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Abstract

A new coronavirus appears in China in December 2019, subsequently threatening the world, it was identified as Covid-19. Its main symptomatic characteristic is directly linked to acute respiratory failure, however there are asymptomatic cases of the disease, mainly in the group not considered at risk. For the treatment of the disease a variety ofantiviral drugs have been tested, with conflicting results. The use of computer-assisted drugs is essential for the development of new therapeutic alternatives for various diseases, once they reduce the time consumed in the initial screening tests, in addition to determining the possible mechanisms of action and reducing toxicity. In our study, we evaluated the interaction of viral components of the coronavirus with potassium usnate, salt derived from lichenic origin and with proven antimicrobial and antitumor activities. Derived from ussic acid, potassium usnate showed low energy for complex formation, this interaction occurs between the usnate salt and the structures of proteinase 3CLpro and enzyme Mpro, all key parts of Covid-19. In addition, in order to prove in silico the use of potassium usnate, they were tested and compared with other approved drugs and candidates for clinical trials to combat the new coronavirus.

Keyword: Covid-19; potassium usnate; antivirals, molecular docking.

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ABSTRACT

A new coronavirus appears in China in December 2019, subsequently threatening the world, it was identified as Covid-19. Its main symptomatic characteristic is directly linked to acute respiratory failure, however there are asymptomatic cases of the disease, mainly in the group not considered at risk. For the treatment of the disease a variety ofantiviral drugs have been tested, with conflicting results. The use of computer-assisted drugs is essential for the development of new therapeutic alternatives for various diseases, once they reduce the time consumed in the initial screening tests, in addition to determining the possible mechanisms of action and reducing toxicity. In our study, we evaluated the interaction of viral components of the coronavirus with potassium usnate, salt derived from lichenic origin and with proven antimicrobial and antitumor activities. Derived from ussic acid, potassium usnate showed low energy for complex formation, this interaction occurs between the usnate salt and the structures of proteinase 3CLpro and enzyme Mpro, all key parts of Covid-19. In addition, in order to prove in silico the use of potassium usnate, they were tested and compared with other approved drugs and candidates for clinical trials to combat the new coronavirus.

Keyword: Covid-19; potassium usnate; antivirals, molecular docking.

INTRODUCTION

At the end of 2019, China comes to know a new coronavirus, identified from Covid-19, an invisible enemy to the eye, but with a great mortality power, and that a time later, the world started to be affected by it. There are three types of coronavirus in humans: they are human coronavirus 229E (HCoV-229E), HCoV-OC43 and coronavirus associated with severe acute respiratory syndrome (SARS) (SARS-CoV) [1, 2].

The main feature of Covid-19 is related to acute respiratory infections (ARI), the disease in its severe condition causes death of the alveoli and consequently respiratory failure [2,3].

This virus has non-segmented and enveloped positive RNA, which is widely disseminated in humans and other mammals [4]. Although most people who are infected do not show symptoms, the coronavirus is considered a pandemic responsible for syndromes of severe acute respiratory diseases [4-6].

Covid-19 has two important structures: the protease M^{pro}, an enzyme that mediates replication and virus transition [8-9] and the non-structural proteinase of polyprotein or $3CL^{pro}$, responsible for controlling the activities of the replication process of the Covid-19 [23].

The present time, with the discovery of this new Covid-19 coronavirus, there is no definitive pharmacological treatment for combat it. Using molecular modeling together with artificial intelligence is the initial step to combat the coronavirus. Many antiviral drugs that are already familiar are being tested to combat Covid-19, but with no concrete results.

A possible drug acyclovir is an example that can be used to against viral infections, being specific to the genus Simplexvirus, among the antimicrobial actions, intracellular half-life of one hour, decreases viral activity, increases healing kinetics and prevents appearance of new injuries [12-15].

Another drug widely advocated for the fight against Covid-19 is hydroxychloroquine, a medicine used to combat malaria and which has had pharmacological therapy against rheumatic diseases, such as lupus [16-17].

Also used as a test, remdesevir is another antiviral used to fight infections caused by RNA viruses, and which presented a mechanism of action against covid-19 [24].

Polypyrrole is another compound used in silico tests to combat covid-29, this polymer has been studied in several therapies, its electrical and biocompatible characteristics can be useful against the virus [25].

