IN SILICO STUDY OF FARNESOL AND ITS USE IN EMULSION AS A POTENTIAL TREATMENT FOR GASTRIC ULCER

ESTUDO IN SILICO DO FARNESOL E SUA UTILIZAÇÃO EM EMULSÃO COMO POTENCIAL TRATAMENTO PARA ÚLCERA GÁSTRICA

ESTUDIO IN SILICO DE FARNESOL Y SU UTILIZACIÓN EN EMULSIÓN COMO POSIBLE TRATAMIENTO PARA ÚLCERAS GÁSTRICAS

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ABSTRACT

Farnesol is an organic component found in various natural essential oils with antioxidant, antimicrobial, and antidiarrheal properties. It emerges as an alternative in treating inflammatory diseases such as gastric ulcers, characterized by an imbalance between protective components and aggressive factors affecting the entire gastrointestinal tissue. Conventional medications, although practical, cause adverse effects such as rebound and increased risk of gastric cancer, underscoring the need to develop safer alternative and natural treatments. This study aimed to conduct in silico studies of Farnesol and develop an emulsion containing farnesol targeted at gastroprotective activity in a standardized gastric ulcer induction model. The in silico study investigated the therapeutic action of Farnesol in the treatment of gastric ulcers through molecular docking with specific targets. Our analyses indicated interactions with the COX-2 enzyme, suggesting possible inhibition of this enzyme by Farnesol. We also observed interactions with the M^3 muscarinic receptor, TNF-α, and TGF-β. We developed an emulsion containing Farnesol, which exhibited satisfactory physicochemical characteristics with a pH of 6.13 and conductivity of 13.29 µS/cm, enhancing emulsion stability and reducing the risk of phase separation. The average zeta potential was -38.9 mV, and the average particle size of the emulsion was 1133 nm, reducing the likelihood of aggregation and increasing emulsion stability. The in vivo study was conducted with experiments on mice with gastric ulcer induction using an experimental model that employs ethanol as an aggressive agent. The results showed a reduction in lesion size of 43.8%, 42%, and 74.38% at the tested doses of 25, 50, and 100 mg/kg, respectively. The

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research utilized a descriptive methodology. We suggest that Farnesol may present significant anti-inflammatory potential, and we found, through a standardized model, that the emulsion constitutes a therapeutic option for protecting the gastric mucosa.

Keywords: Farnesol. Molecular Docking. Emulsion. Gastric Ulcer.

RESUMO

O farnesol é um componente orgânico encontrado em vários óleos essenciais naturais com propriedades antioxidantes, antimicrobianas e antidiarreicas. Ele surge como uma alternativa no tratamento de doenças inflamatórias, como úlceras gástricas, caracterizadas por um desequilíbrio entre componentes protetores e fatores agressivos que afetam todo o tecido gastrointestinal. Os medicamentos convencionais, embora práticos, causam efeitos adversos, como rebote e aumento do risco de câncer gástrico, ressaltando a necessidade de desenvolver tratamentos alternativos e naturais mais seguros. Este estudo teve como objetivo realizar estudos in silico do Farnesol e desenvolver uma emulsão contendo farnesol direcionada à atividade gastroprotetora em um modelo padronizado de indução de úlcera gástrica. O estudo in silico investigou a ação terapêutica do Farnesol no tratamento de úlceras gástricas por meio do acoplamento molecular com alvos específicos. Nossas análises indicaram interações com a enzima COX-2, sugerindo uma possível inibição dessa enzima pelo Farnesol. Também observamos interações com o receptor muscarínico M³, TNF-α e TGF-β. Desenvolvemos uma emulsão contendo Farnesol, que apresentou características físico-químicas satisfatórias com pH de 6,13 e condutividade de 13,29 µS/cm, aumentando a estabilidade da emulsão e reduzindo o risco de separação de fases. O potencial zeta médio foi de -38,9 mV, e o tamanho médio das partículas da emulsão foi de 1133 nm, reduzindo a probabilidade de agregação e aumentando a estabilidade da emulsão. O estudo in vivo foi realizado com experimentos em camundongos com indução de úlcera gástrica usando um modelo experimental que emprega etanol como agente agressivo. Os resultados mostraram uma redução no tamanho da lesão de 43,8%, 42% e 74,38% nas doses testadas de 25, 50 e 100 mg/kg, respectivamente. A pesquisa utilizou uma metodologia descritiva. Sugerimos que o Farnesol pode apresentar um potencial anti-inflamatório significativo e descobrimos, através de um modelo padronizado, que a emulsão constitui uma opção terapêutica para proteger a mucosa gástrica.

Palavras-chave: Farnesol. Acoplamento Molecular. Emulsão. Úlcera Gástrica.

RESUMEN

El farnesol es un componente orgánico presente en varios aceites esenciales naturales con propiedades antioxidantes, antimicrobianas y antidiarreicas. Se presenta como una alternativa en el tratamiento de enfermedades inflamatorias, como las úlceras gástricas, caracterizadas por un desequilibrio entre los componentes protectores y los factores agresivos que afectan a todo el tejido gastrointestinal. Los medicamentos convencionales, aunque prácticos, causan efectos adversos, como rebote y aumento del riesgo de cáncer gástrico, lo que destaca la necesidad de desarrollar tratamientos alternativos y naturales más seguros. El objetivo de este estudio fue realizar estudios in silico del farnesol y desarrollar una emulsión que contenga farnesol dirigida a la actividad gastroprotectora en un modelo estandarizado de inducción de úlcera gástrica. El estudio in silico investigó la acción terapéutica del farnesol en el tratamiento de úlceras gástricas mediante el acoplamiento molecular con objetivos específicos. Nuestros análisis indicaron interacciones con la enzima COX-2, lo que sugiere una posible inhibición de esta enzima por el farnesol. También observamos interacciones con el receptor muscarínico M³, TNF-α y TGF-β. Desarrollamos una emulsión que contiene Farnesol, que presentó características fisicoquímicas satisfactorias con un pH de 6,13 y una conductividad de 13,29 µS/cm, lo que aumentó la estabilidad de la emulsión y redujo el riesgo de separación de fases. El potencial zeta medio fue de -38,9 mV y el tamaño medio de las partículas de la emulsión fue de 1133 nm, lo que redujo la probabilidad de agregación y aumentó la estabilidad de la emulsión. El estudio in vivo se realizó con experimentos en ratones con inducción de úlcera gástrica utilizando un modelo experimental que emplea etanol como agente agresivo. Los resultados mostraron una reducción del tamaño de la lesión del 43,8 %, 42 % y 74,38 % en las dosis probadas de 25, 50 y 100 mg/kg, respectivamente. La investigación utilizó una metodología descriptiva.

