbq_6l?usp=sharing

	coniferyl alcohol$_{(R)}$	ASP 11; ASP 11; CYX 6; CYX 14; CYX 14; CYX 20; CYX 20; GLU 5; GLU 5; GLY 12; GLY 12; GLY; 18; VAL 19	https://drive.google.com/drive/folders/1JERDM5YxqFkpUnfRyevZZ1xAUoqxuGd7?usp=sharing
	coniferyl aldehyde$_{(I)}$	No residues	https://drive.google.com/drive/folders/15l_ib6CVPqEiv03KtF1nthYcZ-wMj_jb?usp=sharing
	coniferyl aldehyde$_{(R)}$	ASP 11; ASP 11; CYX 14; CYX 14; CYX 20; CYX 20; GLY 12	https://drive.google.com/drive/folders/1MTxOBWaQsduMG2i43k5sILdPwAVg052r?usp=sharing
	(+)-lariciresinol	ASP 17; CYX 6; CYX 6; CYX 14; CYX 14; GLU 5; GLU 5; GLY 12; HIS 16	https://drive.google.com/drive/folders/18pNFvqXabM3T62YrZ71qx3VKnphV_De4?usp=sharing
	(-)-matairesinol$_{(I)}$	ASP 17; ASP 17; CYX 6	https://drive.google.com/drive/folders/1N0SxsGbLyA3mzCYqgnFH1uLXXhSMOq9z?usp=sharing
	(-)-matairesinol$_{(R)}$	ASP 17; ASP 17; CYX 6	https://drive.google.com/drive/folders/1U4idAfknOk7fWADyyybyfTqwKGr1UU_M?usp=sharing
	(+)-pinoresinol	ASP 11; ASP 11; ASP 17; ASP 17; ASP 17; CYX 6; CYX 14; GLU 5; GLY 12; GLY 18	https://drive.google.com/drive/folders/1gdNsCS7sQwpR-QILq4QyLolNz_z3YbVG?usp=sharing
	(-)-secoisolariciresinol	ASP 11; ASP 17; ASP 17; CYX 6; GLU 5; GLU 5; GLU 5; GLY 12; GLY 18; VAL 19	https://drive.google.com/drive/folders/1zJsbvuVL3lqOfZ5GR4DjlfpNpHNy1qkK?usp=sharing
IL-1β	coniferyl alcohol$_{(I)}$	GLN 81; GLU 25; GLU 25; LEU 26; LEU 80; LEU 80; LEU 82; LEU 134; PHE 133; TYR 24; VAL 132	https://drive.google.com/drive/folders/1cvyAOx-h2lNqzzMYrttqiGTC1vl0mFrS?usp=sharing
	coniferyl alcohol$_{(R)}$	GLN 81; GLU 25; GLU 25; LEU 26; LEU 80; LEU 80; LEU 82; LEU 134; PHE 133; TYR 24; VAL 132	https://drive.google.com/drive/folders/1Shn2uQPJuvyzXosvfwv63xhoSahN3rkL?usp=sharing
	coniferyl aldehyde$_{(I)}$	No residues	https://drive.google.com/drive/folders/1qp8dwUr6ExBvhEgRnc-A6wpX9E_42m0E?usp=sharing
	coniferyl aldehyde$_{(R)}$	GLN 81; GLU 25; GLU 25; LEU 80; PRO 131; VAL 132	https://drive.google.com/drive/folders/1UnD72L-tD-jdSWh3iwlKTIv72YAEu9tP?usp=sharing
	(+)-lariciresinol	GLN 81; LEU 26; LEU 80; LEU 80; LEU 82; LYS 77; PHE 133; TYR 24; VAL 132	https://drive.google.com/drive/folders/18A_W0yqGeLfp7-Tjm0IzCOYRwWl_DoWE?usp=sharing
	(-)-matairesinol$_{(I)}$	GLN 81; LEU 26; LEU 82; LEU 82; LEU 134; LYS 77; TYR 24; VAL 132	https://drive.google.com/drive/folders/1WSgynGllS0PtJY6OFa73rlX_XPZULn1P?usp=sharing
	(-)-matairesinol$_{(R)}$	GLN 81; LEU 26; LEU 80; LEU 82; LEU 82; LEU 134; LYS 77; TYR 24; VAL 132	https://drive.google.com/drive/folders/1mSJYgT4VbzJ6TiVn4NMzNsoH17jfiXLd?usp=sharing
	(+)-pinoresinol	GLU 5; LEU 80; LEU 134; LYS 77; LYS 77; LYS 77; PHE 133; PHE 133; PHE 133; THR 79; TRP 120; TYR 24; VAL 132	https://drive.google.com/drive/folders/1y2UoJqkU7GtPJLpT4KarZq5dfXtXrtrs?usp=sharing
	(-)-secoisolariciresinol	ASP 142; GLY 136; LEU 80; LEU 134; LYS 77; PHE 133; PHE 133	https://drive.google.com/drive/folders/1II1OMW_9JoT5kacolV8a2pvf7J3yufDt?usp=sharing

