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Research Article

Keywords: Docking molecular, Copaíba oil, Covid-19, Inhibitors

Posted Date: August 30th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-841081/v1

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Abstract

COVID-19 triggered by Sars-CoV-2 has caused hundreds of thousands of deaths worldwide. Organic and inorganic compounds have been tested as potential in-

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hibitors of this lethal virus. For these tests, several techniques are use to design molecules of biological interest for drug composition, in which molecular coupling plays an important role. In the present work, the compounds acids kaurenoic, copalic, and beta-caryophyllene that form the copaiba oil were studied as anti-inflammatories and opens the possibility to inhibit Sars-CoV-2. Molecular docking showed alkyl, pi-alkyl, conventional H-bond, unfavorable bump, and Van der Waals interactions. The calculated electrostatic potential maps showed the nucleophilic and electrophilic regions. The negative binding energies obtained for the three acids suggest the stability of the complexes. The minimum energy states for β-caryophyllene are lower than the other compounds analyzed, and it can be predicted that this is the most stable.

Key words: Docking molecular; Copaíba oil; Covid-19; Inhibitors.

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1. Introduction

The first Coronavirus was discovered in the 1930s [1], but severe acute respiratory syndrome (Sars) gained notoriety in the world between the years 2002-2003 [2]. At the end of 2019, Sars-CoV-2 triggered a pandemic that has already caused nearly 3.5 million deaths worldwide [3].

From serological analyzes and genetic studies, it it is possible to classify the coronaviruses into four different genera: α, β, γ and β-CoV [4]. β-CoV type is the cause of the COVID-19 found in Wuhan, China [5]. The Coronaviruses are enveloped, spherical, or pleomorphic viruses and can vary their shape according to the period of the reproductive life cycle or environmental conditions, with typical sizes ranging from 80 to 120 nm [4]. The coronavirus spike protein is a multifunctional molecular machine that initially binds to a receptor on the surface of the host cell through its S1 subunit and then fuses viral and host membranes through its S2 subunit, leading to viral binding [6].

We are investigating the inhibitory potential of Copaiba oil against the COVID-19 virus, and we associated the oil compounds with the binding of the Sars-COV-2 spike protein receptor as a target using molecular docking for these calculations. Molecular docking has been used by pharmaceutical companies to study the Structure-Activity Relationship of drugs for more than three decades. New drugs have been discovered and developed during these years [7].

This method gives the possibility to predict both the binding affinity between ligand and protein and the structure of the protein-ligand complex using the computational method, which is relevant information for optimization [8, 9]. Molecular docking techniques aim to predict the best matching binding mode of a ligand to a macromolecular partner. It consists of the generation of several possible conformations/orientations [10]. Docking is a technique of designing drug molecules by simulating the geometry of these molecules and their intermolecular forces [3]. In this way, molecular docking optimizes the ligand bound to the active site of the receptor protein and investigates protein-ligand interactions. Molecular coupling algorithms provide results for quantitative energy

binding markers, including a variety of coupled compounds supported by the binding affinity of ligand-receptor complexes with pharmacokinetic properties. From this calculation, we can predict the different interactions between the oil compounds and the spike protein. Ligand-protein interactions are involved in many biological processes with consequent pharmaceutical industry implications [10].

Several studies have been done on Copaiba oils, mainly due to the interest from the pharmacological and food industries around the globe [11]. The Brazilian Amazon concentrates a large number of natural resources species with various therapeutic applications in alternative medicine. Copaiba oil is an oleoresin extracted from the trunk of trees of the Copaifera genus (Fabaceae). Frequently, copaiba grows in tropical regions of South America. The oil-resin is a natural product of the Amazon's biodiversity. Copaiba oil is commonly used in folk medicine to treat multiple diseases, such as ulcers, wounds, syphilis, bronchitis, and inflammation [12].

Scientific researches with copaiba demonstrated that the copaifera reticulate oleoresin exhibits some biological actions such as anti-inflammatory, analgesic, antioxidant, anxiolytic, and antimicrobial activities, and neutrophilic activation [13–15].

Besides these properties, some studies suggest that these species are free from toxicity and teratogenic activity during pregnancy [16]. Also, the copaiba oil can be used as an anti-tumor, anti-inflammatory, antimicrobial against a wide range of microorganisms, and healing on different tissues of the human body.

In several animal models, studies demonstrated that copaiba oil has healing and anti-inflammatory effects. Besides, anti-inflammatory and anti-tumor properties of copaiba oils have been described in several works [17–20].Those results are significant because they can the designed as applications to improve the quality of life in a society.

