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Title: Metal-curcumin complexes as potential inhibitors in RdRp and Mpro of SARS-COV-2 using quantum mechanics, molecular docking and molecular dynamics.

Keywords: SARS-Cov-2, nsp12, RdRp, Mpro, curcumin, magnesium, metallodrugs.

Introduction

The computational scientific community is intensely studying the chemical mechanisms about produced by Covid-19. The beta-coronavirus that causes it, SARS-CoV-2, is one of the seven human-reported coronaviruses (HCoV). It consists of two groups of proteins:

1. Structural proteins: spike (S), nucleocapsid (N), matrix (M), and envelope (E)

2. Nonstructural proteins: proteases (nsp3 and nsp5) and RdRp (nsp12)

This RdRp has its active site highly conserved, being one of the main targets for the application of antivirals, not only in coronaviruses, but also in hepatitis C and Zika. In this site, two aspartates are important because they are successive and accessible on the surface (Elfiky, 2020).

On the other hand, curcumin, the main bioactive component of *Curcuma longa* and classified as a safe compound by the FDA, has demonstrated therapeutic activities, such as antioxidant, analgesic, anti-inflammatory, antiseptic and anticarcinogenic;

highlighting among them, its antiviral activity against HIV, herpes simplex, hepatitis, Ebola and influenza. Previous researches concluded that curcumin interacts directly with almost 30 proteins, such as, DNA polymerase, focal adhesion kinase (FAK), thioredoxin reductase, protein kinase (PK), lipoxygenase (LOX), and tubulin. This accumulated evidence indicated curcumin plays an inhibitory role against infection of numerous viruses, so represent an antiviral potential against SARS-CoV-2 (Mathew & Hsu, 2018).

Based on this, we propose the use of biometals, such as magnesium, zinc, copper, and iron, in the computational design of potential anti-Covid 19 metallodrugs. Because to the multiligand transport effect of $[Me^{II}(curcumin)_2]$ (Meza-Morales & Estevez-Carmona, 2019) and also based on preliminary computational studies, carried out by our group. We calculated high affinity energies (-9.08 Kcal/mol, Figure 1) for magnesium complex in the main protease Mpro, other important target (Jin et al., 2020; Liu & Wang, 2020), that it would act through a possible allosteric mechanism (Shen, 2010).

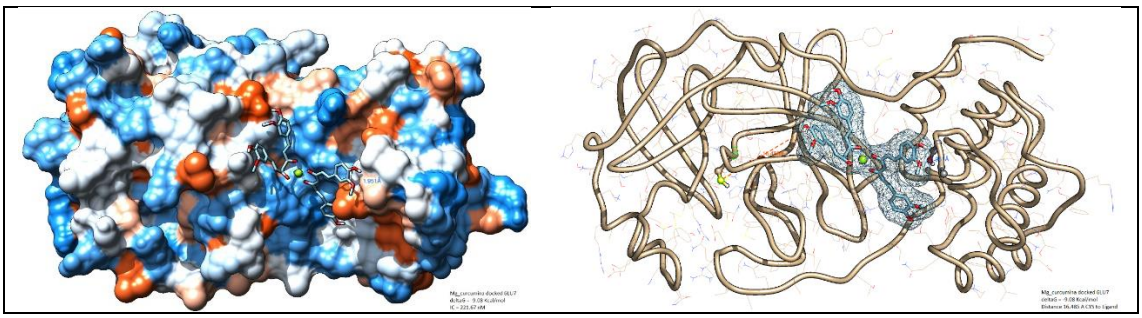

Figure 1. Mg-curcumin in Mpro (PDB ID 6LU7)

Objectives

Evaluate a new family of metallodrugs MeL (Me: magnesium, zinc and copper, L: curcumin derivatives) as potential inhibitors of RdRp (nsp12) and Mpro of SARS-CoV-2 using molecular docking.

Metodology

This work consist in three stages.

In the first stage, we used free software for 3D design of molecules MeL. After that, these molecules are optimize with quantum mechanics. Reactivity indicators using HOMO and LUMO molecular orbitals are estimate too. On the other hand, we employed scripts for automatize the exportation of Mulliken charges to the other extension files.

This processing is necessary because metal's influence on the complex. These files are the inputs of "ligands" for the virtual screening and molecular docking. While the protein will be treated by protocols standard. At this stage we want to use the DockThor program for estimate the best binding energy between ligand-receptor and evaluate the molecular interactions with the principal amino acids in the active site.

Finally, we use those best positions as input for molecular dynamics. Thus, estimate the stability (RMSD, RMSF) of the best interactions between ligand-receptor employing Desmond software with collaboration of the Computational Chemistry Group in the Instituto de Química of USP.

Perspective

We estimate 6 months to complete this work and submit it for evaluation to be published.

Those molecules with the highest inhibitory potential will be synthesized and characterized in our laboratory.

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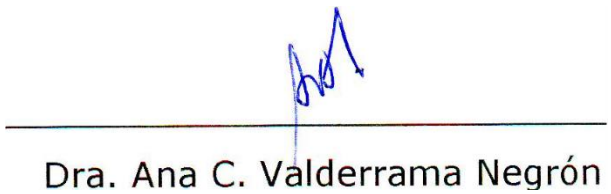
Signature



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