	coniferyl alcohol$_{(I)}$	ARG 179; ARG 179; ARG 179; ARG 179; GLN 75; GLN 183; PHE 74; PHE 74; PHE 74; PHE 74; SER 176; SER 176	https://drive.google.com/drive/folders/1qMZaUo1VEo1M56K0m_6zdRgdd0rJgBxr?usp=sharing
	coniferyl alcohol$_{(R)}$	ARG 179; ARG 179; ARG 179; GLN 75; GLN 183; PHE 74; PHE 74; PHE 74; PHE 74; SER 176; SER 176	https://drive.google.com/drive/folders/1FF3y9oBHmf1NE9uh5gkg64kHfuRk8hjm?usp=sharing
	coniferyl aldehyde$_{(I)}$	No residues	https://drive.google.com/drive/folders/1OHxOJ367Wekf_qvZBsJYM9bm9UtpFYR3?usp=sharing
	coniferyl aldehyde$_{(R)}$	GLN 75; GLN 183; GLN 183; PHE 74	https://drive.google.com/drive/folders/1AnAE78-yHEy6OYjfQ-z52l9w_0_5YPot?usp=sharing
IL-6	(+)-lariciresinol	ARG 179; ARG 179; GLN 75; GLN 175; GLN 183; PHE 74; SER 176	https://drive.google.com/drive/folders/1GYsfDccfIfu9EwuR6x5zLLwnxgufw76I?usp=sharing
	(-)-matairesinol$_{(I)}$	GLN 75; GLN 183; LYS 66; PHE 74; PHE 74; PHE 74; SER 176	https://drive.google.com/drive/folders/1HTBm-G1lBjIRO3oGGRA99_RqO6TR96A3?usp=sharing
	(-)-matairesinol$_{(R)}$	GLN 75; GLN 183; LYS 66; LYS 66; PHE 74; PHE 74; PHE 74; SER 176	https://drive.google.com/drive/folders/1GFdYHlAhrklg71d870VlYLxSiBD1URxC?usp=sharing
	(+)-pinoresinol	ARG 179; ARG 179; ARG 179; GLN 75; GLN 175; GLN 183; PHE 74; PHE 74; PHE 74; SER 176	https://drive.google.com/drive/folders/1Qp6gbpt8tiF8YYWMxFcQx8WK01d5cQge?usp=sharing
	(-)-secoisolariciresinol	ARG 179; ARG 182; CYX 73; GLN 75; GLN 75; GLN 183; GLN 183; PHE 74; PHE 74; PHE 74; PHE 74; SER 176	https://drive.google.com/drive/folders/1l6WU_tXjQFmsVp_dy3t2FP4-gF8vp8je?usp=sharing
	coniferyl alcohol$_{(I)}$	ARG 52; ARG 52; ARG 52; ARG 54; ARG 54; GLY 64; HIS 62; LYZ 75; LYS 75; PHE 51; PHE 51	https://drive.google.com/drive/folders/1v31yfnG9Ovd2Es28R-Sjvz5gE8_YCSem?usp=sharing
	coniferyl alcohol$_{(R)}$	ARG 52; ARG 52; ARG 52; ARG 54; ARG 54; GLY 64; HIS 62; LYS 75; LYS 75; PHE 51; PHE 51	https://drive.google.com/drive/folders/18FST1HQSH9i5PdeTrdzTGX3gZYd8K6YJ?usp=sharing
	coniferyl aldehyde$_{(I)}$	No residues	https://drive.google.com/drive/folders/18FST1HQSH9i5PdeTrdzTGX3gZYd8K6YJ?usp=sharing
	coniferyl aldehyde$_{(R)}$	ARG 54; ARG 54; ARG 54; HIS 62; HIS 62; SER 220	https://drive.google.com/drive/folders/1YtxSRP6Z3nataaHJfcjORQ7tT6eHwBfj?usp=sharing
NF-κB	(+)-lariciresinol	ARG 49; ARG 49; ARG 49; ASP 316; ASP 316; ASP 319; LEU 228; VAL 317	https://drive.google.com/drive/folders/1LyDw1Us1zdudc3qmlF8OUe-YhgqwGuXD?usp=sharing
	(-)-matairesinol$_{(I)}$	ARG 52; ARG 54; GLY 50; HIS 62; PHE 51; PRO 66	https://drive.google.com/drive/folders/1EMv-DUQTjXb5XKFVTUHfbqCF2TKJ9aHP?usp=sharing
	(-)-matairesinol$_{(R)}$	ARG 52; ARG 54; GLU 71; GLU 71; GLY 50; HIS 62; LYS 47; PHE 51; PRO 66	https://drive.google.com/drive/folders/1mzjbfcPwulzyedv2qW7H7IhCsjy0zb9I?usp=sharing
	(+)-pinoresinol	ARG 49; ARG 49; ARG 49; ASP 316; ASP 316; ASP 319; ASP 319; ASP 319; LEU 228; VAL 317; VAL 317	https://drive.google.com/drive/folders/1qadPnW_dViXRwOUrz2wy5sLToREH1grG?usp=sharing
	(-)-secoisolariciresinol	ARG 52; ARG 52; ARG 52; ARG 52; ARG 54; ARG 54; ASN 227; GLY 50; GLY 64; HIS 62; LYS 75; LYS 75; LYS 75; LYS 75; SER 220; SER 220	https://drive.google.com/drive/folders/1q6n_Cz2qx7ZcMjzAlRsXvI5Gg1H2XG4I?usp=sharing