2. Computational details

Initially, the constituent compounds of the copaiba oil were accessed in the ChemSpider database. All compounds were subjected to a classical simulation to find the lowest energy geometries, based on the lamarckian genetic algorithm (LGA) algorithm, using the Forcite Code [21, 22].

The universal force field (UFF) was selected to perform the calculations. After obtaining the best conformation of the geometries, the structures were submitted to a new optimization at the DFT level using the DMOL3 Code [23, 24], where the generalized gradient approximation (GGA) considers all the electrons of the molecules.

Molecular electrostatic potential surfaces were investigated to identify the most reactive nucleophilic and electrophilic regions. We performed molecular docking with the ArgusLab 4.0.1 program. There are two options for docking algorithms, the first one is GA dock (Genetic Algorithm), and the other one is Argusdock (Shape-Based Search Algorithm).

The calculations are from GAdock docking algorithms, which take into account the Lamarckian Genetic Algorithm. The docking location was defined using a box with coordinates $47.25 \times 36.00 \times 49.75$ Å, spacing of 0.400 Å, and flexible binder coupling mode.

3. Results and discussion

3.1. Optimization and electrostatic interaction

Figures 1A, B and C show the optimized structures and the numbering of the atoms forming the acids kaurenoic, copalic, and β-caryophyllene. The H bond represents an interaction between two electronegative atoms.

Table 1 illustrates their total energies (ET), binding energy (BE) and maximum cartesian force (MCF) of these acids. The global minimum energies are found to be -922.5966100 a.u (-25105 eV), -924.0927850 a.u (-25145 eV), -580.6642644 (-15800 eV) for kaurenoic, copalic and β-caryophyllene, respectively.

Table 1: Calculated total energies (ET), binding energy (BE) and maximum cartesian force (MCF) of acids kaurenoic, copalic and β-caryophyllene.

Molecules	ET (Hartree)	BE (Kcal/mol)	MCF
Kaurenoic	-922.5966100	-10.56	0.139052×10^{-2}
Copalic	-924.0927850	-10.77	0.495639×10^{-3}
β-caryophyllene	-580.6642644	-10.96	0.196084×10^{-2}

The binding energy of the protein spike with kaurenoic acid was -10.56 kcal/mol, with copalic it was -10.77 kcal/mol, and with β-caryophyllene, it was -10.96 kcal/mol. Negative values of binding energies suggest the stability of the complexes.

Their maximum Cartesian forces are found to be 0.139052×10^{-2}, 0.495639×10^{-3} and 0.196084×10^{-2}, as can be seen in table 1. The addition of other atoms in the geometry of compounds influences their stability. We can notice in table 1 that the β-caryophyllene compound is the most stable because the global-minimum energy is the smallest compared to the other acids ones.

Fig. 2 shows the maps of molecular electrostatic potential (MEPs) of the copaiba oil-forming acid molecules. The MEP is a tool used to describe the most reactive nucleophilic and electrophilic regions of a molecule against reactive biological potentials and intermolecular interactions [25, 26]. The electrophilic site indicates strong attraction and the nucleophilic site indicates strong repulsion. In these regions, the formation of hydrogen bonds occurs. MEPs provide regions of negative, positive and neutral electrostatic potential in terms of color grading and are an indicator in researching molecular structure properties. Atoms in red represent the most electronegative electrostatic potential; atoms in this region tend to attract electrons (electrophilic). Atoms in blue indicates the most electropositive potential atoms in this region tend to repel electrons (nucleophilic).

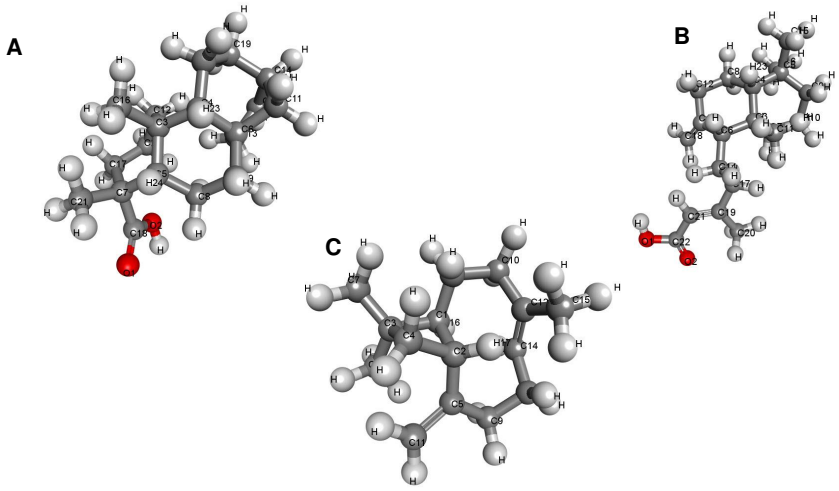

Figure 1: Optimization of acids kaurenoic in A, copalic in B and β-caryophyllene in C.