A promising one for the proposed covid-19 fight is potassium usnate, a compound derived from ussic acid, this acid that is present in lichens, organisms inhabit large vulnerable geographic areas and found mainly in bark, tree trunks, rocks and soils [18-20].

Ussic acid is widely used in the pharmaceutical, chemical and cosmetic industries, being one of the active ingredients for the production of medicines, being the most active and most important compound produced by the secondary metabolism of lichens [5, 6]. Starting from ussic acid, the derived compound, potassium usnate, in the form of salt, has less toxicity and is easily synthesized.

The binders used for silico evaluation were the antivirals acyclovir, hydroxychloroquine and remdesevir, in addition to the polypyrrole polymer, compared with potassium usnate, a promising possible to combat covid-19 (figure 1). Potassium usnate showed in silico an antiviral potential in combating the new coronavirus.

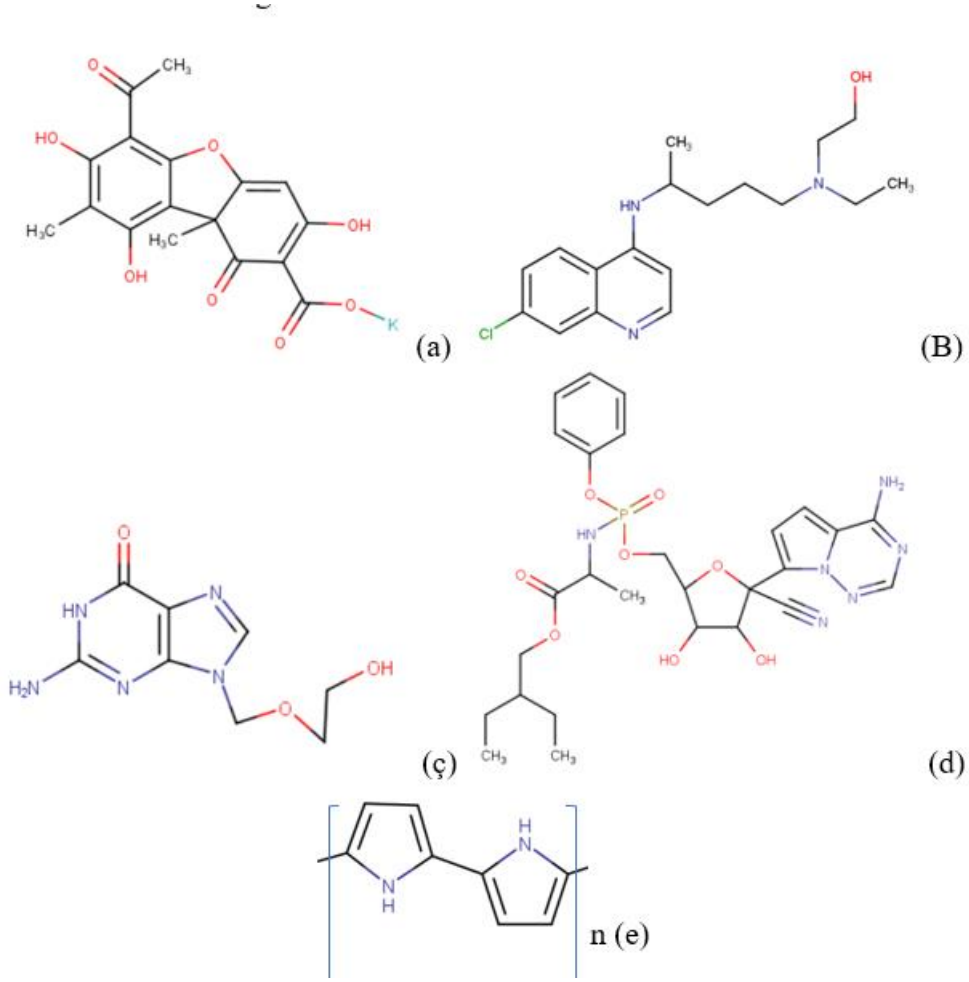


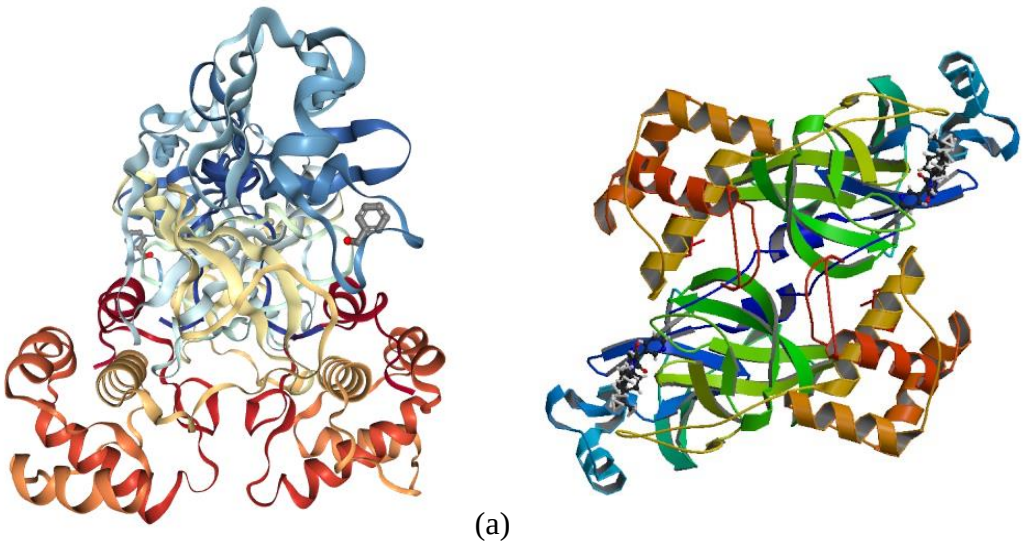
Figure 1. Potassium usnate (a), hydroxychloroquine (b), acyclovir (c) and remdesevir (d), polypyrrole (ppy) (e), respectively.

MATERIALS AND METHODS

For the design of the molecules, the MarvinSketch extension was used, part of ChemAxon's JChem package (https://www.chemaxon.com/). The software allows the construction of drug structures, such as potassium usnate, which were designed in the program and had their energies calculated according to the standardization configuration.

DOCKING FOR MPRO PROTEASE AND 3CL PROTEINASE

The crystal structure of the Covid-19 M^{pro} protease (PDB ID 6LU7) and the Covid-19 $3CL^{pro}$ polyprotein non-structural proteinase structure (PDB ID 6W63) were downloaded from the Protein Data Bank (http://www.rcsb.org/pdb/home/home.do), (figure 2).