Sugerimos que el farnesol puede presentar un potencial antiinflamatorio significativo y descubrimos, a través de un modelo estandarizado, que la emulsión constituye una opción terapéutica para proteger la mucosa gástrica.

Palabras clave: Farnesol. Acoplamiento Molecular. Emulsión. Úlcera Gástrica.

INTRODUCTION

Gastric ulcer is a disease characterized by an opening in the mucosa of the digestive tract, with multifactorial etiology influenced by an imbalance between mucosal protection, dietary factors, bicarbonate secretion, nitric oxide, blood flow, sulfhydryls, prostaglandins, and aggressive factors such as acid secretion, pepsin, and free radicals, promoting the expansion of the inflammatory process (Viana, 2016). Epidemiological data in Brazil indicate that between 2014 and 2023, 112,456 deaths due to gastric ulcers were recorded (Parente, 2024) According to (Lins, 2024) it is estimated that population aging will cause approximately 13.2 million new cases of gastric cancer by 2030.

The etiology of these lesions is associated with stress, smoking, alcohol, Helicobacter pylori infection, and the intake of non-steroidal anti-inflammatory drugs (Pinheiro, 2015). The patient's quality of life significantly declines, resulting in high economic costs, both direct and indirect (Martins, 2019). Consequently, treating this disease aims to restore the balance of the disrupted gastroduodenal mucosa. Initially, drugs neutralized gastric content through the action of antacids. Subsequently, new drugs entered the market, such as cimetidine and ranitidine (H_2 histamine antagonists), followed by the development of cytoprotective drugs like misoprostol, in addition to gastroprotective agents, with omeprazole as the standard substance (Olbe, 2003). Doctors prescribe antibiotics when they diagnose patients with Helicobacter pylori infection (Soally,2018).

Continuous use of these drugs can produce adverse effects and increase the risk of gastric cancer, as well as contribute to the development of osteoporosis, fractures, pneumonia, headaches, diarrhea, insomnia, and renal inflammation (Welterman, 2021). Furthermore, these medications can cause a rebound effect, where initial symptoms temporarily disappear but return

after some time. Therefore, it is necessary to encourage the development of new drugs with fewer adverse effects and lower recurrence risk.

There is a growing interest in drugs derived from natural sources in this context. A promising alternative for treating gastric ulcers is using natural products, predominantly plants, and their secondary metabolites, such as sesquiterpenes, due to their diverse biological effects (Bartikola,2014). Farnesol is a sesquiterpene with 15 carbon atoms($C_{15}H_{26}O$) synthesized by animals and plants (Costa, 2021). This molecule exhibits various biological activities, including antioxidant, antimicrobial (Costa,2021), cardioprotective (Silva, 2021), neuroprotective (Khan,2011), and antidiarrheal (Da Costa, 2020).

However, Farnesol faces limitations regarding solubilization, prompting research to improve its solubility, dissolution rates, and bioavailability (Silva,2017). In response to this need, a biotechnological solution, an emulsion, was developed to enhance the solubilization and dissolution rates of drugs, protect unstable molecules from degradation, and increase the surface area for contact, thereby facilitating the transport and absorption of active principles (Ahmed,2011). Given this context, the study aimed to develop an emulsion containing farnesol and evaluate the therapeutic potential of this formulation using in silico and in vivo techniques to treat gastric ulcers.

RESULTS AND DISCUSSION

The physicochemical parameters, lipophilicity, and solubility of Farnesol predicted by the SwissADME software showed a molecular weight of 222.37 g/mol, 16 atoms, one hydrogen bond acceptor, and one hydrogen bond donor, with a TPSA (Topological et al. Area) of 20.23 $Å^2$, an average lipophilicity of 4.32, and intermediate water solubility.

The results of the pharmacokinetic profile (Frame 1), analyzed by SwissADME software, evaluated Farnesol's absorption, distribution, metabolism, and excretion. The bioactivity score provided by the Molinspiration program indicated potential activity sites of Farnesol. Notably, the binding scores with GPCR (-0.13), kinase (-0.60), and protease inhibition (-0.43) suggest potential interactions with these targets.

Frame 1. Pharmacokinetic Profile of Farnesol

Pharmacokinetic profile	**SwissADME**
Gastrointestinal absortion	High
Permeant of the blood-brain barrier	Yes
P-glycoprotein substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log Kp (skin permeation)	-3,81

Source: Prepared by the authors - Swiss ADMC Software
Caption: CYP - Citocromo

Regarding pharmacokinetics, Farnesol absorbs effectively through the gastrointestinal tract, reaching the bloodstream, a positive point for its therapeutic efficacy. It is well absorbed through the skin and distributed in the body, with the potential to cross the blood-brain barrier. This supports its pharmacological action in anxiety and depression models (Shahnouri, 2016), as well as its analgesic (Shahnouri,2016) and neuroprotective effects (Lisha,2019). Farnesol also demonstrated good metabolization capacity, inhibiting only two isoforms of cytochrome P450 (CYP1A2 and CYP2C9), suggesting reduced interactions with other medications and a lower chance of adverse events.

Frame 2 presents the results of Farnesol's pharmacological activities and the possible adverse effects predicted by the online PASS software.

Frame 2. Pharmacological activities and predicted adverse reactions for farnesol

Pa	**Pi**	**Pharmacological activities**
0,953	0,003	Mucomembranous protector
0.840	0,003	TNF expression inhibitor
0,807	0,031	Treatment of phobic disorders
0,770	0,004	Anti-ulcer
0,717	0,004	Gastrin inhibitor
Adverse reactions		
0,951	0,002	Skin irritation
0,925	0,005	Anemia
0,878	0,004	Hyperglycemia

Source: Prepared by the authors - Pass Software
Caption: Pa – Probability of bein g active; Pi – Probability of being inactive.