In yellow we can see the forming acids of the copaiba oil (binders). As a result, the surfaces of the MEPs range from -0.100 a.u (deepest red) to 0.100 a.u (deepest blue) for the three compounds.

3.2. Molecular docking and 2D visual representations

Figures 3A, B, and C show the molecular docking of kaurenoic, copalic, and β-caryophyllene acids interacting with the spike protein of Sars-CoV-2. The purpose of docking is determine the modes of interaction of ligands (copaiba oil-forming acids) while organizing favorable orientations for the binding of a ligand to a receptor [27–31].

The receptor represents the COVID-19 protein that has one or more specific active sites. In this work, before coupling, all native ligands and water molecules were removed from the protein structure. In addition, polar hydrogen atoms are added and Kollman atom charges are assigned to protein atoms. At each step of the calculation, the interactions are affected, and the best orientation of ligands was determined to investigate the different types of interactions between the copaiba oil-forming compounds and the protein.

Figures 4A, B, C, and table 2 illustrate the dockings of the copaiba oil compounds against the Sars-CoV-2 receptor binding site complexed with its receptor (PDB ID: 6M0J). The figs and table also show the interaction of kaurenoic acid with TRP:271, ARG:273, LEU:144, TYR:127, LEU:503, HIS:505, PHE:504, PHE274, MET:270, ASN:149 and ASP:269; Copalic acid with HIS:505, PHE:504, ARG:273, TYR:515, TYR:127, ASN:508, SER:128, TRP:271 and LEU:503, and β-caryophyllene acid with LEU:733 , LEU:391, PHE:390, PHE:32, TRP:69, PHE:40, ARG:393, ASN:271, LEU:100 and ALA:36

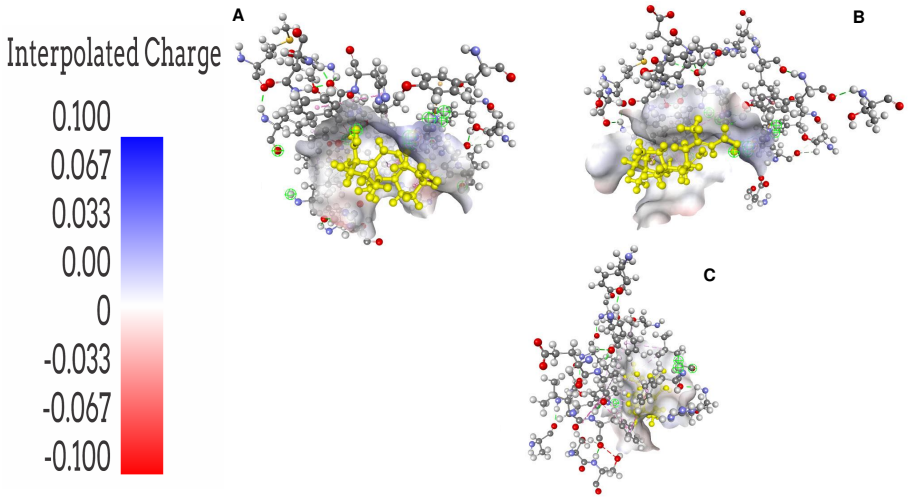

Figure 2: Different interactions between the kaurenoic acids in A, copalic acids in B and β-caryophyllene in C and protein spike.