(a) (b)

Figure 2. Secondary structure of M^{pro} protease (a) and non-structural polyprotein proteinase $3CL^{pro}$ (b) from Covid-19.

The molecular structures were submitted to molecular fitting using the Molegro Virtual Docker, v. 6.0.1 (MVD) [10]. All water molecules were excluded from viral structures and compounds that were prepared using the same standard parameter settings in the software package (scoring function: MolDock score; ligand evaluation: internal ES, internal HBond, Sp2-Sp2 twists , all verified; number of executions: 10; search algorithm: MolDock SE; maximum interactions: 1500; maximum population size: 50; maximum steps: 300; distance factor from neighbor: 1.00; and maximum number of poses returned. The coupling procedure was performed using a GRID of 10Å radius and 0.20 resolution to cover the ligand binding site of the structure in question.

RESULTS AND DISCUSSION

Potassium usnate, polypyrrole, acyclovir, hydroxychloroquine and remdesevir were incorporated into the crystalline structures of the M^{pro} protease and the $3CL^{pro}$ proteinase involved in the antiviral mechanism. The results are shown in tables 1 and 2 and indicate that potassium usnate shows greater affinity in the two structures of the coronavirus, when compared to the hydroxychloroquine ligand, acyclovir and polypyrrole, which are possible ligands to combat Covid-19. Two compounds showed excellent affinities for potassium usnate for the two structures and showed interaction only with the protease M^{pro}.

Binders	Binding energy
Hydroxychloroquine	-97.4764
Potassium usnate	-112.2900
Acyclovir	-89.8323
Polypyrrole	-78.3817
Remdesevir	-127.8850

Table 1: MolDock Score energies for the ligands in the mechanism of antiviral action, being potassium usnate and remdesevir with the best interaction for M^{pro} protease.