	coniferyl alcohol$_{(I)}$	ARG 158; ARG 158; ARG 158; GLY 262; ILE 254; ILE 254; ILE 254; MET 160; PRO 98; SER 99; THR 256; THR 256	https://drive.google.com/drive/folders/1UpnlcRBYzr2bealqqCH1CsrZMW8gPleq?usp=sharing
	coniferyl alcohol$_{(R)}$	ARG 158; ARG 158; ARG 158; GLY 262; ILE 254; ILE 254; ILE 254; MET 160; PRO 98; SER 99; THR 256; THR 256	https://drive.google.com/drive/folders/118SiXO8BCyfEVyFIDmYeBFhaAqy1FxMm?usp=sharing
	coniferyl aldehyde$_{(I)}$	No residues	https://drive.google.com/drive/folders/15nle9r0vtqJr4QCE0wa0AMQS3RBftWbm?usp=sharing
	coniferyl aldehyde$_{(R)}$	ARG 158; ARG 158; ILE 254; MET 160; MET 160; PRO 98; THR 256; THR 256; THR 256	https://drive.google.com/drive/folders/1TX-vVKgHUhqqE0uvOv11lzO2uia1A6Mi?usp=sharing
P53	(+)-lariciresinol	ARG 156; ARG 158; ARG 158; ARG 158; ARG 158; GLU 258; GLU 258; GLY 262; LEU 206; MET 160; MET 160; PRO 98; SER 99; THR 256; THR 256	https://drive.google.com/drive/folders/1BQNjCXPI3Vfhx_MAvfmNVKJVunCtn2-h?usp=sharing
	(-)-matairesinol$_{(I)}$	ASP 208; GLY 262; PRO 98; SER 99; THR 256	https://drive.google.com/drive/folders/1gESkAMbM5TUBeCdk-U87KCo80mw2YmPL?usp=sharing
	(-)-matairesinol$_{(R)}$	ASP 208; GLY 262; PRO 98; SER 99; THR 256	https://drive.google.com/drive/folders/1Gy9Y5pN4nXegYBmTSMzHFKA3axhm37T0?usp=sharing
	(+)-pinoresinol	ARG 156; ARG 158; ARG 158; ARG 158; ARG 158; GLU 258; GLY 262; GLY 262; LEU 206; MET 160; SER 99	https://drive.google.com/drive/folders/1D95ezC6pdqNu0u7ORNzCglmKPqD3p0fp?usp=sharing
	(-)-secoisolariciresinol	ARG 158; ASP 208; GLY 262; LEU 264; MET 160; PRO 98; SER 99; THR 211; THR 211; THR 256	https://drive.google.com/drive/folders/1KNItGYxkZFyVAp8sEV9NOGS2kTI1kXlK?usp=sharing
	coniferyl alcohol$_{(I)}$	ALA 139; ARG 135; ARG 142; ARG 142; ARG 143; GLU 136	https://drive.google.com/drive/folders/1GlXgmyOtQDpHnRT239wco2NrI1tpxTPn?usp=sharing
	coniferyl alcohol$_{(R)}$	ALA 139; ARG 135; ARG 142; ARG 142; ARG 143; GLU 136	https://drive.google.com/drive/folders/1PtXHZ2jiSGPUDr8tMo7h12e30y7AUPbN?usp=sharing
	coniferyl aldehyde$_{(I)}$	No residues	https://drive.google.com/drive/folders/1EhiH948eFKQnQyNvn8RYycnJYpPVImpZ?usp=sharing
	coniferyl aldehyde$_{(R)}$	GLN 140; ILE 137	https://drive.google.com/drive/folders/1SfTumoi6A7BZsI1spotn1fvLzJH89gMJ?usp=sharing
PUMA	(+)-lariciresinol	ALA 134; GLU 130; GLU 130; GLU 130; GLU 131	https://drive.google.com/drive/folders/1Cp6V58qbFGMbAs0H-5wC7j9lJQK_-xQF?usp=sharing
	(-)-matairesinol$_{(I)}$	GLU 131; GLU 131	https://drive.google.com/drive/folders/1c3MiGEKuZv1iVOVAOEn6eEUAVnAN5Aha?usp=sharing
	(-)-matairesinol$_{(R)}$	GLU 131; GLU 131	https://drive.google.com/drive/folders/1zBA8TvWC0ovAHwVrMeu0T-NTa6ErYTaX?usp=sharing
	(+)-pinoresinol	ALA 139; ARG 135; ARG 135; ARG 142; ARG 142; ARG 143; GLU 136	https://drive.google.com/drive/folders/1t-VvjnuRIGB3ClFVP2oLAwmXvU2C-I55?usp=sharing
	(-)-secoisolariciresinol	ARG 135; ARG 142; ARG 142; ARG 143; GLN 132; GLN 132; GLU 136; GLU	https://drive.google.com/drive/folders/1qRmfn-R5ak3E1VMhCup_fKAkrMl3Fv6k?usp=sharing