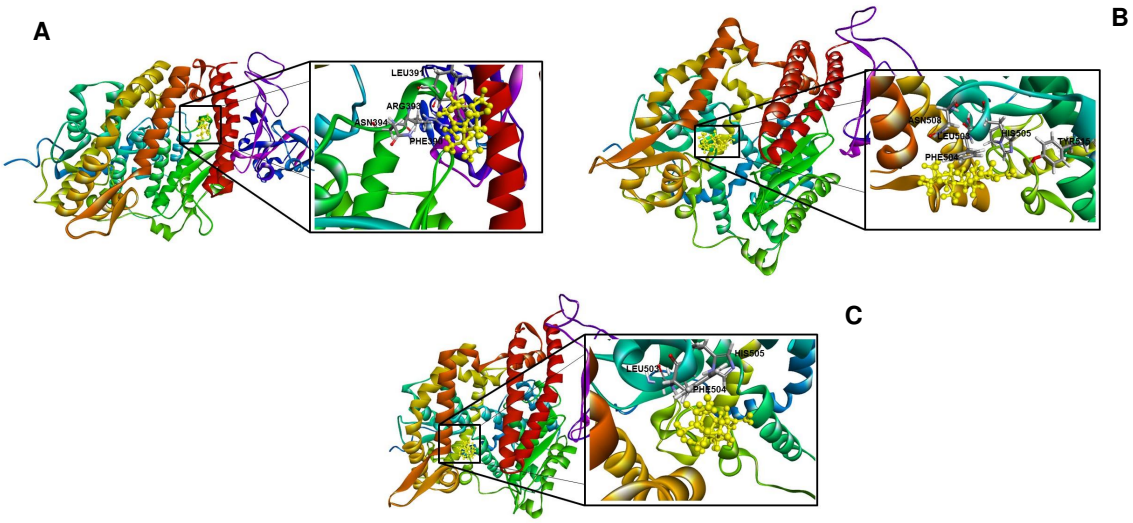

Figure 3: Amino acids were obtained from RBD. Orientation of acids kaurenoic in A, copalic in B, and β-caryophyllene in C on the active sites of COVID-19 proteins.

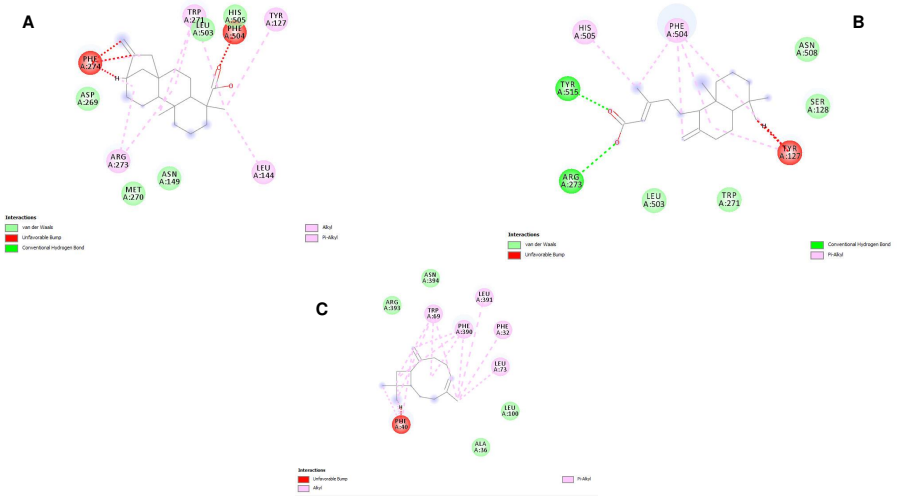

Figure 4: 2D visual representations of the acids kaurenoic in A, copalic in B and β-caryophyllene in C.

Furthermore, in kaurenoic acid the alkyl interaction was observed surrounded by the amino acid TRP:271 having a distance of 1.54616 Å. Pi-Alkyl interactions are surrounded by amino acids ARG:273, LEU:144, and TYR:127 having distances of 1.53098 Å, 1.52469 Å, and 1.44887 Å, respectively. Conventional H-bond interactions are surrounded by amino acids LEU:5034 and HIS:505 with 1.53046 Å and 1.09958 Å, respectively.

Unfavorable bump interactions are surrounded by amino acids PHE:504 and PHE:274 with 1.40918 Å and 1.55124 Å, respectively. Van der Waals interactions are surrounded by amino acids MET:270, ASN:149, and ASP:269 with of 1.80711 Å, 1.54968 Å, and 1.52356 Å, respectively.

In copalic acid, alkyl interactions were observed surrounded by amino acids HIS:505 and PHE:504 with 1.51632 Å and 1.53555 Å, respectively. Conventional H-bond interactions are surrounded by amino acids ARG:273 and TYR:515 with 1.53098 Å and 1.36785 Å, respectively. Van der Waals interactions are surrounded by amino acids ASN:508, SER:128, and TRP:271 with 1.53108 Å, 1.52889 Å, and 1.54616 Å, respectively.

In the β-caryophyllene acid, the alkyl interaction is surrounded by the amino acid LEU:733 with 1.52373 Å. Pi-Alkyl interactions are surrounded by amino acids LEU:391, PHE:390, PHE:32, and TRP:69 with 1.52737 Å, 1.53217 Å, 1.52478 Å, and 1.53147 Å, respectively. The Unfavorable bump interaction is surrounded by the amino acid PHE:40 with 1.09015 Å. Van der Waals interactions are surrounded by amino acids ARG:393, ASN:271, LEU:100, and ALA:36 with 1.52876 Å, 1.51483 Å, 1.52757, and 1.52554 Å, respectively.

