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THE USE OF DOCKING IN THE SEARCH FOR SECONDARY COMPOUNDS OBTAINED FROM PASSIFLORA FOETIDA AGAINST SARS-COV-2 PROTEINS

O USO DO *DOCKING* NA PESQUISA DOS COMPOSTOS SECUNDÁRIOS OBTIDOS DE PASSIFLORA FOETIDA CONTRA PROTEÍNAS DO SARS-COV-2

EL USO DEL *DOCKING* EN LA BÚSQUEDA DE COMPUESTOS SECUNDARIOS OBTENIDOS DE PASSIFLORA FOETIDA CONTRA PROTEÍNAS DEL SARS-COV-2

RESUMO

A propagação global do SARS-CoV-2 foi seguida de uma adaptação graduação do vírus nos seres humanos e de saltos de transmissibilidade e virulência que preocuparam os cientistas mundialmente, mobilizando esforços para obtenção de compostos que fossem úteis ao tratamento e/ou contenção desta pandemia. O objetivo deste ensaio foi uma abordagem *in-silico* para testar alguns fitocompostos selecionados de *Passiflora foetida* a partir de estudos descritos na literatura científica utilizando contra proteínas do *SARS-CoV-2*. Aplicando as estruturas tridimensionais, cristalográficas e modeladas das proteínas estruturais e não estruturais do *SARS-CoV-2* obtidas do banco de dados PDB (Protein Database) e do Zhang Lab, e com o software Vina AutoDock foram confeccionados os soquetes moleculares. Verificamos que as moléculas de flavonóides desempenharam melhor papel de interação com as proteínas e foram selecionadas para *docking*. Como resultados do *docking* molecular para verificar as interações, descobrimos que a Luteolina-7-O-β-D-glucopiranosídeo ($C_{21}H_{20}O_{11}$) foi a molécula que apresentou maior afinidade energética com o alvo *ExoN*, portanto pode ser considerada como um potencial inibidor molécula. Estudos de dinâmica molecular ainda são necessários para verificar a estabilidade desta interação.

PALAVRAS-CHAVE

COVID-19; Fitoquímica; Passifloraceae.

ABSTRACT

The global spread of SARS-CoV-2 was followed by a gradual adaptation of the virus in humans and by leaps in transmissibility and virulence that worried scientists worldwide, mobilizing efforts to obtain compounds that would be useful in the treatment and/or containment of this disease. pandemic. The objective was an *in-silico* approach to test some phytocomposites selected from studies described in the scientific literature using *Passiflora foetida* against SARS-CoV-2 proteins. Applying the three-dimensional, crystallographic, and modeled structures of the structural and non-structural proteins from SARS-CoV-2 obtained from PDB (Protein Database) and from Zhang Lab, and with the Vina AutoDock software the molecular sockets were made. The flavonoids molecules played a better role of interaction with the proteins and were selected for docking. As results from molecular docking to check the interactions we found that the Luteolin-7-O-β-D-glucopyranoside ($C_{21}H_{20}O_{11}$) was the molecule that exhibits a higher energy affinity with the ExoN target, so it can be considered as a potential inhibitory molecule. Molecular dynamics studies are still required to verify the stability of this interaction.

KEYWORDS

COVID-19; Phytochemistry; Passifloraceae.

RESUMEN

La propagación global del SARS-CoV-2 fue seguida por una adaptación gradual del virus en los seres humanos y por aumentos en su transmisibilidad y virulencia, lo que generó preocupación entre los científicos de todo el mundo y movilizó esfuerzos para obtener compuestos útiles en el tratamiento y/o la contención de esta pandemia. El objetivo de este estudio fue realizar un enfoque in silico para evaluar algunos fitocompuestos seleccionados a partir de investigaciones descritas en la literatura científica sobre Passiflora foetida frente a proteínas del SARS-CoV-2. Se utilizaron las estructuras tridimensionales, cristalográficas y modeladas de proteínas estructurales y no estructurales del SARS-CoV-2 obtenidas de la PDB (Protein Data Bank) y del Zhang Lab, y se realizaron estudios de docking molecular mediante el software AutoDock Vina. Las moléculas de flavonoides mostraron un mejor perfil de interacción con las proteínas y fueron seleccionadas para el docking. Como resultado de los análisis de docking molecular para verificar las interacciones, se encontró que la Luteolina-7-O-β-D-glucopiranósido ($C_{21}H_{20}O_{11}$) fue la molécula que presentó la mayor afinidad energética con la diana ExoN, por lo que puede considerarse una molécula con potencial inhibidor. Sin embargo, aún son necesarios estudios de dinámica molecular para verificar la estabilidad de esta interacción.