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TNF-α	coniferyl alcohol$_{(I)}$	CYX 101; GLH 116; GLU 116; GLU 116; LYS 98; PRO 100	https://drive.google.com/drive/folders/1ym2gYdH__QGaQXGgYiXzdh0V67SbJLM7?usp=sharing
	coniferyl alcohol$_{(R)}$	CYX 101; GLH 116; GLU 116; GLU 116; LYS 98; PRO 100	https://drive.google.com/drive/folders/1hC13_SDfhYpcdYNGO-eGEojxPhD40Fau?usp=sharing
	coniferyl aldehyde$_{(I)}$	No residues	https://drive.google.com/drive/folders/14Je_59I1U6DWaBSilEhytzUg5u2apwNx?usp=sharing
	coniferyl aldehyde$_{(R)}$	PRO 117; TYR 119	https://drive.google.com/drive/folders/1LWW78qGGaVyuPuMAs5MfM9JuGhJOuzP0?usp=sharing
	(+)-lariciresinol	ARG 103; ARG 103; GLH 116; GLN 102; GLN 102; GLN 102; GLN 102; GLN 102; GLN 102; GLU 104; GLU 116	https://drive.google.com/drive/folders/1haUb3wJ6S5-scLFEEJW7n8CPvJoWj99q?usp=sharing
	(-)-matairesinol$_{(I)}$	ARG 103; GLH 116; GLN 102; GLN 102; GLU 104; GLU 104; GLU 104; GLU 116	https://drive.google.com/drive/folders/1CxG09l4TzDnRX6ekFaAYhUhhAecSygbn?usp=sharing
	(-)-matairesinol$_{(R)}$	ARG 103; GLH 116; GLN 102; GLN 102; GLN 102; GLU 104; GLU 104; GLU 104; GLU 116	https://drive.google.com/drive/folders/1WS4eLXipQZ-ZfVetjYCH8N0ozmz6D_VC?usp=sharing
	(+)-pinoresinol	ARG 103; GLN 102; GLN 102; GLN 102; GLN 102; GLN 102; GLU 104; GLU 116; GLU 116; GLU 116; GLU 116; GLU 116; TYR 115	https://drive.google.com/drive/folders/1iAlVaGJw2gzdZt11PvC-cYH8KqbKVkLj?usp=sharing
	(-)-secoisolariciresinol	ARG 103; GLH 116; GLN 102; GLN 102; GLN 102; GLN 102; GLU 104; LYS 98; PRO 100; TYR 115	https://drive.google.com/drive/folders/14oCwUGAEgj4Olx7OrIgmEswZUUQm7kSG?usp=sharing