The molecule exhibited anti-inflammatory potential from a pharmacodynamic perspective, focusing on the digestive system and acting on the central nervous system. The predicted adverse reactions may be considered typical; however, further toxicological investigations are necessary, raising the possibility of additional studies in the field of toxicology.

Frame 3 presents the results of the interaction energies of Farnesol and the simulation of the farnesol- lecithin emulsion. Figure 1 shows the 3D structures of Farnesol and the farnesol-lecithin emulsion simulation.

Frame 3. Interaction energy, in Kcal/mol, of Farnesol and Farnesol-lecithin complex, in three different programs.

		Vina	**Autodock**	**Molegro**
COX-2	**3MLD** Farnesol	-6.7	-6.21	-110.4
COX-1	**5WBE** Farnesol	-6.9	-6,92	-117.4
TNF-α	**2AZ5** Farnesol	-3.2	-4.38	-106.6
COX-1	**5IKR** Farnesol	-5.8	-8.08	-108.8
COX-2	**5ZHP** Farnesol	0.0	-7.00	-63.9
TGF-β	**5E8S** Farnesol	-3.2	-6.99	-82.5
Muscarinic receptor	**6Y3C** Farnesol	-6.2	-5.11	79.3
Proton bomb	**5Y1U** Farnesol	0	-6,69	-94.9
Urease	**6ZJA** Farnesol	-5.3	-3.87	71.0
COX-2	**3MLD** Farnesol-lecithin	-6.9	0	-122.3
COX-1	**5WBE** Farnesol-lecithin	-5.6	0	0
TNF-α	**2AZ5** Farnesol-lecithin	-3.2	0	26.2
COX-1	**5IKR** Farnesol-lecithin	-6.7	0	0
TGF-β	**5E8S** Farnesol-lecithin	-4.8	0	44
COX-2	**5ZHP** Farnesol-lecithin	0	0	0
Muscarinic receptor	**6Y3C** Farnesol-lecithin	-6.1	0	0
Proton bomb	**5Y1U** Farnesol-lecithin	0	0	0
Urease	**6ZJA** Farnesol-lecithin	-5.5	0	0

Source: Prepared by the authors - Virna, Autodock, Molegro, Software
Caption: COX - Cyclooxygenase; TGF - Transforming Growth Factor; TNF - Tumor Necrosis Factor.

Figure 1. 3D Farnesol structure (A) and (B) Farnesol-Lecithin.

(A) **(B)**

Caption: The colors represent their respective atoms: Oxygen (red), Nitrogen (blue), Carbon (gray), Phosphorus (yellow) and Hydrogen (white).

The interaction energy results obtained with the three programs used showed that, among the evaluated targets, COX-1 and COX-2 enzymes exhibited the best interactions with Farnesol, followed by the M³ muscarinic receptor, TGF-β, gastric proton pump (H^+/K^+-ATPase), TNF-α, and urease.

Due to the large size of the farnesol-lecithin complex molecular chain, we could not calculate the interaction energies using the Autodock program. However, we obtained this energy using the VINA and MOLEGRO programs. In the VINA program, the target that showed the best interaction was COX-2, with the PDB code 3MLD. We obtained results similar to those of the MOLEGRO program.

Molecular docking considered at least three critical variables: binding energy, efficiency constant, and inhibition constant. These variables indicated the possible interaction between the molecule and its target. The more negative the binding energy and efficiency constant, the greater the interaction between the molecule and the target. For the studied targets, COX-2 exhibited the highest interaction with isolated Farnesol, with binding energies of -8.08 kcal/mol,

and when complexed with lecithin, with a binding energy of -6.7 kcal/mol, suggesting an inhibitory effect. Regarding the inhibition constant (Ki), lower values indicate stronger interactions. The results show that COX-2 had the lowest Ki values, meaning it formed stronger bonds, including hydrogen bonds, with Farnesol. According to Ahmed (2020), presented molecular docking data with the COX-2 protein, showing in vivo anti-inflammatory activity and gastric protective effect of a substance compared to indomethacin as a positive control.

Other relevant targets for inflammation and gastric ulcers, such as TGF-β, TNF-α, the M³ muscarinic receptor, and the gastric proton pump, were also evaluated in this study. Farnesol showed good docking scores with the M³ muscarinic receptor and TGF-β, suggesting that other mechanisms may also be involved in its anti-ulcer effect, highlighting the importance of further

research in this area (Santos,2022). Frame 4 presents the interactions between the targets and Farnesol, detailing the types of bonds present. All tested targets formed hydrogen bonds and predominant Van der Waals interactions with the ligand. The gastric proton pump (H^+/K^+-ATPase) was the target with the highest number of hydrogen bonds, totaling three bonds.

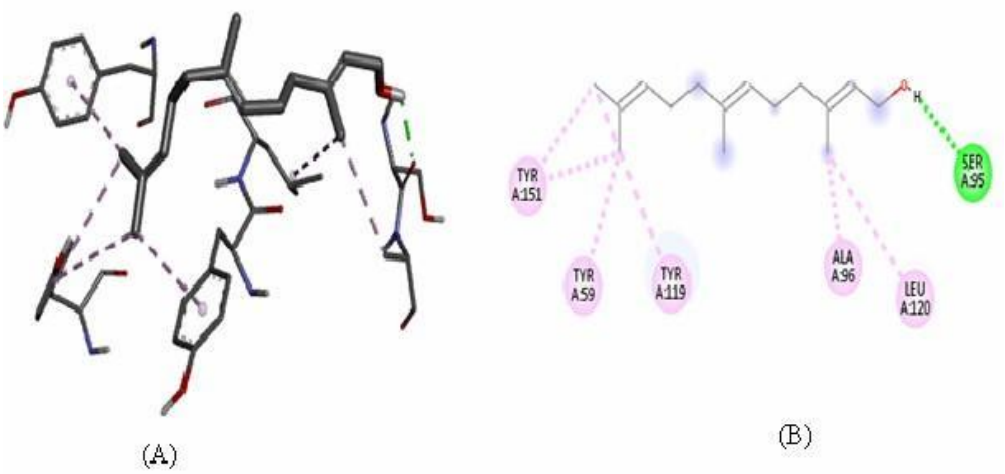
Frame 4. Molecular interactions of farnesol with target of interest.