PALABRAS CLAVE

COVID-19; Fitoquímica; Passifloraceae.

INTRODUCTION

COVID-19 (coronavirus disease 2019) was declared a pandemic illness by The World Health Organization (WHO) (Cucinotta; Vanelli 2020). This disease is beginning by an RNA virus strain from the family *Coronaviridae* (Wu et al., 2020) that also causes a novel pneumonia similar to Severe Acute Respiratory Syndrome (SARS) caused by SARS-CoV (Zhou et al., 2020). This outbreak is causing thousands of millions of deaths since the first case was reported in Wuhan, Hubei province, China (Zhou et al., 2020; Wu et al., 2020).

Studies report that the SARS-Cov-2 exhibits almost 80% of similarity with the genome of *SARS-CoV* described the first time 18 years ago (Zhou et al., 2020; Andersen et al., 2020). Like *SARS-CoV*, the *SARS-CoV-2* binds the Spike protein (S), a type I glycoprotein on the surface of the virus, in the human angiotensin-converting enzyme 2 (hACE2) receptor to penetrate the host cells and then merge its genomic material to starts

replication in the human cells (Hoffman et al., 2020; Yan et al., 2020). In this point of view, this S protein plays a crucial role during virus entry into the host cells (Luan et al., 2020).

In view of this novel coronavirus disease remains a sickness without cure and has only palliative treatments for symptoms, studies that proposed identifying new potential compounds against the virus are essential. The screening of compounds using virtual methods enables identify promising drug molecules (Abraham Peele et al., 2020). Using bioinformatics strategies some studies attempted to design anti-Spike peptides for *SARS-CoV-2* (Barh et al., 2020; Yu et al., 2020; Abraham Peele et al., 2020). Considering this, peptide-based drugs seem to be a better choice than conventional drugs if we consider their higher efficiency combined with lower toxicity and side effects (Castel et al., 2011; Barh et al., 2020).

The urgency for an effective treatment for COVID-19 encourages the search for new compounds that are effective and have a low level of toxicity, as well as few side effects, that can serve the development of new drugs. In this sense, vegetable compounds add an immense arsenal of opportunities for use in the composition of new medicines (Ghosh et al., 2020). Antioxidant properties of polyphenolic compounds, such as some flavonoids, for instance, show activity as free radical scavengers, reducing agents, and quenchers of single oxygen formation (Wu et al., 2018).

Recently, a study that shows many bioactive molecules including a polymerized polyphenol (Oolonghomobisflavan-A) from tea plant (*Camellia sinensis* L.) act as effective *SARS-CoV-2* main pro inhibitors (Bhardwaj et al., 2020). Yu et al. (2020), showed that flavonoid luteolin, major constituents in several plants, can be used as a potent compound against *SARS-CoV*-2.

Some species of Passiflora shows interesting activity against other viruses, as Herpes simplex viruses 1 and 2 (HSV-1, HSV2) and on Varicella-Zoster virus (VZV) (Jabareen; Huleihil 2013) e Epstein-Barr virus (Hameed et al., 2017). *Passiflora* species (Passifloraceae) are native to South America and some species are popularly used as sedatives and tranquilizers. Although there are many studies on its anxiolytic activity, there are few studies on the chemical components and other pharmacological activities (Gosmann et al., 2011).

The phytocomposites found in greater quantity in *Passiflora foetida* are alkaloids, phenols, glycosidic flavonoids, and cyanogenic compounds (Dhawan et al., 2004), which sparked interest in verifying the interactions of the compounds described for the species against *SARS-CoV-2* proteins. The aim of this study was to perform an in-silico approach to test some flavonoid compounds described from phytochemistry studies in *Passiflora foetida* reported previously on scientific literature.

MATERIAL AND METHODS

Selection of molecules

A literature review was carried out to survey the compounds verified in *Passiflora foetida* already described. A total of 11 compounds were listed being cyanogenic glycosides, polyketides α-pyrononeS and flavonoids. Amongst these groups of compounds, flavonoids played a better role of interaction with the proteins and were selected for docking.

