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Supporting Materials

Theophylline: Old Drug in a New Light, Application in COVID-19 through Computational Studies

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Methodology

Molecular modeling of the E protein from SARS-CoV-2

Based on the primary sequence YP_009724392 of the E protein from SARS-CoV-2, it was possible to build the E protein of this virus by employing the crystal structure PDB: 5X29, which corresponds to the E protein of SARS-CoV. The identity percentage between the sequence of the E protein of SARS-CoV-2 and the crystal structure is 91.379%. A three-dimensional model of the pentamer of the E protein of SARS-CoV-2 was built by using Modeller 10.1 Software [1]. Obtaining the three-dimensional structure of the Spike protein of SARS-CoV-2 Crystal 7WK3, downloaded from the pdb database [2], which is the Omicron variant SARS-CoV-2 Spike protein crystal; therefore, it is the crystal that we will use for the Docking.

Molecular docking

For the molecular docking of theophylline with both proteins (Spike and E of SARS-CoV-2) docking was performed directed at the RBD site (Spike protein) and the ion channel (E protein) respectively. The Vina program was used, with the following parameters: num_modes = 20, energy_range = 6 and exhaustiveness= 25. For the case of the Spike protein: center_x = 210.0, center_y = 170.0, center_z = 270.0, size_x = 60.00, size_y = 60.00 and

size_z = 60.00. And for protein E: center_x = -7.0,center_y = 1.0, center_z = -6.0, size_x = 35.00, size = 30.00 and size_z = 30.0 [3].

Table S1. Theophylline Simulation Conditions.

Parameter	Theophylline
Lipophilicity (Log Units)	0.89
Binds To	Albumin
Fraction Unbound	0.44
Molecular Weight (g/mol)	180.17
Compound Type And Pka	Acid / 8.8
Solubilility At Ref-Ph (mg/L)	14300
Ref-pH	6.5
Metabolizing Enzymes	CYP1A2
Metabolizing Enzymes Clearence (1/Min)	0.00843
Renal Clearence	0.15
Administration Protocol	Simple protocol
Administration Type	Intravenous bolus
Dose (mg/Kg)	1 and 10
Dosing Interval	Single

Table S2. Individuals Simulation Conditions.

	Healthy	***Renal impaired***
Population	Mexican American – White (NHAES, 1997)	Mexican American – White (NHAES, 1997)
Age (Years)	70	70
Gender	Male	Male
Weight (Kg)	74.43	74.43
Height (cm)	165.96	165.96
BMI (Kg/m²)	27.02	27.02
Body Surface Area (m²)	1.85	1.85
Hematocrit	0.46	0.33
EHC continuos fraction	0	1
GFR Specific (ml/min/100 g organ)	26.6	5
Metabolizing enzymes expression	CYP1A2	CYP1A2