Complex tox	Hydrogen bond	Van der Waals
2AZ5	SER95	TRY59, ALA96, TYR119, TYR151, LEU120
5E8S	GLU245	LEU340, TYR282, HIS283, ALA230, VAL219, LYS232, LEU278, PHE262, TYR249, ILE211
5IKR	PHE529, ASN375	VAL344, VAL228, PHE205, TYR385, PHE209, LEU534, LEU384, TRP387, TYR348, VAL349, LEU352
5YLU	LEU811	LEU809, TYR799, ALA339, ILE816, LEU796
5ZHP	ASN152, TRP199, TYR148	ILE116, TRP503, CYS532, TYR533, TYR529, TYR506
6Y3C	PRO84, ARG83	PRO86, LYS473, LEU123, HIS43
6ZJA	ASP209, ARG176	TRP224, LYS198

Source: Prepared by the authors - Docking Molecular
Caption:SER-Serine;GLU-Glutamic acid;PHE-Phenylalanine;ASN-Asparagine;LEU-Leucine;TRP-Tryptophan;TYR-Tyrosine; PRO-Proline;AGR-Arginine;ASP-Aspartic acid.

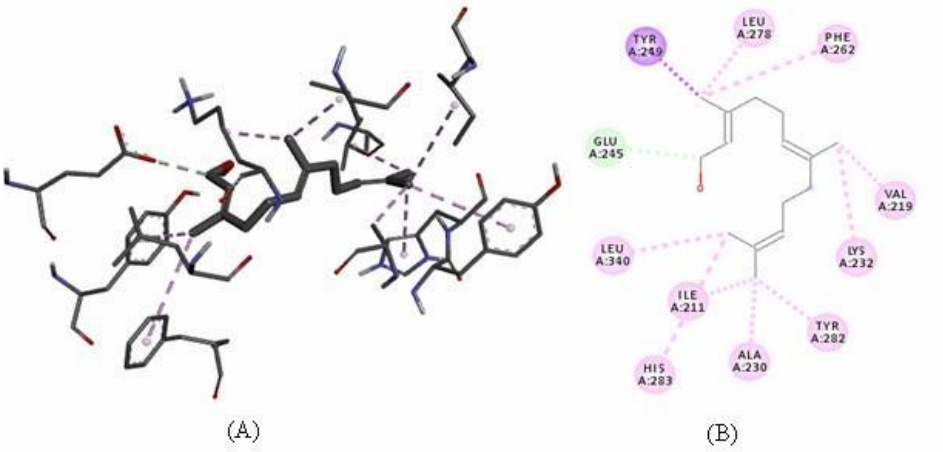
In this context, Figures 2 to 8 illustrate the interactions molecular existing in the complexes above.Representation in 2D and 3D.

Figure 2. Representation of the interactions between farnesol and TNF-α (2az5).



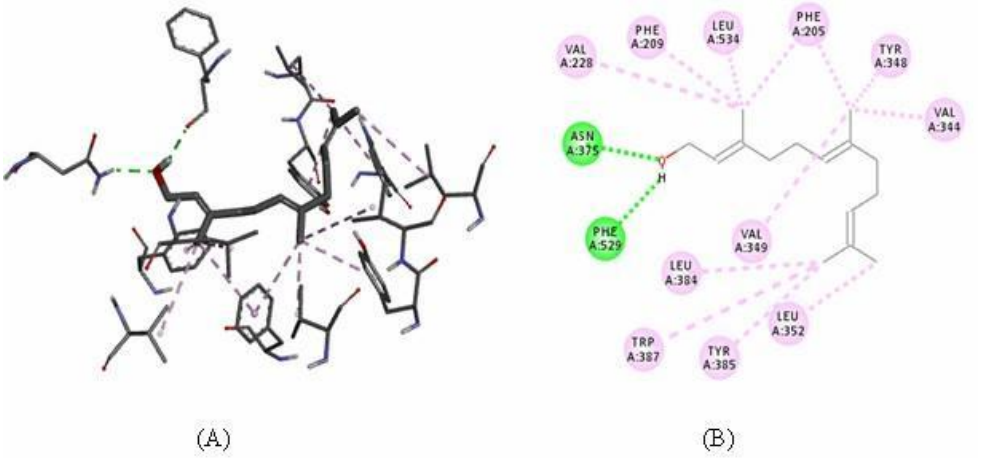
Caption: (A) 3D representation; (B) 2D representation. The purple dotted lines represent van der Waals interactions and the green dotted lines represent hydrogen bonds.

Figure 3. Representation of the interactions between Farnesol and TGF-β (5e8s).



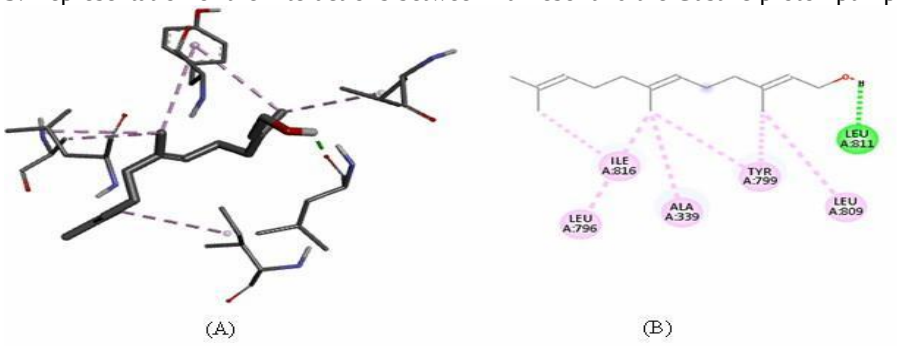
Caption: (A) 3D representation; (B) 2D representation. The purple dotted lines represent van der Waals interactions and the green dotted lines represent hydrogen bonds.