Protein targets of SARS-CoV-2

The three-dimensional, crystallographic, and modeled structures of the structural and non-structural proteins of SARS-CoV-2 were obtained from the PDB database (https://www.rcsb.org/) and from the Zhang Lab. (Https://zhanglab.dcmb.med.umich.edu/COVID-19/).

Molecular coupling studies

The chemical structures obtained from *Passiflora foetida* were designed and stereochemically adjusted using the Marvin 15.4.20 program and converted to the mol2 format. The designed ligands were then subjected to molecular coupling calculations together with the 3D structures of the viral targets.

The stages of conformational search and pose evaluation were carried out in the Autodock Vina programs, where the binders were prepared with the Autodock Tools 1.5.6 program (Morris et al., 2009), following the protocol: (a) detection of the torsion roots and conversion to the pdbqt format, (b) configuration of the Gridbox with the delimitation of the active sites of each protein, (c) coupling calculation.

The evaluation of the molecular tracking methods was carried out based on the analysis of the positioning of conformers and interaction maps using the programs Pymol 2.0 (Schrödinger, 2013), UCSF Chimera 1.14 (Pettersen et al., 2004), and Discovery Studio 2020 (Dassault Systèmes BIOVIA, 2021). To understand the molecular interactions between proteins and natural ligands, we use the web server PLIP (Protein-Ligand Interaction Profiler), four steps are used to detect and report relevant interactions: structure preparation, functional characterization, rule-based correspondence, and interaction filtering (Selentin et al., 2015).

RESULTS

In this Molecular Fit study, we used a total of twenty-one (21) model protein targets from the *SARS-CoV-2* genome and with the Vina AutoDock software were made the molecular sockets. The molecules used are from the *Passiflora foetida* specie according to literature and are listed in Table 1. The choice of these classes of compounds is related to availability, in terms of their concentration in the species and their respective general biological activity.

Non-structural protein 4 (nsp4)

In the interaction of the compound Luteolin-7-O-β-D-glucopyranoside (Figure 1 A) with the nsp4 protein, it demonstrates three interactions of the type of hydrogen bonding with the ASP195, LYS424 and SER481 residues with most of the hydrogen donor interactions due to amino acids from the active site. And yet three hydrophobic interactions with the VAL192, GLU230 and ASP484 residues due to the nonpolar characteristics of both the amino acids and the ligand.

In Figure 1 B, the Chrysoeriol ligand interacts with the nsp4 protein with three interactions of the type of hydrogen bond, with residues SER229, LYS424 and SER483 due to the oxygen accepting the ligand and the nitrogen donors of the amino acids. It still interacts with two VAL192 and GLU230 residues.

The Luteolin ligand interacts with nsp4 with four interactions of the type of Hydrogen bond with residues SER197, GLU230, LYS424 and SER481 (Figure 1 C), due to a mixture of two accepting oxygen and two nitrogen donors of the amino acids of the active site with the oxygen available in the binder. And two more hydrophobic interactions with two VAL192 and GLU230 residues, with nonpolar characteristics.

Helicase (Hel)

In Figure 2, the compound Luteolin 7-O-β-D-glucopyranoside interacts with Helicase (QHD43415_12) with ten (10) hydrogen bonds with residues GLY285, GLY287, LYS288, SER289, GLY538, GLU540, ARG567. This large amount of hydrogen bonding type interactions is due to the large amount of oxygen distributed in the compound, in addition to the docking position that interacts with groups characteristic of the waste such as donors (Nitrogen) and acceptors (Oxygen). In addition, hydrophobic interactions with the residue ALA313 and ALA316 and an interaction of the type *Salt Bridges* which is a non-covalent interaction between two ionizable sites (such as hydrogen bonding and ionic bonding). This interaction occurs with the LYS288 residue (with the NH3 + group) and the carboxylate group (-O-) of the molecule.

The compound Vitexin-2"-O-xyloside also interacts with ten (10) hydrogen bonding type interactions with residues GLY285, SER289, LYS320, ARG443, GLY538, GLU540, ARG567 and LYS569, also due to amount of oxygen in its structure (Figure 2 B). In addition, it interacts with Helicase with two hydrophobic interactions with residues ALA316 and GLU540 and two interactions of the type π-Cation with residues LYS320 and ARG443 mainly due to aromatic rings.