$_{(I)}$: ideal form; $_{(R)}$: representative form

* The link leads to a folder containing two files: the structure of each inflammatory target with fixed balajaponin D and the evaluated ligand, and images demonstrating the location of each residue.

APÊNDICE D – Filtro de busca para a seleção dos mediadores inflamatórios

Table 4S. Search filter for OM-related inflammatory targets.

PubMed-Medline* – *Search filters*
#1 Clinical condition (Mucositis): (Mucositis[TIAB] OR Mucositides[TIAB] OR "Oral Mucositis"[TIAB] OR "Mucositides, Oral"[TIAB] OR "Oral Mucositides"[TIAB] OR Oromucositis[TIAB] OR Oromucositides[TIAB] OR "Mucositis, Oral"[TIAB])
#2 Inflammatory mediators (Inflammation targets): (Cytokines[TIAB] OR "Chemokines"[TIAB] OR "Inflammatory mediators"[TIAB] OR "Inflammation Mediators"[TIAB] OR Prostaglandins[TIAB] OR "Mediators, Inflammation"[TIAB] OR "Mediators of Inflammation"[TIAB])
#3 Combined search: (#1 AND #2)
#4 Search limits: Filters: Clinical Trial, Randomized Controlled Trial, English

Database search was concluded in July 09, 2020, at 10:48.

APÊNDICE E – ESTRUTURA 3D DOS MEDIADORES INFLAMATÓRIOS RELACIONADOS À MUCOSITE ORAL (ALVOS)

Table 5S. 3D structure of OM-related inflammatory targets.

TARGETS	LINK*
CRP	https://drive.google.com/file/d/1bkBFCfp9BBrI-TJeqoBiNcmMLoMR3yjs/view?usp=sharing
EGF	https://drive.google.com/file/d/1wTkzMBy-gZvK8wtkWLFnY1bNA-bPAp6u/view?usp=sharing
IL-6	https://drive.google.com/file/d/1XDiL6l95HTXsFAjVhubMX_I3lYu_8cIq/view?usp=sharing
IL-1β	https://drive.google.com/file/d/1hIefrcNzhlcc64NOoGBD9-8YWrg8_jyA/view?usp=sharing
NF-κB	https://drive.google.com/file/d/1uzD1EyPHJK6LdwbbmWIlI7LfdIpj1EXW/view?usp=sharing
P53	https://drive.google.com/file/d/1HSh_zNSPfwQiwUV2F4reQRnxSXEKWwBJ/view?usp=sharing
PUMA	https://drive.google.com/file/d/1jckolsOzlSkpoZNmqUbzra2TW0WCQDR1/view?usp=sharing
TNF-α	https://drive.google.com/file/d/1Uf34OP4hVEqunbp54Iasab-pslWArrls/view?usp=sharing

*The link leads to a video showing the inflammatory target.

APÊNDICE F – ESTRUTURA 3D DAS BIOMOLÉCULAS IDENTIFICADAS DA PO1 (LIGANTES)

Table 6S. 3D structure of identified OP1 biomolecules (ligands).