Figure 4. Representation of the interactions between farnesol and COX-1 (5ikr).



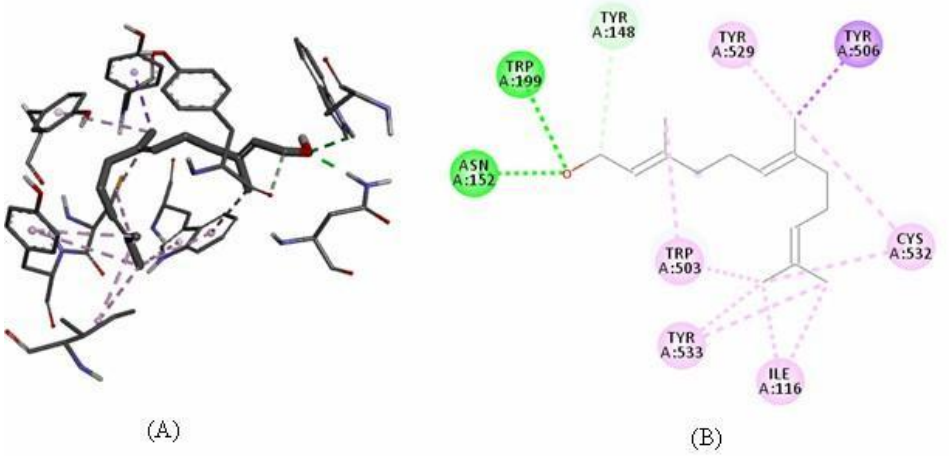
Caption: (A) 3D representation; (B) 2D representation. The purple dotted lines represent van der Waals interactions and the green dotted lines represent hydrogen bonds.

Figure 5. Representation of the interactions between Farnesol and the Gastric proton pump (5ylu).



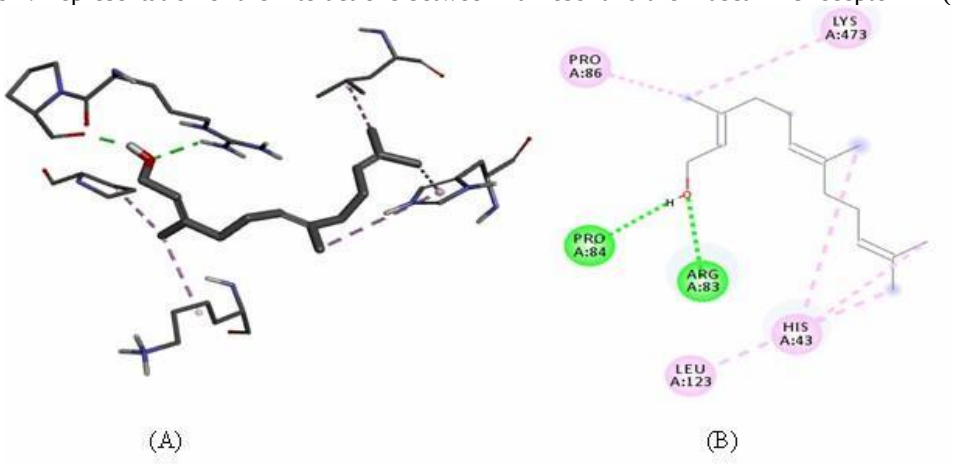
Caption:(A) 3D representation; (B) 2D representation. The purple dotted lines represent van der Waals interactions and the green dotted lines represent hydrogen bonds.

Figure 6. Representation of the interactions between Farnesol and COX-2 (5zhp).



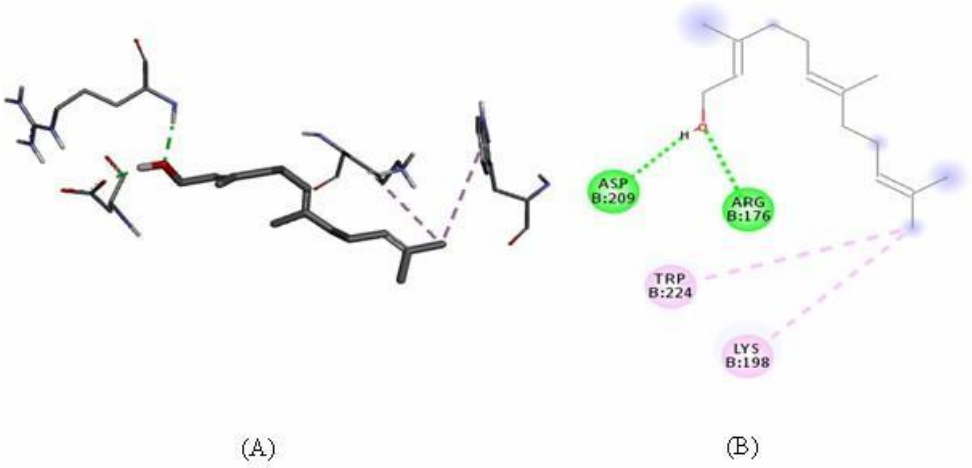
Caption: (A) 3D representation; (B) 2D representation. The purple dotted lines represent van der Waals interactions and the green dotted lines represent hydrogen bonds.

Figure 7. Representation of the interactions between Farnesol and the muscarinic receptor M³ (6y3c).



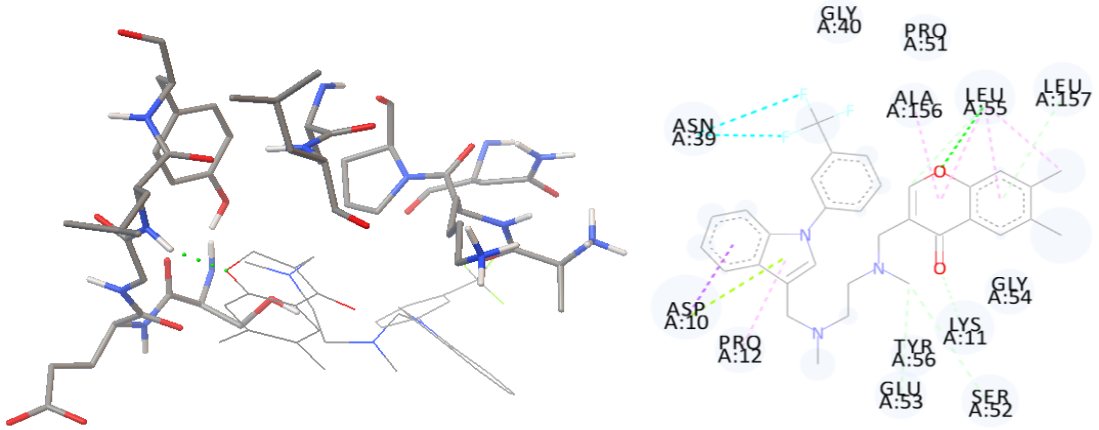
Caption:(A) 3D representation; (B) 2D representation. The purple dotted lines represent Van der Waals. The interactions of Waals and the green dotted lines represent hydrogen bonds.