The Luteolin ligand (Figure 2 C) interacts with Helicase in the residues GLY285, LYS288, GLY538 AND ARG567 of the hydrogen bond type also due to their own molecule oxygen. It is a hydrophobic interaction with the GLN537 residue.

Exoribonuclease/ Guanine-N7 methyltransferase (ExoN)

In Figure 3 A, the ligand Luteolin-7-O- β-D-glucopyranoside interacts with the enzyme ExoN with nine (9) interactions of the type of Hydrogen bond, with residues TRP292, GLN354, ASN388, HIS424, HIS427. This large amount of hydrogen bonds is due to two main factors, the large amount of oxygen (or hydroxyls –OH) of the Luteolin-7-O-β-D-glucopyranoside ligand and because the active site of the enzyme ExoN has several groups with Nitrogen (N).

Thus, providing a promising interaction between donor and hydrogen acceptor. In addition, it interacts with ExoN, also of the hydrophobic interactions type, due to the nonpolar aromatic characteristic of residues such as VAL290 and PHE426, respectively.

The Vitexin-2"-O-xyloside ligand makes seven (7) hydrogen bonding interactions with the TRP292, ASN334, GLN354, ASN386, ASN388 AND ASN422 residues with the same principles as the Luteolin 7- O-β-D-glucopyranoside, due to the donor and acceptor characteristics of the ligand and the amino acids of the active site (Figure 3 B). The fitting mode also favors these interactions. Furthermore, the ligand performs two hydrophobic interactions with the VAL290 residue and an interaction π-Stacking (parallel) with residue PHE426, because two aromatic rings interact in parallel, in the T format.

The interaction, in Figure 3 C, shows that the Luteolin ligand interacts with sei (6) Hydrogen bonds with residues GLN354, ASN386, ASN422, LYS423 AND HIS424 and with two (2) hydrophobic interactions with residues PRO335 and HIS424, mainly with the aromatic rings of the compound.

Uridylate-specific endoribonuclease (NendoU)

In the interaction of the Luteolin-7-O-β-D-glucopyranoside ligand in Figure 4 A with NendoU, nine (9) Hydrogen bonding interactions occur between residues HIS234, ASP239, GLN244, VAL291, SER293, THR340 AND TYR342 with the hydroxyl and carbonyl groups of the molecule, favored by the hydrogen donor groups of the highlighted residues. In addition, two hydrophobic interactions with the THR340 and TYR342 residues due to the nonpolar groups of these amino acids and an π-stacking (parallel) interaction due to the aromatic rings of the molecule and the TYR342 residue.

Figure 4 B demonstrates that the Vitexin-2"-O-xyloside ligand interacts with NendoU with six (6) hydrogen bonding interactions with the residues GLY247, HIS249, LYS289, THR340, PRO343 and GLN346, in a balanced way, with three donors and three acceptors, and it also interacts with two residues, one of the hydrophobic type (THR340 residue) and one of the π-stacking type (with the TYR342 residue) with the aromatic ring of the compound.

The Luteolin compound (Figure 4 C), on the other hand, the interaction with NendoU shows six (6) interactions of the type of hydrogen bond with residues GLY247, LYS289, VAL291, SER293 and THR340, mainly with the characteristic of the hydrogen acceptor ligand. The other interactions are of the hydrophobic type with two amino acid residues, THR340 and TYR342 and an π-stacking (parallel) interaction due to the two aromatic rings, one from the ligand and the other from the TYR342 residue.

The molecular docking reveals that Luteolin-7-O-βD-glucopyranoside ligand exhibits a calculated ligation energy of -7,9 kcal/mol with a nsp4, -8,1 kcal/ mol with Hel, -9,8 kcal/ mol with ExoN and this hydrophobic bound helps in the stabilization for these interactions.

DISCUSSION

Computational approaches to drug discovery are useful to accelerate drug development processes, minimizing steps in traditional approaches. Considering the context of a pandemic, these are essential characteristics, as they denote a significant reduction in the time to obtain effective substances against the virus in question (Abel et al., 2020). The study of phytocompounds through molecular docking emerges as a rapid screening solution for biological activities of interest for different pathologies. for example, cyanogenic glycosides that can act by releasing toxic hydrogen cyanide after tissue damage. Passifloricins, for instance, are natural compounds with high leishmanicidal activity, however cytotoxic properties were also observed (Cardona; Quiñones; Echeverri, 2004).