LIGANDS	LINK*
coniferyl alcohol$_{(I)}$	https://drive.google.com/file/d/1idDLmcZtVplMqJgee1TN_cQ_4JpVkJg4/view?usp=sharing
coniferyl alcohol$_{(R)}$	https://drive.google.com/file/d/15XRGKgWRuzm2MTu226C87vPLUb4mBZeC/view?usp=sharing
coniferyl dehyde$_{(I)}$	https://drive.google.com/file/d/1J7qtFDQYyj6TfJ5xbHFsUfeT8hYXsLGa/view?usp=sharing
coniferyl dehyde$_{(R)}$	https://drive.google.com/file/d/1pj9_g0OEbYa74BB1HahPRQ5WZOSTtUs0/view?usp=sharing
(+)-lariciresinol	https://drive.google.com/file/d/1NdQ7tTqknZS9KGDRiUHYwfzUq3zV9fcM/view?usp=sharing
(-)-secoisolariciresinol	https://drive.google.com/file/d/1_qhGvlOCfblf-2CZ3AOCyazDjgoa2Y2D/view?usp=sharing
balajaponin D	https://drive.google.com/file/d/1CEf4gEBTwQGZXlxYMOFHg0GLjLCpOpcR/view?usp=sharing
(+)-pinoresinol	https://drive.google.com/file/d/1PDU6ax1KJpjoUcFQBhbtzE997ECRZ1Va/view?usp=sharing
(-)-matairesinol$_{(I)}$	https://drive.google.com/file/d/1LaoPDVL2JRZ0fVeIb3IzUZWkXFiAoqFO/view?usp=sharing
(-)-matairesinol$_{(R)}$	https://drive.google.com/file/d/1v50nDSlCpHn36Kq-K5II6q4DxN4PIe3t/view?usp=sharing

$_{(I)}$: ideal form; $_{(R)}$: representative form

*The link leads to a video showing the ligand.

APÊNDICE G - SMILES DOS COMPOSTOS NO MOMENTO PRÉ-DOCKING

Table 7S. SMILES of the ligands at the pre-docking moment.

LIGANDS	SMILES PRE-DOCKING
coniferyl alcohol$_{(I)}$	C(=C\C/C=C/CO)(\[C@@H](C)O)/OC/tmp/T98XKS0
coniferyl alcohol$_{(R)}$	C(=C(\C)/O)(\CCCCCO)/OC/tmp/F0WMFDG
coniferyl dehyde$_{(I)}$	C=CC=O/tmp/T0AKDZ0
coniferyl dehyde$_{(R)}$	C(=C(\O)/[C@@H](C)OC)/C.C=CC=O/tmp/8QPXN08
(+)-lariciresinol	O1[C@@H]([C@H]([C@H](C1)Cc1ccc(c(c1)OC)O)CO)c1ccc(c(c1)OC)O/tmp/1YAYZVR
(-)-secoisolariciresinol	[C@@H](Cc1ccc(c(c1)OC)O)([C@H](CO)Cc1cc(c(cc1)O)OC)CO/tmp/YJTTYB8
balajaponin D	Oc1ccc(cc1OC)[C@H](O)[C@H](C/C=C/c1ccc(c(c1)OC)O)CO/tmp/S23JD00
(+)-pinoresinol	O1[C@@H]([C@H]([C@H](C1)Cc1cc(c(cc1)O)OC)C)c1ccc(c(c1)OC)O/tmp/T17V018
(-)-matairesinol$_{(I)}$	[C@@H]1(COC(=O)[C@@H]1Cc1ccc(c(c1)OC)O)CC/C=C\C(=C\OC)\O/tmp/64RDYS0
(-)-matairesinol$_{(R)}$	[C@@H]1(COC(=O)[C@@H]1Cc1ccc(c(c1)OC)O)CC/C=C\[C@@H](COC)O/tmp/2Q6CCMG

$_{(I)}$: ideal form; $_{(R)}$: representative form

APÊNDICE H - SMILES DOS COMPOSTOS NO MOMENTO PÓS-DOCKING

Table 8S. SMILES of the ligands at the post-docking moment.