Binders	Binding energy
Hydroxychloroquine	-86.6906
Potassium usnate	-99.8391
Acyclovir	-90,114
Remdesevir	3.9727
Polypyrrole	-66.0040

Table 2: MolDock Score energies for ligands in the mechanism of antiviral action, potassium usnate with better interaction of $3CL^{pro}$ proteinase.

The potassium usnate interacts with amino acids through hydrogen bonds (blue lines) and electrostatic interactions (red lines), figure 3.

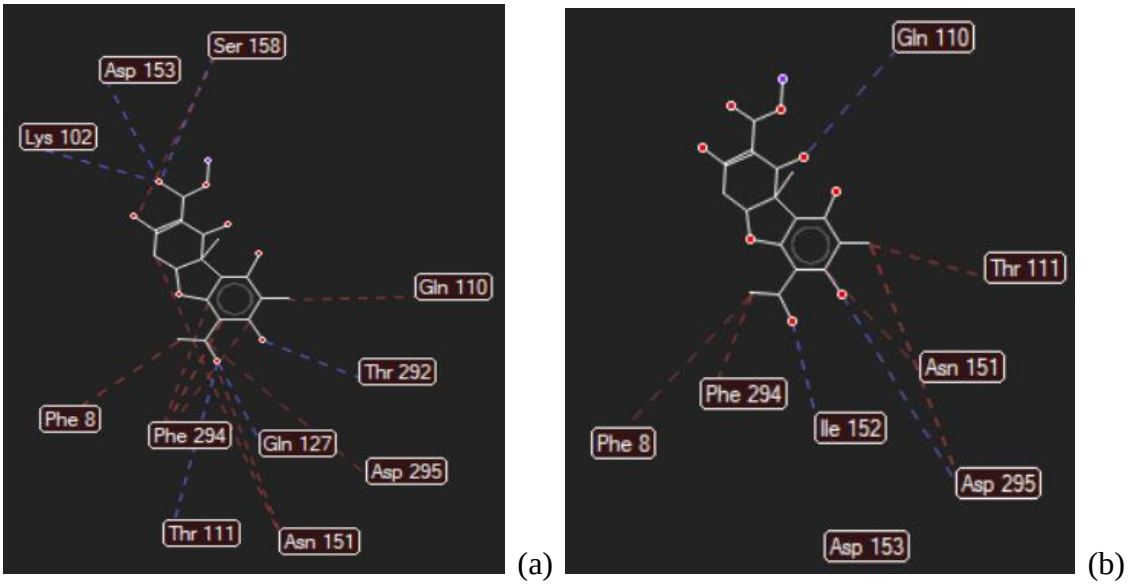


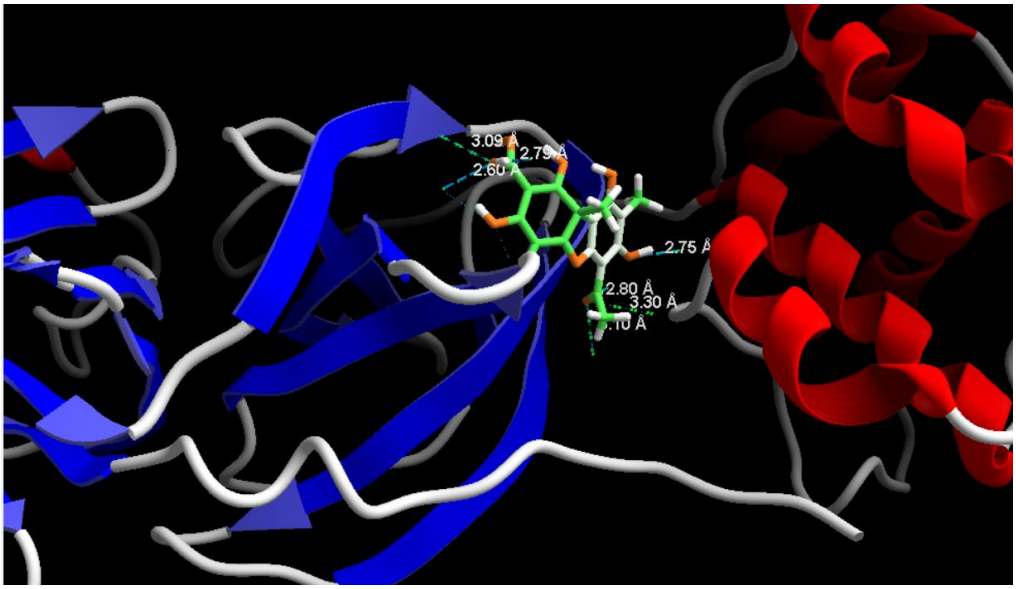
Figure 3. Intermolecular attractions by hydrogen bonds and electrostatic interactions of potassium usnate in the crystalline structures of the M^{pro} protease (a) and in the $3CL^{pro}$ proteinase (b).