From the perspective of the different activities previously evidenced by studies regarding the considerably promising biological activities of *Passiflora foetida*, such as luteolin and its anti-inflammatory role (Nguyen et al., 2015), or even antibacterial activities (Mohanasundari et al., 2007; Akila; Haroon, 2022), antiproliferative and antioxidative (Sisin; Abdullah; Sul'ain, 2017) we chose to evaluate the *in silico* activity to fight SARS-CoV-2 due this relevance as a pandemic virus.

The coronaviruses exhibit a genome with approximately 30 kb, being a single-stranded, positive-sense RNA-virus enveloped. The structural protein S can specifically bind to the host receptor of the cell, so this is the key protein that helps viruses to invade susceptible cells. Proteins M and E are involved in the formation of the virus envelope, while protein N is involved in the assembly of the virus (Yang; Wang, 2020).

Considering that the Coronavirus viral genome encodes proteins called structural (sp) and non-structural (nsp), within the group of nsps, which total 16, nsp12 is known as RdRp (RNA-dependent RNA polymerase). RdRp forms a complex with two other nsps (nsp7 and nsp8) to operate in the cellular environment, while nsp14 is the ExoN exoribonuclease (Ogando et al., 2019; Abel et al., 2020).

According to molecular dynamics studies this 3'-to-5' exoribonuclease (ExoN) in non-structural protein 14 (nsp14), is responsible for excises nucleotides including antiviral drugs mis-incorporated by the low--fidelity viral RNA-dependent RNA polymerase (RdRp) (Moeller et al., 2021). N-terminal ExoN domain and N7-methyltransferase (N7-MTase) C-terminal domain that is involved in messenger RNA (mRNA) capping (Tahir, 2021). The ExoN has also been related in viral RNA recombination and resistance to innate immunity (Abel et al., 2020; Moeller et al., 2021), thus configuring an important target for the discovery of molecules that are able to block its activity.

In general, the plant compounds had a relatively high affinity for all important proteins of SARS-CoV-2. But according to our results, the glycoside cyanogenic Linarin is an active ingredient that may prevent the binding, entry, multiplication, and development of the virus. These results are in accordance with the findings of Mahmoudi et al., 2021.

Several recent studies have reported the computational screening of inhibitors for specific single targets, such as the main protease (Mpro) or the spike protein (Abel et al., 2020; Wang, 2020; Barh et al., 2020). The development of anti-CoV drugs is reached dramatically by the ability of CoVs, during their viral genome replication and transcription steps, to use a strategy to review and eliminate incompatible nucleotides (Tahir, 2021). Thus, ExoN also is a promising strategy to develop new coronavirus inhibitors and antiviral sensitizers (Smith et al., 2013).

Described by their use of the energy released during nucleotide hydrolysis to facilitate these activities, helicases have been targeted in studies that experimentally confirmed the strategic direction of SARS--CoV-2 helicases using reported antiviral drugs (Ahmad et al., 2021). Helicases are enzymes responsible for the unfolding of double-stranded nucleic acids in the 5'-3' direction during biological processes, which include replication and recombination repair (White; Lin; Cheng, 2020). Thus, these enzymes can also be a therapeutic target for the search for new molecules that can inhibit their essential activity in Coronaviruses (Briguglio et al., 2011).

Corroborating to Yu *et al.* (2020), that affirms Luteolin is a molecule that has binding sites in Mpro so consistently that it can be considered as an effective compound against SARS-CoV-2, in this study we found this molecule as a potential target in anti-CoV drugs. However, this is an observation restricted to its analysis by molecular docking without validation by simulations of molecular dynamics.

CONCLUSIONS

Our study reports potential inhibitors for the SARS-CoV-2 by a computational approach. In our analyses was demonstrated, at least *in silico*, the potential molecular interactions between the Luteolin 7-O-β-D-glucopyranoside ($C_{21}H_{20}O_{11}$), Vitexin-2"-O-xyloside ($C_{26}H_{28}O_{14}$), Luteolin (C15H10O6) from *P. foetida* and ExoN, Hel, NendoU e nps 4 from SARS-CoV-2, including these molecules as attractive therapeutics against this virus. However, *in vitro,* and *in vivo* experiments are required to evaluate and ensure their potential therapeutic efficacy.

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