LIGANDS	TARGETS	SMILES POST-DOCKING
coniferyl alcohol$_{(I)}$	EGF	[C@@H]([C@@H](C)O)(OC)/C=C/C=C/CO/tmp/WG7XHM0
	IL-1β	[C@@H]([C@@H](C)O)(OC)CC/C=C/CO/tmp/WPSHAN8
	IL-6	[C@@H]([C@@H](C)O)(OC)CC/C=C/CO/tmp/1VNZ32G
	NF-κB	[C@@H]([C@@H](C)O)(OC)CC/C=C/CO/tmp/WNBPTW0
	P53	[C@@H]([C@@H](C)O)(OC)CC/C=C/CO/tmp/1XCJ520
	PUMA	C(=C\C/C=C/CO)(/[C@@H](C)O)\OC/tmp/HET7PVR
	TNF-α	[C@@H]([C@@H](C)O)(OC)CC/C=C/CO/tmp/MQD6WBG
coniferyl alcohol$_{(R)}$	EGF	[C@H](CCCCCO)(OC)[C@H](C)O/tmp/RWCT3Y8
	IL-1β	[C@H](CCCCCO)(OC)[C@H](C)O/tmp/79SPC0G
	IL-6	[C@H](CCCCCO)(OC)[C@H](C)O/tmp/06EGQF8
	NF-κB	[C@H](CCCCCO)(OC)[C@@H](C)O/tmp/7E72BPR
	P53	[C@H](CCCCCO)(OC)[C@@H](C)O/tmp/XTRJCQR
	PUMA	[C@H](CCCCCO)(OC)[C@@H](C)O/tmp/T5FCCMG
	TNF-α	C(=C(\C)/O)(/CCCCCO)\OC/tmp/TES073R
coniferyl dehyde$_{(I)}$	EGF	C=CC=O/tmp/3PJZYTG
	IL-1β	C=CC=O/tmp/NABMDP8
	IL-6	C=CC=O/tmp/WKK5NRG
	NF-κB	C=CC=O/tmp/54C7998
	P53	C=CC=O/tmp/XZ490A8
	PUMA	C=CC=O/tmp/F9WRR5G
	TNF-α	C=CC=O/tmp/WP9ASQ8
coniferyl dehyde$_{(R)}$	EGF	C(=C)[C@H](O)[C@@H](C)OC.C=CC=O /tmp/4MJ7Z3G
	IL-1β	C(=C)[C@H](O)[C@@H](C)OC.C=CC=O/tmp/HE0PPX0
	IL-6	C(=C)[C@H](O)[C@@H](C)OC.C=CC=O/tmp/02EVMKG
	NF-κB	C(=C)[C@H](O)[C@@H](C)OC.C=CC=O/tmp/22CW48G
	P53	C(=C(\O)/[C@@H](C)OC)\C.C=CC=O/tmp/3TTXMHR
	PUMA	C(=C)[C@H](O)[C@@H](C)OC.C=CC=O/tmp/6XWF6RR
	TNF-α	C(=C)[C@H](O)[C@@H](C)OC.C=CC=O/tmp/ZMG917R