Figure 8. Representation of the interactions between Farnesol and the Urease (6zja).



Caption:(A) 3D representation; (B) 2D representation. The purple dotted lines represent van der Waals interactions and the green dotted lines represent hydrogen bonds.

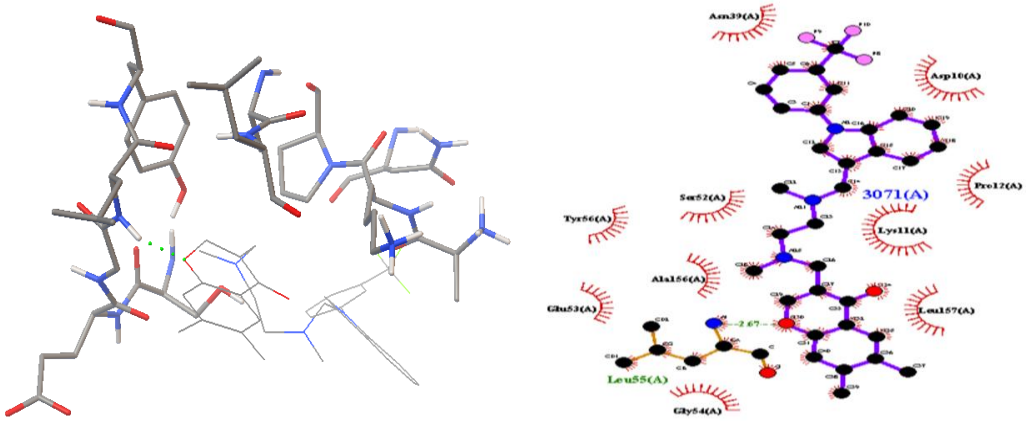
Figure 9. Representation of the interactions between Farnesol-lecithin and the COX-2 (3mld).



(A) (B)

Figure 9. Representation of the interactions between Farnesol-lecithin and the COX-2 (3mld).
Caption:(A) 3D representation; (B) 2D representation. The purple dotted lines represent van der Waals interactions and the green dotted lines represent hydrogen bonds.

Figure 10. Representation of the interactions between Farnesol-lecithin and the COX-1 (5ikr).



(A) (B)

Caption:(A) 3D representation; (B) 2D representation. The purple dotted lines represent van der Waals interactions and the green dotted lines represent hydrogen bonds.

Farnesol also maintained critical molecular interactions with the gastric proton pump, similar to the interactions presented by vonoprazan, especially with the residue ALA339. Therefore, the anti-ulcer effect of Farnesol may be related to the inhibition of the proton pump. The last target studied was urease, an enzyme used as a biomarker for H. pylori bacteria. Farnesol exhibited four interactions with urease (ASP209, ARG176, TRP224, and LYS198). Inhibition of H. pylori urease is relevant for the treatment of ulcers, as the continuous production of ammonia by urease increases the pH of the gastric environment, which can cause inflammation and increase the risk of developing ulcers, gastric adenocarcinoma, and gastric lymphoma. Thus, urease

inhibition is a promising approach for treating infections caused by H. pylori and preventing these pathological conditions (Shi,2016).

Our docking study results demonstrated that Farnesol is a promising alternative for research and development in treating gastric ulcers. As a result, we can use this substance in future research, potentially formulating it as an emulsion. Regarding the emulsion formulation, the objective was to prepare, with Farnesol, thermodynamically stabilized monophasic isotropic mixtures by surfactants composed of two immiscible, transparent, and isotropic liquids (Tartaro,2020), as described in the following protocol, also previously described in the methods.

The emulsion preparation resulted in a final system with 1.5 mg/g of Farnesol. Starting with a solution of PBS in deionized water (1 PBS tablet for 200 mL), the tablet was placed under slow magnetic stirring until completely dissolved. The process was prolonged but duly completed. Subsequently, the team prepared the organic phase by weighing the components of the emulsion on an analytical scale. They weighed all items, both with and without Farnesol, as demonstrated in Frame 5.

Frame 5. Preparation of the emulsion.

Description	Weight (g)	Weight (g) without Farnesol	Weight (g) with Farnesol
Ethanol	9,3 g	9,3061 ml	9,2990 ml
Lecithin	18,7 g	18,707 g	18,726 g
Olive oil	2,0 g	2,0101 ml	2,0020 ml
Farnesol	0,075 g	--	19,9933 ml

Source: Prepared by the authors.

Caption:Science and Technology Innovation Laboratory – Lacitec - Department of Biophysics – UFPI. Caption: Ethanol: SAL R - Solution - Batch: 12/52 - Made: 01/14/2022 – Shelf life: 01/14/2026 Pure soy lecithin: ACS - Made: 09/10/2023 – Shelf life: 09/10/2029 Olive oil: Brand: Gallo Extra Virgem - Batch:L320258317 – Shelf life: 01/2025 Farnesol 95% - 25 g - MERCK - Made: 13/092021 - Shelf life: Indeterminate

The substances were meticulously weighed on the analytical scale and then mixed, including lecithin and ethanol, under constant stirring at 40°C, using magnetic stirring of at least 300 rpm, until the solution became translucent, with clumps. After obtaining the translucency of the solution, olive oil was added, maintaining stirring and temperature constant, and left to rest for 5 minutes. Subsequently, Farnesol was added and also left to rest for 5 minutes. Then, the team added the PBS solution to the previously prepared solution and subjected the mixture to a sonication process for 3 minutes, using maximum power and continuous pulse. At the end of the protocol, they observed characteristics such as pH, conductivity, and zeta potential.