Potassium usnate interacts by hydrogen bonds with the M^{pro} protease the amino acids threonine (111), lysine (102), serine (158) and aspartic (153), and with proteinase $3CL^{pro}$ the isoleucine (295) and aspartic (152).

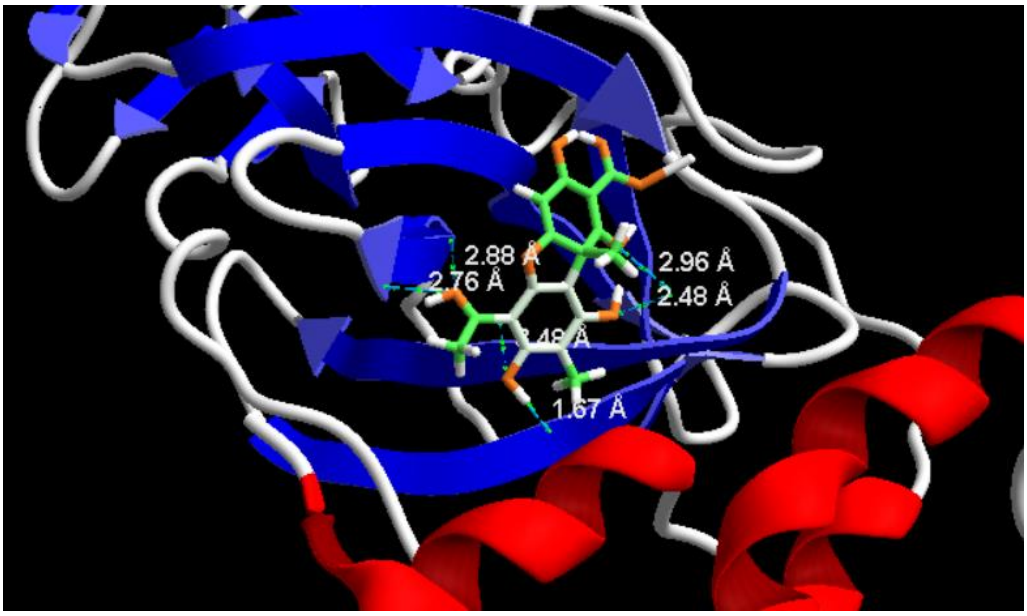
For electrostatic attractions there were interactions with the M^{pro} protease, the amino acids serine (158), phenylalanines (8 and 294), glutamic (110 and 127), asparagine (151), aspartic (295) and with the $3CL^{pro}$ proteinase the phenylalanine amino acids (8 and 294), aspartic (153 and 295), asparagine (151), threonine (111) and glutamine (110).

The interactions of these intermolecular forces by hydrogen and electrostatics highlight the potential for conformational stabilizations, that is, it induces the interaction of ligands with their targets.

In figure 4 it shows the interaction distances of the connections between the potassium usnate and the ligands, protease M^{pro} and proteinase $3CL^{pro}$, this recommends in which of the conformations are closest to the active site of the targets and the ligand.



(a)



(b)

Figure 4. Distances of interactions of potassium usnate with protease M^{pro} (a) and proteinase $3CL^{pro}$ (b).

CONCLUSION

This study compared the use of hydroxychloroquine, remdesevir and acyclovir to combat Covid-19 and potassium usnate as a substitute for the drugs in question.

Therefore, it is concluded that potassium usnate showed antiviral activity in silico with interaction energy, between the target molecules and the ligand, much lower when compared with hydroxychloroquine.

Despite presenting a slightly higher interaction energy than remdesevir in the protease Mpro, potassium usnate is a low toxicity salt and has low energy in both structures.

Thus, potassium usnate becomes promising for vitro test achievements in the against.

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