Table 2: Amino acid residues of acids kaurenoic, copalic and β-caryophyllene. Target protein ID: 6M0J.

Ligand	Binding residue	Type	Bond length (Å)	Interactions
Kaurenoic	TRP:271	Tryptophan	1.54616	Alkyl
	ARG:273	Arginine	1.53098	Pi-Alkyl
	LEU:144	Leucine	1.52469	Pi-Alkyl
	TYR:127	Tyrosine	1.44887	Pi-Alkyl
	LEU:503	Leucine	1.53046	Conventional H-bond
	HIS:505	Histidine	1.09958	Conventional H-bond
	PHE:504	Phenylalanine	1.40918	Unfavorable bump
	PHE:274	Phenylalanine	1.55124	Unfavorable bump
	MET:270	Methionine	1.80711	Van der Waals
	ASN:149	Asparagine	1.54968	Van der Waals
	ASP:269	Aspartate	1.52356	Van der Waals
Copalic	HIS:505	Histidine	1.51632	Alkyl
	PHE:504	Phenylalanine	1.53555	Alkyl
	ARG:273	Arginine	1.53098	Conventional H-bond
	TYR:515	Tyrosine	1.36785	Conventional H-bond
	TYR:127	Tyrosine	1.36785	Unfavorable bump
	ASN:508	Asparagine	1.53108	Van der Waals
	SER:128	Serine	1.52889	Van der Waals
	TRP:271	Tryptophan	1.54616	Van der Waals
	LEU:503	Tryptophan	1.54616	Van der Waals
β caryophyllene	LEU:733	Leucine	1.52373	
	Alkyl			
	LEU:391	Leucine	1.52737	
	Pi-Alkyl			
	PHE:390	Phenylalanine	1.53217	Pi-Alkyl
	PHE:32	Phenylalanine	1.52478	Pi-Alkyl
	TRP:69	Tryptophan	1.53147	
	Pi-Alkyl			
	PHE:40	Phenylalanine	1.09015	Unfavorable bump
	ARG:393	Arginine	1.52876	Van der Waals
	ASN:271	Asparagine	1.51483	Van der Waals
	LEU:100	Leucine	1.52757	Van der Waals
	ALA:36	Alanine	1.52554	Van der Waals

4. Conclusion

Considering the anti-inflammatory properties of copaiba oil, we studied three compounds that form the oil. We performed the classical optimizations calculations to obtain the most stable geometric conformation, using the conjugate gradient (LGA) and quantum gradient (GGA). The total and binding energies obtained for the three compounds were negative, which shows that the investigated complexes are stable. The β-caryophyllene is the most stable of the compounds, as its total energy was the lowest.

The calculated MEPs showed that regions with positive potentials are favorable to nucleophilic attack, while those regions with negative potentials are favorable to electrophilic attack. The results of molecular docking were discussed based on different interactions between acids (ligands) and proteins (receptors).

From the results obtained, it can be inferred that the acids that form the copaiba oil can be used as an inhibitor of COVID-19. These results encourage further in vitro and in vivo investigations into the pharmacological properties of copaiba oil.

Acknowledgements

The financial support for this research by CAPES (Coordenacão de Aperfeicoamento de Pessoal de Ensino Superior), is gratefully acknowledged W. O. Santos and J. R. da C. Venâncio were supported by a studentship from CAPES. LSCMN-PB (Laboratório de Simulação Computacional e Modelagem de Nanomateriais), LCC-PA (Laboratório de Computação Científica) of Federal University of the South and Southeast of Pará, CENAPAD-SP (Centro Nacional de Processamento de Alto Desempenho), LFA-PA (Laboratório de Física Aplicada) of Federal University of the South and Southeast of Pará and LFM-SE (Laboratório de Física Médica) of Federal University of Sergipe.

Declarations

Funding The research developed in this article had no financial support.

Conflict of interest/ Competing interests Authors declare any not has financial and personal relationships with other people or organizations that could inappropriately influence in this work.
Availability of data and material The article files will be available upon request.
Code availability Not applicable.
Ethical approval Not applicable. The ethical standards have been met.
Authors' contributions Data collection, and analysis were performed by WO Santos, ALF Novais and ERP Novais. The first draft of the manuscript was written by WO Santos, ALF Novais, GC A Oliveira, JRC Venâcio and AM Rodrigues and all authors commented on previous versions of the manuscript. All authors contributed to the study conception and design and approved the final manuscript.

Consent to participate Authors consent to participate in the research project, and they assure this research may not bring commercial benefit to us. Our participation is completely voluntary.
Consent for publication The authors declare that they agree with the submission and eventual publication..

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