The macroscopic aspect of both formulations was similar: clear and milky. The team measured the pH of the emulsions with a potentiometer calibrated with buffer solutions of pH 4.0

and 7.0. They obtained a pH of 6.13 for the formulation with Farnesol and 6.09 without Farnesol. Conductivity in the formulations with and without Farnesol was 13.29 µS/cm and 29 µS/cm, respectively, as demonstrated in Frame 6.

Frame 6. Emulsion characterization.

Property	**with Farnesol**	**without Farnesol**
Macroscopic aspect	Clear and milky	Clear and milky
pH	6,13	6,09
Conductivity	13,29 microS/cm	29, microS/cm

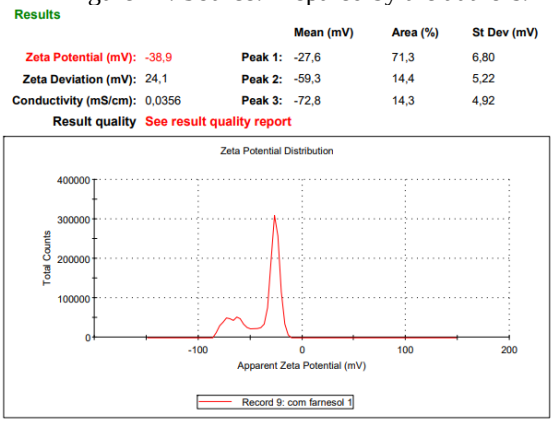
Source: Prepared by the authors: Phmeter

The average Zeta Potential value of the farnesol emulsion was -38.9 mV, suggesting good colloidal stability. High absolute values of Zeta Potential(above 30 mV, both negative and positive) indicate that the particles repel each other, reducing the chance of aggregation and thus promoting a stable suspension. Additionally, three Zeta Potential peaks (27.6 mV, -59.3 mV, and -72.8 mV) suggest slight heterogeneity, with different subpopulations of particles possibly due to variation in surface charge or how Farnesol interacts with them.

Significant electric charge in the formulations prevents aggregation due to repulsive forces between the particles. Among the available surfactants, lecithin and Tween 80 provide adequate steric stability for single-layer emulsions (Arshed,2024). Figures 11 and 12 show the zeta potential analysis of the emulsions with and without Farnesol, respectively.

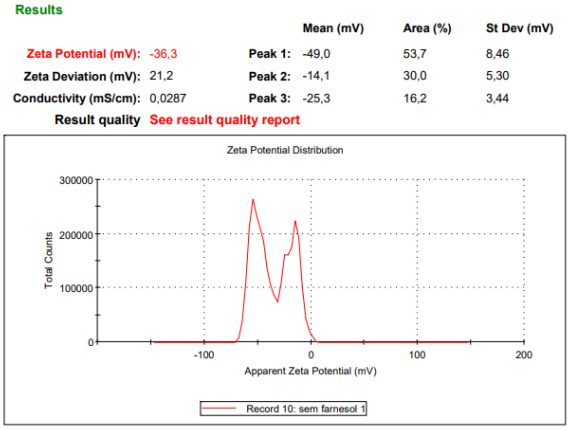
When compared to the formulation containing Farnesol, the addition of Farnesol reduced the heterogeneity of the surface charge. In the formulation with Farnesol, the first peak is more predominant and concentrated around -27.6 mV, while in the analysis without Farnesol, the values are more spread out. The conductivity for the formulation without Farnesol was 0.0287 mS/cm, slightly lower than that of the formulation with Farnesol. This value suggests a slight difference in ionic mobility, possibly due to the absence of Farnesol, which impacts the organization and structure of the emulsion.

Figure 11. Source: Prepared by the authors.



Caption: Zeta Potencial with Farnesol. Zeta potential and size obtained through the equipment Malvern Zetasizer nanoseries ZS90. Program (Zetasizer Software version 7.03, file in dts), from the Interdisciplinar Laboratory of Advanced Materials - LIMAV – Chemistry Department – Natural Science Center - CCN - Federal University of Piauí.

Figure 12. Source:Prepared by authors

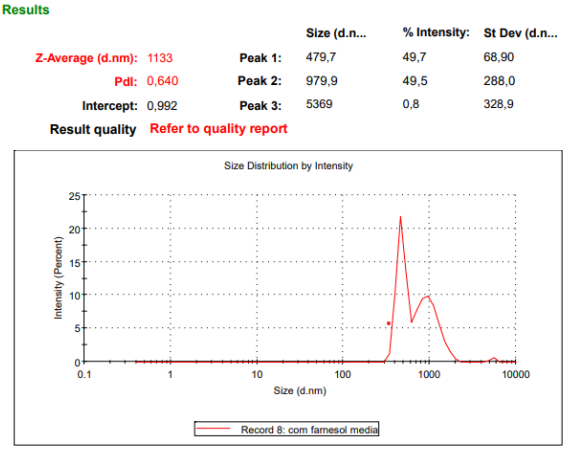


Caption: Zeta Potencial without Farnesol. Zeta potential and size obtained through the equipment Malvern Zetasizer nanoseries ZS90. Program (Zetasizer Software version 7.03, file in dts), from the Interdisciplinary Laboratory of Advanced Materials- LIMAV – Chemistry Department - Natural Sciences Center - CCN - Federal University of Piauí.

The formulation without Farnesol presents acceptable stability, but three distinct peaks in the charge distribution suggest slight heterogeneity. As seen in Figure 11, the addition of farnesol uniforms the charge distribution, possibly providing more excellent stability to the formulation. These data indicate that Farnesol not only acts as the active ingredient of the emulsion but may also contribute to the structural organization and stability of the formulation.