	EGF	[C@@H]1(COC(=O)[C@@H]1Cc1ccc(c(c1)OC)O)CCCC/C(=C/OC)/O/tmp/3GKA0E8
	IL-1β	[C@@H]1(COC(=O)[C@@H]1Cc1ccc(c(c1)OC)O)C/C=C/C/C(=C/OC)/O/tmp/CRYY5KR
	IL-6	[C@@H]1(COC(=O)[C@@H]1Cc1ccc(c(c1)OC)O)CC/C=C/C(=C/OC)/O/tmp/X065YQ8
(-)-matairesinol$_{(I)}$	NF-κB	[C@@H]1(COC(=O)[C@@H]1Cc1ccc(c(c1)OC)O)C/C=C\C/C(=C/OC)/O/tmp/CSCESNR
	P53	[C@@H]1(COC(=O)[C@@H]1Cc1ccc(c(c1)OC)O)CCCC/C(=C/OC)/O/tmp/ZJVWYCG
	PUMA	[C@@H]1(COC(=O)[C@@H]1Cc1ccc(c(c1)OC)O)CC/C=C/C(=C/OC)/O/tmp/VCKERGG
	TNF-α	[C@@H]1(COC(=O)[C@@H]1Cc1ccc(c(c1)OC)O)CCCC/C(=C/OC)/O/tmp/MKVASY8
	EGF	[C@@H]1(COC(=O)[C@@H]1Cc1ccc(c(c1)OC)O)CCCC[C@@H](COC)O/tmp/BEN3ENR
	IL-1β	[C@@H]1(COC(=O)[C@@H]1Cc1ccc(c(c1)OC)O)CCCC[C@@H](COC)O/tmp/MARYMN0
	IL-6	[C@@H]1(COC(=O)[C@@H]1Cc1ccc(c(c1)OC)O)CCCC[C@@H](COC)O/tmp/CYK4X90
(-)-matairesinol$_{(R)}$	NF-κB	[C@@H]1(COC(=O)[C@@H]1Cc1ccc(c(c1)OC)O)CCCC[C@@H](COC)O/tmp/ZWM8QZR
	P53	[C@@H]1(COC(=O)[C@@H]1Cc1ccc(c(c1)OC)O)CCCC[C@@H](COC)O/tmp/BF2TW8R
	PUMA	[C@@H]1(COC(=O)[C@@H]1Cc1ccc(c(c1)OC)O)CC/C=C\[C@@H](COC)O/tmp/ZPEYJ8R
	TNF-α	[C@@H]1(COC(=O)[C@@H]1Cc1ccc(c(c1)OC)O)C/C=C/C[C@@H](COC)O/tmp/B5C7GZ0

$_{(I)}$: ideal form; $_{(R)}$: representative form

APÊNDICE I – METODOLOGIA ADOTADA NA ESTRATÉGIA I: DOCKING DE APENAS UM LIGANTE

Table 9S. The methodology adopted in Strategy I: one ligand docking.

PHASES	LINK*
1ª phase: the selection of one chain in inflammatory target;	It can be realized in the 'txt' archive or through the MGLTools software: https://drive.google.com/file/d/1urCLxBsViSRVKES8ZsJ5cFi1RCBwKQq1/view?usp=sharing
2ª phase: exclusion of water molecules in the inflammatory target;	It can be realized in the 'txt' archive or through the MGLTools software: https://drive.google.com/file/d/1JOx6VigkjVvmErqMOQNQH-3F413IMAD0/view?usp=sharing
3ª phase: addition of hydrogen (H);	It is realized in MGLTools software; it is indicated to add all types of H since the nonpolar H will be excluded in the save process of the structure: https://drive.google.com/file/d/1Cn-YpUfIK4Mu1q_aDDVCvKi8daAXIqd6/view?usp=sharing
4ª phase: construction of Gridbox: containing all spatial information of inflammatory target that should be analyzed in the docking);	It is realized in MGLTools software: https://drive.google.com/file/d/1f6TeCp5L34s8xMN_Q23snxUxhTxUU1eW/view?usp=sharing https://drive.google.com/file/d/1js8EfqgCbIuZi0lC6jlf7ccyTWgZqmeX/view?usp=sharing
5ª phase: addition of ligand and detection of torsion;	It is realized in MGLTools software: https://drive.google.com/file/d/1durxaPmIh4Ey6u_Qr2EwSmWRk61WjCzs/view?usp=sharing
6ª phase: construction of 'config' archive: there will be the information of inflammatory target and ligand, the spatial information of the target, the final archive that will be generated at the end of the docking, the seed of the simulation, and the number of times that docking was realized;	It is realized in MGLTools software: https://drive.google.com/file/d/1SG51HSm75GQQCRSLtEEr1xzZCgYfvT0b/view?usp=sharing https://drive.google.com/file/d/1FN53X3Zs_clhpApXx3P8FxZA-nBpIyrh/view?usp=sharing
7ª phase: docking.	It is realized in the Vina software, with the 'config' archive: https://drive.google.com/file/d/1uBLwC-acYhbugsxHreYa6QB9BJIOW8Sn/view?usp=sharing The results can be visualized in the MGLTools software: https://drive.google.com/file/d/1VLrkWDGSbOZ9CZNs_qOBIl0IHf1Tv0Qy/view?usp=sharing

*The link leads to a picture that illustrates each phase.

ANEXO A – SUBMISSÃO À REVISTA Journal of Medicinal Chemistry

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