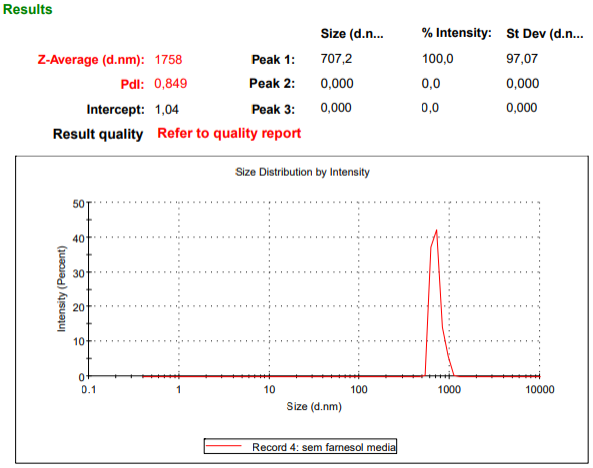
Figures 13 and 14 present the analysis of the particle size of the emulsion with and without Farnesol, respectively.

Figure 13. Source:Prepared by the authors



Caption: Potencial Zeta without Farnesol. Zeta potential and size obtained through the equipment Malvern Zetasizer nanoseries ZS90. Program (Zetasizer Software version 7.03, file in dts), from the Interdisciplinar Laboratory of Advanced Materials- LIMAV – Chemistry Department - Natural Sciences Center - CCN - Federal University of Piauí.

Figure 14. Source:Prepared by the author



Caption: Zeta Potencial without average Farnesol. Zeta potential and size obtained through the equipment Malvern Zetasizer nanoseries ZS90. Program (Zetasizer Software version 7.03, file in dts), from the Interdisciplinar Laboratory of Advanced Materials- LIMAV – Chemistry Department - Natural Sciences Center - CCN - Federal University of Piauí.

The average particle size of the emulsion containing Farnesol, or Z-Average, was measured at 1133 nm. This indicates that most particles are in the nanometer scale but relatively larger for a standard emulsion. This value may affect how Farnesol is absorbed and distributed in the body. The Polydispersity Index (PdI) value was 0.640, indicating a relatively wide size dispersion. PdI values below 0.5 generally indicate a more homogeneous distribution, while values above 0.5, as in this case, suggest more significant heterogeneity. This means that the particles have varied sizes, which may impact the long-term stability of the emulsion.

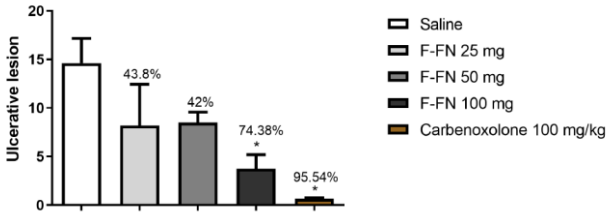
The average particle size of the emulsion containing Farnesol, or Z-Average, was measured at 1133 nm. This indicates that most particles are on the nanometer scale but relatively more extensive than those in a standard emulsion. This value may affect how Farnesol is absorbed and distributed in the body.

The Polydispersity Index (PdI) value was 0.640, indicating a relatively wide size dispersion. PdI values below 0.5 generally indicate a more homogeneous distribution, while values above 0.5, as in this case, suggest more significant heterogeneity. This means the particles have varied sizes, which may impact the emulsion's long-term stability.

The particle size analysis reveals that the emulsion has a bimodal distribution, with particles around 479.7 nm and 979.9 nm. The high PdI indicates heterogeneity, which may be an essential consideration for researchers when making future adjustments to the formulation if they desire increased stability and homogeneity. However, this size distribution may still be effective for controlled release, especially in gastroprotective applications, where varying particle sizes can influence the release rate of Farnesol.

In the in vivo study (Figure 15), doses of 25 mg/kg and 50 mg/kg of Farnesol in the emulsion reduced the lesion area by 43.8% and 42%, respectively, indicating that these doses exhibit a gastroprotective effect, although without significant difference. In contrast, the 100 mg/kg dose reduced the lesion area by 74.38%, showing a significant difference. Thus, the data allow for inferences regarding the gastroprotective activity of the farnesol-containing emulsion, particularly at the dose of 100 mg/kg.

Figure 15. Source: Prepared by the authors



Caption: F-FN(Farnesol).Effect of oral administration of emulsion containing farnesol and carbenoxolone on ethanol-induced gastric ulcers in mice. The results are expressed as mean ± s.d. ANOVA followed by the Newman Keuls test. ***p<0.05, compared with the control group (Saline). The asterisk above the dose of 100 mg/kg and carbenoxolone indicates the existence or not of statistical differences.

CONCLUSION

The pharmacokinetic parameters derived from the in silico study of Farnesol suggest favorable absorption through the oral gastrointestinal tract, satisfactory distribution throughout the body, and permeation of the blood-brain barrier, which may enable the use of the substance in areas beyond the gastrointestinal tract. The pharmacodynamic data provide insight into Farnesol's safety and efficacy profile, highlighting its potential as an anti-inflammatory and gastric protective agent. It also warns researchers to evaluate possible adverse effects in in vivo studies. These findings reinforce the need for more detailed studies to confirm these predictions and determine safe and effective doses for therapeutic use.

The molecular docking analysis revealed a more favorable interaction of Farnesol with COX-1 and COX-2 enzymes, suggesting its capacity to act as an inhibitor of these enzymes. Additionally, Farnesol showed satisfactory scores in docking with the M^3 muscarinic receptor and TGF-β growth factor, suggesting that other mechanisms may be involved in the compound's anti-ulcer effects. Farnesol also demonstrated anti-ulcer effects by inhibiting the gastric proton pump. Furthermore, we observe four molecular interactions between Farnesol and urease, suggesting a promising approach for treating infections caused by Helicobacter pylori and preventing its respective pathological complications.

The formulation of an emulsion containing Farnesol emerges as a promising alternative for developing better solubility of Farnesol and presents adequate characteristics, including pH, conductivity, zeta potential, and particle size. The in vivo study demonstrated the efficacy of the farnesol-containing emulsion via oral administration, highlighting significant gastroprotective activity at a dose of 100 mg/kg of Farnesol. These results indicate the potential of Farnesol as an effective natural alternative for gastric protection, reinforcing its therapeutic value and opening possibilities for further in vivo studies that complement these findings.

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